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Untersuchungen von prognostischen Parametern hinsichtlich klinischer, epidemiologischer und behandlungsrelevanter Aspekte bei Patienten mit myelodysplastischen Neoplasien (MDS)

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Inhaltsverzeichnis

Zusammenfassung

Die vorliegende Arbeit umfasst Erkenntnisse meiner sechs Originalarbeiten, die ich als Erstautorin verfasst habe und die sich mit diagnostischen, prognostischen und epidemiologischen Fragestellungen bei Patienten mit myelodysplastischen Neoplasien (MDS) beschäftigen.

Fußend auf einer systematischen Neuanalyse der Erstdiagnosepräparate von 128 Patienten mit MDS konnte ich für die Diagnostik bei MDS durch direkten Vergleich zytomorphologischer und histopathologischer Diagnoseverfahren nachweisen, dass eine systematische Beurteilung von Knochenmarkhistologien für MDS-Patienten unabdingbar ist, da sie Informationen wie die Zellularität oder eine etwaig vorliegende Fibrose beitragen, die in der für MDS-Erstdiagnosen üblichen Beurteilung der Zytomorphologie nicht verlässlich oder der Methodik geschuldet gänzlich nicht erhoben werden können, jedoch eine hohe prognostische Relevanz tragen. Hier habe ich auch eine Vielzahl einzelner diagnostischer Parameter im Detail untereinander auf ihr mögliches prognostisches Potential untersucht.

Im Rahmen meines Interesses für die Prognose von MDS Patienten habe ich mich zudem mit den Todesursachen bei unbehandelten MDS-Patienten beschäftigt, die zuvor noch nicht detailliert analysiert wurden. Hier wurden 3792 Patienten des Registers hinsichtlich ihrer Todesursachen, insbesondere in Blick auf krankheitsassoziierte versus nicht krankheitsassoziierte Todesursachen analysiert. Die exakte Erfassung der zum Tode führenden Ursache war nur für einen Teil des Kollektives möglich und unterstreicht, weshalb es bis dato noch keine derartig detaillierte Analyse gab. Wir konnten nachweisen, dass ein überwiegender Anteil von MDS Patienten (83,4 %) an krankheitsassoziierten Ursachen wie Infektionen versterben. Es fand sich zudem eine klare positive Korrelation zwischen MDS Risikosubtyp und zunehmender Wahrscheinlichkeit, an solch einem Ereignis zu versterben gegenüber nicht krankheitsassoziierten Ursachen wie kardialen Komorbiditäten. Diese Arbeit unterstrich und bestätigte die bisher vorliegenden Erkenntnisse, dass, wenngleich das Patientenkollektiv mit MDS ein höheres medianes Lebensalter aufweist, diese Erkrankung eine hohe prognostische Relevanz birgt und entsprechend der Weiterentwicklung krankheitsmodifizierender Therapien eine hohe Bedeutung zukommt.

In einer auf Daten unseres mittlerweile >7000 Patienten umfassenden MDS-Registers basierenden Arbeit habe ich dann die aktuellen Erkenntnisse zur Diagnostik, Prognose und Therapie bei MDS darlegen können und ein umfassendes vereinheitlichtes Prozedere vorgeschlagen. Weiterhin habe ich mich mit der im Jahr 2022 beinahe zeitgleich erschienenen aktualisierten WHO Klassifikation und neu geschaffenen ICC Klassifikation für MDS beschäftigt, die in der Fachwelt große Kontroversen ausgelöst hat. Neben der Validierung mittels des MDS Registers Düsseldorf habe ich versucht, die Vergleichbarkeit und möglicherweise Überlegenheit einer der beiden Systeme herauszuarbeiten. Aufgrund der inhärenten Problematik nun zweier miteinander konkurrierender prognostisch relevanter Diagnosesysteme habe ich eine neue

fusionierte Klassifikation im Rahmen der Arbeit auf Basis meiner Analyse vorgeschlagen.

Ich widmete mich schließlich in zwei Arbeiten den Therapieansätzen bei MDS Patienten, um mich mit dem Einflusspotential von Therapieoptionen auf die Prognose zu befassen. In einer großen retrospektiven Studie mit Matched Pairs Analysen habe ich verschiedene bei MDS Patienten zur Anwendung kommende therapeutische Ansätze auf ihren Einfluss auf das Gesamtüberleben und das Risiko der Entwicklung einer sekundären akuten myeloischen Leukämie (AML) durch den direkten Vergleich mit manuell nach definierten Parametern ausgewählten, ausschließlich supportiv behandelten Patienten untersucht. Es war die erste Arbeit, die sich mit dem Gesamtüberleben und dem direkten Vergleich von Therapieoptionen versus „best supportive care“ (BSC) beschäftigt hat. Schließlich untersuchte ich die Zugänglichkeit zu klinischen Studien im „real life setting“ für MDS Patienten. Hier konnte ich aufzeigen, dass aufgrund der hochspezifischen Ein- und Ausschlusskriterien, vor allem betreffend Industrie-gesponserter Studien, ein überwiegender Teil der MDS Patienten keinen Zugang zu neuen Substanzen oder Verfahren erhalten kann und postulierte einige neue Ideen, um die Machbarkeit, aber auch die Zugänglichkeit für die Patienten, von klinischen Studien in Zukunft zu erhöhen.

Einleitung

Myelodysplastische Neoplasien (ehemals myelodysplastische Syndrome, jedoch Beibehaltung der Abkürzung „MDS“) sind eine heterogene Gruppe von klonalen myeloischen Stammzellerkrankungen. Genetische Aberrationen und molekulargenetische meist somatische Mutationen, die über den Lauf der Lebensjahre akquiriert werden oder sekundär durch externe Noxen wie eine vorangegangene Strahlen- oder Chemotherapie begünstigt werden, führen zu Bildungs- und Differenzierungsdefekten der hämatopoetischen Stammzelle, welche sich vorrangig in peripheren Zytopenien unterschiedlichen Ausmaßes manifestieren sowie gegebenenfalls in einer Vermehrung von peripheren und medullären Blasten bis zu 20% [1,2]. Es erfolgt eine Kategorisierung zu Subtypen, die entweder auf der Grundlage des Ausmaßes von Dysplasie und Zytopenie und/oder Blastenvermehrung oder in erster Linie aufgrund genetischer oder molekulargenetischer Aberrationen kategorisiert werden [3].

Allen MDS Subtypen gemein ist das Risiko der Entwicklung einer sekundären akuten myeloischen Leukämie (sAML), welche definitionsgemäß ab ≥ 20% Blasten vorliegt. Das mittlere Erkrankungsalter liegt bei 70-75 Jahren. Myelodysplastische Neoplasien zählen zu den häufigsten malignen Stammzellerkrankungen mit einer Inzidenz von circa 4/100.000 Einwohnern mit einer deutlichen Zunahme mit höherem Lebensalter auf >30/100.000 ab 70 Jahren [4].

Aufgrund der Komplexität bzw Diversität der Erkrankungen, die sich in den zahlreichen Subtypen widerspiegelt, und dem Erkenntnisgewinn über die Krankheitsbiologie über die letzten 10 Jahre unterliegt die Evaluation von MDS Patienten in Hinblick auf ihre Prognose einem andauernden und sich auch in den letzten Jahren weiterhin über neue oder revidierte Scoring- und Diagnosesysteme einem fortwährenden Fluss. Es bleibt interessant, sich Fragen zu Prognose, Diagnose und auch Therapie zu stellen und neue Parameter zu ermitteln oder neue Methoden zu erarbeiten oder auch etablierte zu hinterfragen oder mit aktuellen Daten auf weitere Gültigkeit zu überprüfen.

Bereits in den 1980er Jahren wurden erste Prognoseklassifikationen wie die FAB-Klassifikation für MDS veröffentlicht [5]. Im Laufe der folgenden Jahrzehnte folgten viele neue Klassifikationssysteme oder aktualisierte Versionen dieser, um möglichst homogene MDS Subtypen zu etablieren und deren Prognose möglichst exakt abschätzen zu können. Diese beinhalteten zunehmend genetische und molekulargenetische Informationen. Erst im Jahr 2022 wurde eine neue WHO Klassifikation veröffentlicht, die zahlreiche Neuerungen insbesondere in Hinblick auf neue Erkenntnisse im molekulargenetischen Bereich enthielt und der Histopathologie einen berechtigten höheren Stellenwert gibt [6]. In der beinahe zeitgleich publizierten ICC Klassifikation erhielt die WHO 2022 Klassifikation allerdings erstmalig eine kontroverse Konkurrenz [7]. Diese Diagnosesystematik stellt inhärent ein starkes prognostisches Tool dar.

Ein weiterer etablierter Prognosescore ist der IPSS (International Prognostic Scoring System). 1997 von Greenberg et al. unter Beteiligung der Düsseldorfer MDS Arbeitsgruppe veröffentlicht, unterteilt er MDS Patienten anhand ihrer Zytopenien, dem medullären Blastenanteil, aber auch erstmalig anhand ihrer Zytogenetik, in vier Risikogruppen mit signifikant unterschiedlichem medianen Gesamtüberleben und Risiko der Entwicklung einer sekundären akuten myeloischen Leukämie [8]. 2012 erschien die weiterentwickelte Version, der IPSS-R, welcher neben dem bekannten medullären Blastenanteil nun detailliertere Karyotypaberrationen, kategorisierte Blutwerte und den Transfusionsbedarf erfasste und fünf Risikogruppen unterscheidet [9]. Die aktuellste Version von Bernard et al., 2022 erschienen, ist der IPSS-molecular [10]. Dieser Score ist als internetbasiertes Tool anwendbar und trägt den in den letzten Jahren zunehmend detailliert charakterisierten molekulargenetischen Aberrationen und ihrem Einfluss auf die Prognose von MDS Patienten Rechnung. Die aktuellsten allgemein anerkannten Klassifikationssysteme sind die WHO 2022 und die ICC.

Therapeutisch existierten bis in die 2000er Jahre bis auf die allogene Blutstammzelltransplantation wenig krankheitsmodifizierende und damit Einfluss auf die Prognose der Patienten nehmende Therapien. Bis heute stellt die allogene Blutstammzelltransplantation allerdings weiterhin die einzig potentiell kurative Therapieoption dar. Diese intensive und damit nebenwirkungs- und komplikationsträchtige Therapie kann jedoch aufgrund des durchschnittlich höheren Lebensalters der Patienten und damit einhergehender Komorbiditäten oder generell eingeschränkten Allgemeinzustandes bei weitem nicht jedem Patienten angeboten werden. Dennoch wurden und werden weiterhin eine Vielzahl von therapeutischen Optionen untersucht, die eine Verlängerung des Überlebens, eine Risikoreduktion einer AML-Entwicklung oder eine Verbesserung der Lebensqualität zum Ziel haben.

Das Düsseldorfer MDS Register wurde bereits in den 1980ern etabliert und stellt bis heute eines der weltweit größten und umfangreichsten Register für diese Erkrankung dar. Aktuell sind mehr als 10.000 Patienten innerhalb des Registers erfasst. Grundlage ist die detaillierte und systematische Dokumentation zytomorphologischer, (molekular-)genetischer und klinischer Parameter von neu diagnostizierten MDS Patienten, die nach Erteilung ihres Einverständnisses eigeschlossen werden. Hierzu liegen Ethikvota der Ethikkommission der Heinrich-Heine-Universität Düsseldorf vor (Nr. 3008 von 2008 und Nr. 3973 von 2013, letztes Amendment am 10.03.2022). Circa 45% entstammen von innerhalb des Zentrums betreuten Patienten und 55% wurden über kooperierende Kliniken oder niedergelassene Hämatoonkologen übermittelt, da nahezu jeder Patient aus Düsseldorf und dem unmittelbaren Umland mit dem Verdacht auf eine hämatologische Neoplasie aus dem Formenkreis der MDS hiesig vorgestellt wird. Dem Register angeschlossen ist die zentrale MDS Biobank, welche Teil eines von der Deutschen Krebshilfe unterstützten MDS Verbundsprojekts ist und die Blut- und Knochenmarkproben von über 2000 Patienten enthält. Die Daten, die im Register vorliegen, umfassen jedoch nicht alleinig Parameter zum Erstdiagnosezeitpunkt, sondern auch Verläufe über die Zeit wie beispielsweise applizierte Therapien und das Ansprechen hierauf, Laborparameter im Krankheitsverlauf oder Komorbiditäten. Diese

Daten ermöglichen umfangreiche Analysen, um neue Erkenntnisse über die Prognose unbehandelter Patienten und über Therapieeffekte auf die Prognose von MDS Patienten zu gewinnen, und auch um epidemiologische Fragestellungen zu bearbeiten.

Die Zahl zugelassener Therapieoptionen für myelodysplastische Neoplasien ist insbesondere in Deutschland beschränkt. Neben der hypomethylierenden Substanz (HMA) Azacitidin existieren Erythropoetin-α, Lenalidomid sowie Luspatercept für verschiedene Subentitäten von MDS mit definierenden genetischen Aberrationen. Venetoclax erwies sich in zahlreichen Studien als prognoseverbessernd in Kombination mit HMA und ist entsprechend auch durch die FDA bereits zugelassen. All diesen krankheitsmodifizierenden Therapien ist gemein, dass sie einen positiven Einfluss auf das Gesamtüberleben und/oder Risiko der Entwicklung einer sAML ausüben sollen. Aufgrund der insgesamt jedoch geringen Zahl an verfügbaren Optionen, insbesondere bei Niedrigrisiko-MDS ohne del5q oder ringsideroblastischem Phänotyp, ist die Evaluation einer Studienteilnahme für diese Entität angeraten. In der Vergangenheit wurden mannigfaltige Therapieoptionen bei MDS untersucht, so beispielsweise immunsuppressive Therapien wie ATG oder immunmodulatorische Ansätze mit Valproinsäure, jedoch nur mit eingeschränkten oder diskrepanten Daten zur Wirksamkeit. Klassische Chemotherapien verbessern die Prognose von MDS Patienten nicht und sollten nicht mehr zur Anwendung kommen. Einzig kurative Therapieoption ist und bleibt jedoch bis heute die allogene Blutstammzelltransplantation. Aufgrund der Epidemiologie der Erkrankung mit einem medianen Erkrankungsalter >70 Jahre und dem Risikopotential der Stammzelltransplantation kann diese Behandlung nach wie vor nur einem Teil der Patienten angeboten werden. Indikationsstellung, Einschätzung des individuellen Patienten und Entwicklung neuer Therapiekonzepte in der Konditionierungstherapie für die Stammzelltransplantation, der Spenderauswahl und der Gestaltung der Nachtransplantationsphase sind eine Herausforderung und ebenfalls Bestandteil wissenschaftlichen Interesses zur Verbesserung bestehender Verfahren und auch potentiell Eröffnung dieser Therapie weiterer Patienten (z.B. Konzepte der „reduced intensity conditioning“) [11,12]. Zusammengefasst erfordert die Therapie von MDS Patienten ein hohes Maß an Expertise und Erfahrung.

1. Prognostische und epidemiologische Analysen bei MDS Patienten

1.1. Neubewertung diagnostischer Verfahren

Myelodysplastische Neoplasien sind grundlegend gekennzeichnet durch das Vorhandensein von Dysplasiezeichen der hämatopoetischen Zellen im Knochenmark und Blut, die auf Bildungs- und Differenzierungsstörungen der hämatopoetischen Stammzelle fußen. Die Erkennung und Charakterisierung dieser Dysplasiezeichen, nebst der Erfassung des Anteils hämatopoetischer Progenitoren, sind die Domäne der Zytomorphologie, also die mikroskopische Untersuchung von gefärbten Blut- und Knochenmarkausstrichen. Diese Parameter sind unabdingbarer Bestandteil aller Diagnose- und Prognosesysteme wie der WHO-Klassifikation oder den verschiedenen IPSS Scores. Die Untersuchung histopathologischer Knochenmarktrepanate war nicht obligater Bestandteil des diagnostischen Workups von MDS Patienten. In anderen hämatologischen Entitäten wie den malignen Lymphomen sollte zum Erstdiagnosezeitpunkt eine Knochenmarkhistologie erfolgen, um eine Knochenmarkinfiltration auszuschließen. Jedoch gibt es Parameter, die auch bei MDS durch einen Knochenmarkausstrich nicht verlässlich oder auch gar nicht erfasst werden. Hierzu zählen die Evaluation der Zellularität und das Vorhandensein und Grading einer Markraumfibrose. Der Stellenwert dieser Faktoren für MDS Patienten war bislang unzureichend erfasst bzw. wurde unterschiedlich bewertet [13,14,15]. Erst die aktuellste Edition der WHO-Klassifikation aus dem Jahr 2022 trug der prognostischen Relevanz des Vorhandenseins einer Knochenmarkfibrose bei MDS Patienten Rechnung und etablierte erstmals eine eigene MDS-Entität, die MDS-f, für Patienten, die eine Fibrose aufweisen [6].

Unser Interesse galt in meiner Arbeit der Analyse des prognostischen Stellenwertes histopathologisch erhobener Faktoren und der diagnostischen Konformität zwischen beiden Methoden. Zudem beschäftigte ich mich mit der Frage, ob es zytomorphologisch erhobene Parameter gibt, die in der Histopathologie bislang nicht bekannte prognostische Relevanz aufweisen. Hierzu ließen wir zytomorphologische Präparate von 128 Patienten, die bereits als MDS diagnostiziert worden waren, durch einen festgelegten, erfahrenen Zytomorphologen erneut beurteilen und parallel hierzu die dazugehörigen histopathologischen Knochenmarkstanzen neu aufarbeiten, färben und ebenfalls durch einen festgelegten, erfahrenen Histopathologen beurteilen. Diesem war einzig die zytomorphologisch festgelegte Diagnose „MDS“ bekannt. Wir untersuchten unter anderem histopathologisch relevante Parameter (Zellularität, Fibrose), und auch MDS-definierende Faktoren wie den Blastenanteil, Dysmegakaryopoese, Dyserythropoese und nutzten auch innerhalb des MDS Registers bereits erhobene patientenassoziierte Parameter wie Alter, Geschlecht, Diagnosezeitpunkt, definitives Schicksal (Tod, „lost to follow up“, lebend zum letzten Dokumentationszeitpunkt), Zytogenetik.

Wir konnten aufzeigen, dass die prozentuale Einschätzung des medullären Blastenanteils, welcher einen zentralen Aspekt zur korrekten Diagnosestellung

darstellt und hoch prognostisch relevant ist, in der histopathologischen Diagnostik systematisch unterschätzt wird.

TABLE 3 Comparison of blast percentages assessed by cytomorphology with blast percentage assessed by staining of CD34 by histopathology (p<0.001).

		CD34+ cells by histopathology			
Blast count by cytology					
	0-4%	5-9%	10-19%	20-29%	total
0-4%	32	15	2	1	50
5-9%	14	9	4	1	28
10-19%	12	8	5	3	28
20-29%	5	4	6	7	22
					128

Red marked numbers indicate the either most statistically relevant or most strinkingly differing parameters within the comparison of histo- and cytomorphology.

Vergleich der prozentualen Bestimmung des medullären Blastenanteils in Zytomorphologie und Histopathologie (p<0,001). Eigene Abbildung.

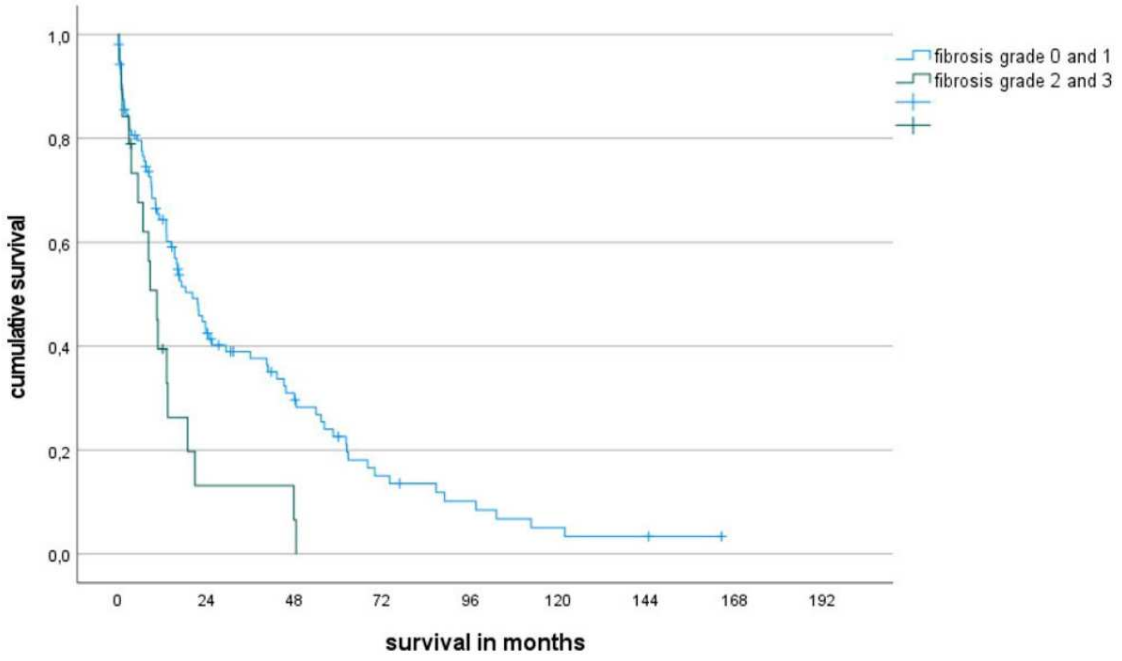
Beweisend zeigte eine Analyse des Gesamtüberlebens der Kohorte in dieser Arbeit, gruppiert nach Blastenanteil, eine erwartbare Unterscheidung der Gesamtgruppe, wenn gemäß zytomorphologischem Befund gruppiert wurde. Dies zeigte sich nicht bei Subgruppierung anhand des histopathologischen Befundes.

Dysplastische Megakarypoese zeigte sich signifikant inkongruent mit vermutet höherer Sensitivität für das Erkennen von Dysplasiezeichen in der Histologie, zudem konnten wir nachweisen, dass eine positive Korrelation zwischen Grad der Dysmegakaryopoese und prognostisch ungünstigen Subtypen sowie der Zellularität vorliegt.

Die Histopathologie bleibt für die Einschätzung der Zellularität Goldstandard. Deutliche Inkongruenzen in der Abschätzung der Zellularität zwischen Zytologie und Histologie, insbesondere bei Hypo- und Hyperzellularität, waren nachweisbar. In der Zytomorphologie wird die Zellularität überschätzt. Dieser Befund wurde insbesondere evident bei Vorliegen von histologisch beschriebener Hypozellularität, bei welcher jeweils fast 50% der Fälle zytomorphologisch als normo- oder gar hyperzellulär beschrieben wurden. Aufgrund der in der WHO 2022-Klassifikation neu eingeführten Entität der MDS-h (hypozelluläres MDS) ist somit nun zumindest einmalig zum Diagnosezeitpunkt die Untersuchung einer Knochenmarkstanze unabdingbar.

Die Kongruenz der via Zytomorphologie versus Histopathologie erhobenen MDS Diagnose gemäß WHO 2016 Klassifikation zeigte Schwächen insbesondere beruhend auf dem obig genannten Aspekt der diskrepant eingeschätzten Blastenzahl. Nichtsdestotrotz gab es übereinstimmende Diagnosen in beinahe 50% der Fälle sowie keinen Kasus, in dem eine chronische myelomonozytäre Leukämie (CMML) nicht als solche erkannt wurde, wenngleich sich auch hier Unterschiede in der detaillierten Subklassifikation in CMML 0, I oder II aufgrund der Zählung des Blastenanteils zeigten.

Vorliegen und Grad einer Fibrose korrelierte in meinen Analysen positiv mit sowohl der Hyperzellularität als auch mit höherem Risikosubtyp. Dies erscheint auf den ersten Blick insofern kontraintuitiv, als Fibrose aufgrund der zunehmenden Verfaserung der Markräume eine Verminderung an hämatopoetischer Nische mit sich bringt. Wir postulieren hier eine möglicherweise bislang unterschätzte Assoziation des Vorliegens von Fibrose insbesondere bei Hochrisiko-MDS, deren zunehmender Anteil myeloischer Progenitoren den baldigen Übergang in eine sekundäre akute myeloische Leukämie anzeigen kann und entsprechend mit Hyperzellularität einhergeht. In unserer Kohorte ließ sich der Grad der Fibrose („hoch“ und „sehr hoch“ versus „keine“ und „mild“) als statistisch relevanter Parameter bezüglich der Prognose in Bezug auf die Gesamtüberlebenszeit nachweisen.



Gesamtüberleben von Patienten mit Fibrose Grad 0-1 versus Grad 2-3 (medianes OS 20 Monate versus 10 Monate, p=0,004). Eigene Abbildung.

In der Zusammenschau belege ich durch diese Arbeit, dass eine histopathologische Diagnostik bei MDS ein wertvolles obligates zusätzliches Instrument darstellt, welche jedoch keine Überlegenheit gegenüber der Zytomorphologie aufweist. Im Gegenteil habe ich hochrelevante Schwächen in der Bewertung zentraler diagnostischer Parameter wie dem myeloischen Blastenanteil aufgezeigt. Eine zumindest einmalige Knochenmarkstanze sollte jedoch zum Erstdiagnosezeitpunkt durchgeführt werden, um die von der WHO neu etablierten Diagnosen MDS-f und MDS-h sicher als solche erkennen zu können.

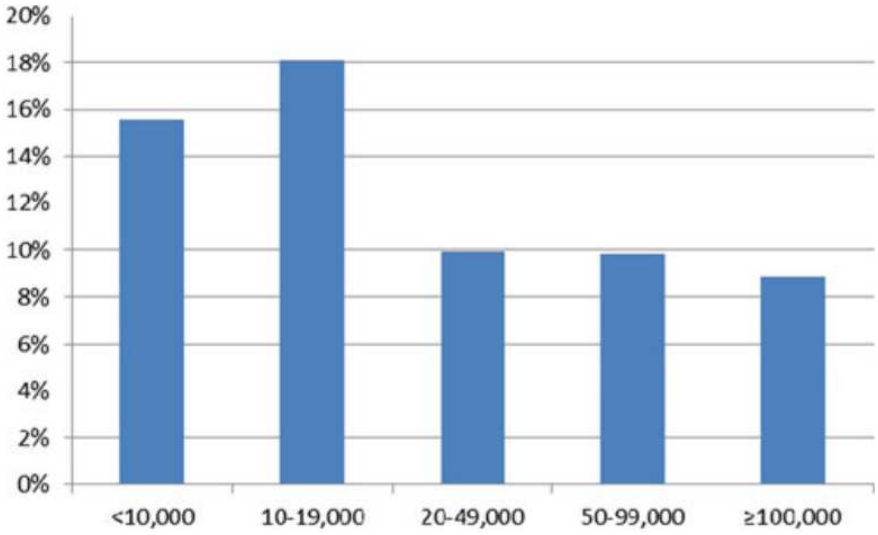
1.2. Prognostische Erkenntnisse bei MDS

Wie bereits dargelegt, liegt das mediane Erkrankungsalter von Patienten mit myelodysplastischen Neoplasien über 70 Jahren. Zudem umfasst der Erkrankungskomplex MDS prognostisch sehr heterogene Subtypen mit einem medianen Überleben von unbehandelt >80 Monaten bis zu <12 Monaten. Aus beiden Faktoren ergibt sich eine potentielle Relevanz prognostischer Einflussfaktoren, die nicht krankheitsassoziiert sind und möglicherweise bedingt sind durch im Alter zunehmende Komorbiditäten. Eine genauere Beleuchtung der zum Tode führenden Ursachen bei Patienten mit MDS, insbesondere anhand einer größeren Kohorte, war bis zum Zeitpunkt meiner Arbeit nicht erfolgt. Wir versuchten uns, dieser Frage mithilfe des MDS Registers zu nähern und analysierten hierzu insgesamt 2877 Patienten hinsichtlich der durch die Todesbescheinigung erfassten oder im Falle des Fehlens dieser Informationen über direkte Nachfrage beim primären Behandler oder der Krankenakte eruierten Todesursachen. Es erfolgte eine Kategorisierung in krankheitsassoziierte Ursachen (AML-Übergang, Infektion und Blutung), möglicherweise assoziierte Ursachen (Hämochromatose) sowie nicht krankheitsassoziierte Ursachen (Herzinsuffizienz/-versagen, solider Tumor, weitere nicht näher bezeichnete nicht-assoziierte Faktoren). In 58% der gesamten Kohorte verstorbener Patienten konnte eine genaue Todesursache dokumentiert werden (n=1665). Wir versuchten, die Gruppe der Patienten ohne eruierbare Todesursache genauer zu beleuchten und konnten herausarbeiten, dass hier eine größere Zahl von Niedrigrisiko-MDS Patienten gemäß WHO und IPSS enthalten war (62% versus 39,5%) und ein statistisch hochsignifikant längeres medianes Gesamtüberleben von 23 Monaten gegenüber 16 Monaten aufwies.

Es zeigten sich Unterschiede in den Kohorten, die am Universitätsklinikum Düsseldorf (UKD) behandelt wurden, und den Kohorten, die außerhalb des Universitätsklinikums behandelt wurden. Bei Patienten, die am UKD behandelt wurden, war eine klare Benennung der Todesursache öfter möglich, die Gesamtüberlebenszeit war höher und es wurden mehr Hochrisiko MDS betreut. Dies beruhte auf mehr intensiven Therapien und mehr Hochrisikopatienten, die insbesondere der allogenen Blutstammzelltransplantation (PBSZT) zugeführt wurden und, damit kausal zusammenhängend, eine bessere Prognose aufwiesen. Bei nicht bekannter Todesursache war das Überleben der Patienten am UKD nicht different von dem an anderen Zentren.

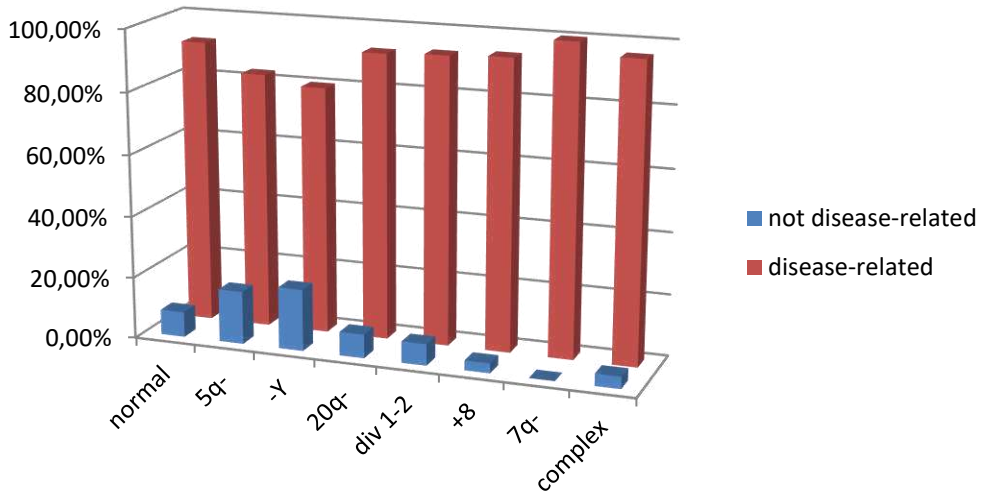
Meine Analysen zeigten, dass insgesamt 83,4% der Patienten mit dokumentierter Todesursache krankheitsassoziiert verstorben waren. Der überwiegende Teil der Patienten verstarb AML-assoziiert, gefolgt von Infektionen und zu knapp 10% an Blutungen. Da der Übergang in eine akute Leukämie an sich nicht unmittelbar zum Tode führt, wurde eine genauere Untersuchung dieser Patienten vorgenommen. Wir konnten für 36% dieser Patienten weitere Informationen herausarbeiten und zeigen, dass auch in dieser Gruppe der bei Weitem überwiegende Anteil an Patienten durch eine nicht beherrschbare Infektion verstorben war (72,1%), gefolgt von Blutungen in

21,6% und Herzinsuffizienz/-versagen. In einem weiteren Schritt untersuchte ich patienten- und krankheitsassoziierte Faktoren in Hinblick auf die Todesursachen. Die Stratifizierung der Kohorte anhand des Alters in </> 80 Jahren wies nach, dass Patienten >80 Jahre in zunehmendem Maße an nicht krankheitsassoziierten Faktoren verstarben. Weitere statistisch relevante Parameter waren die Zahl an neutrophilen Granulozyten (ANC) mit einer Grenze <1000 ANC/µl in Korrelation mit einer relevanten Zunahme von Infektionen als Todesursache, sowie die Zahl an Thrombozyten in Hinblick auf tödliche Blutungsereignisse. Hier war eine Thrombozytenzahl <20.000/µl als signifikante Grenze für eine Zunahme derartiger Ereignisse zu demonstrieren [16].



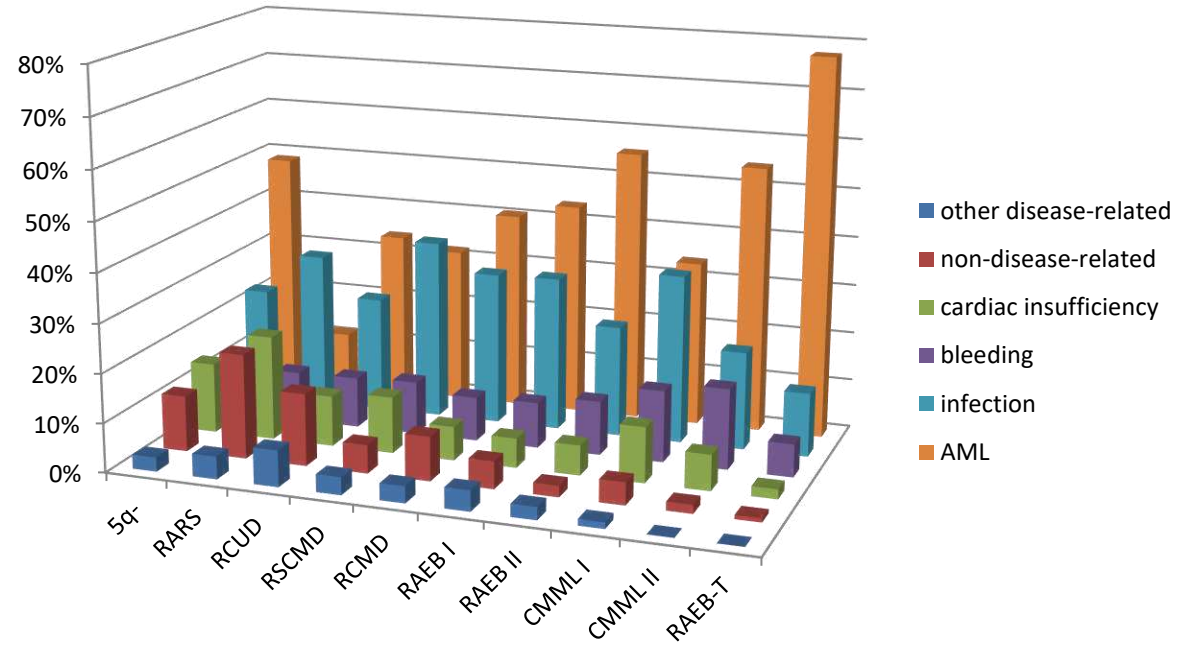
Inzidenz von zum Tode führenden Blutungsereignissen anhand der Thrombozytenzahl (/µl). Eigene Abbildung.

Auch der Hämoglobinwert zeigte eine Assoziation: In meinen Analysen bestand ab einer Unterschreitung <10 g/dl eine erhöhte Zahl an krankheitsassoziierten Todesursachen, am ehesten im Sinne eines Surrogatparameters fußend auf einer aggressiveren oder Hochrisiko-MDS Subgruppe mit einem entsprechenden rascheren Krankheitsverlauf. Es bestand hingegen diesbezüglich keine Korrelation mit einer Zunahme an kardial bedingten Todesursachen. Auch konnte ich demonstrieren, dass der Karyotyp eine eindeutige Korrelation mit krankheits- oder nicht krankheitsassoziierten Todesursachen aufweist. Patienten mit bekanntermaßen günstigen Aberrationen, del(5q) und Verlust des Y-Chromosoms, verstarben häufiger nicht krankheitsassoziiert, und im Gegenzug wiesen Hochrisikoaberrationen, stratifiziert anhand des IPSS-R, eine grenzwertig statistisch signifikant höhere Wahrscheinlichkeit auf, an krankheitsassoziierten Todesursachen zu versterben.

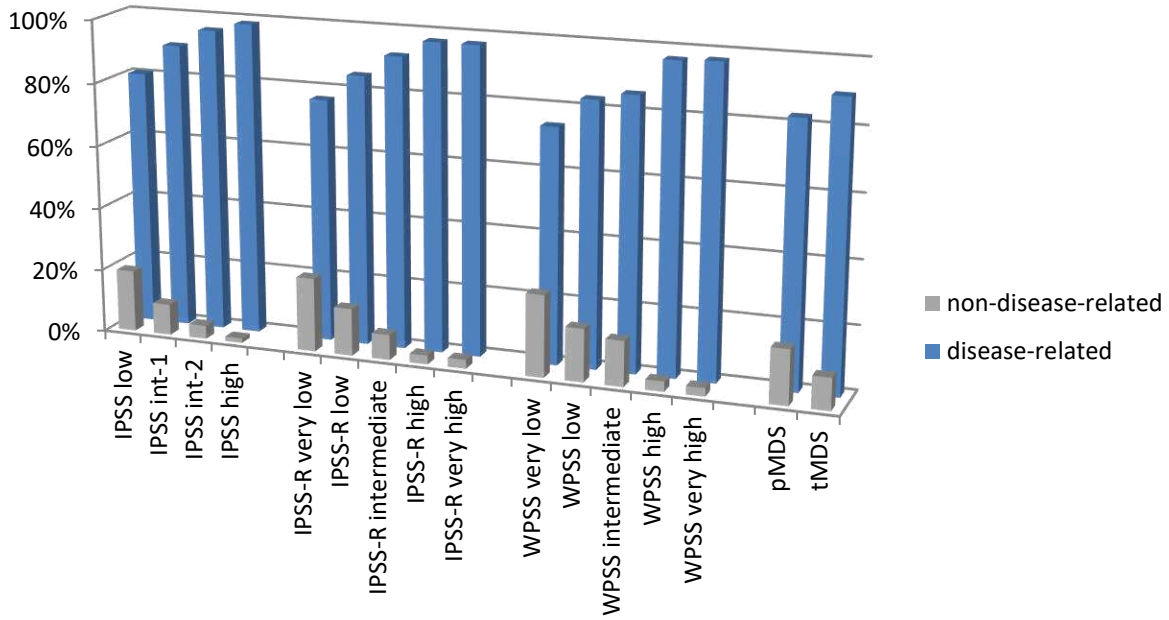


Todesursachen nach Karyotyp. Eigene Abbildung.

Konkordant hierzu ließ sich nachweisen, dass sowohl IPSS-, WHO- und WPSS-Subtypen von höherer Risikokategorie häufiger an AML oder anderen krankheitsassoziierten Ursachen verstarben, dies bereits auch schon gemessen an dem Vorhandensein von multilineärer Dysplasie (RCMD nach WHO 2008).



Todesursachen nach WHO Subtyp. Eigene Abbildung.



Todesursachen nach Klassifikationssystemen (IPSS, IPSS-R, WPSS, t/pMDS). Eigene Abbildung.

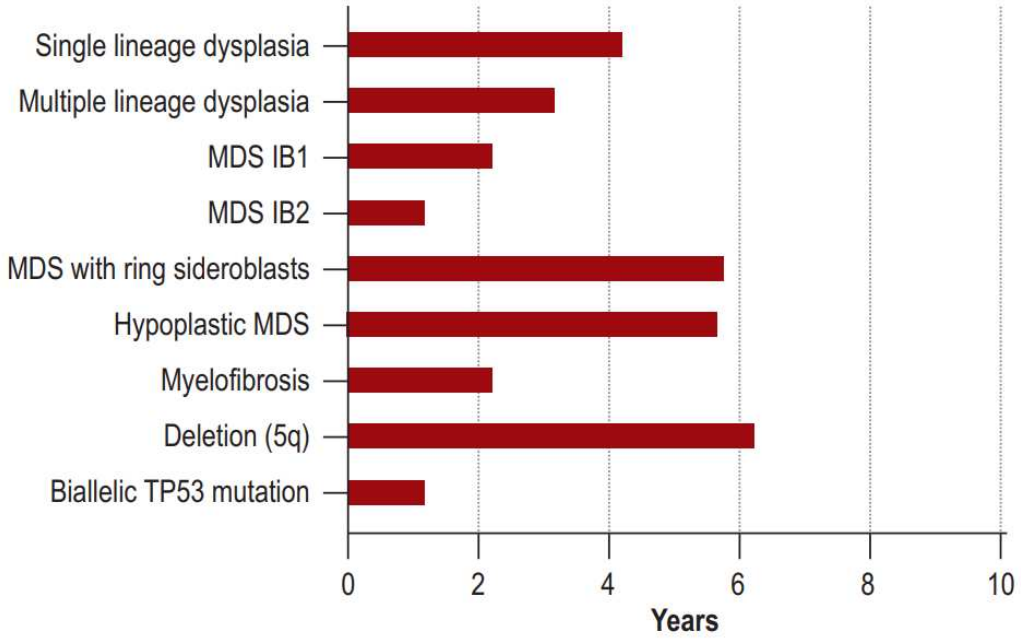
Wir konnten in unserer Kohorte erstmals auch aufzeigen, dass ein größerer Prozentsatz als bisher bekannt im Gefolge einer AML-Entwicklung verstirbt und nicht bereits an MDS-assoziierten Komplikationen. Dies ist möglicherweise darauf zurückzuführen, dass Patienten des MDS Registers deutlich engmaschiger und detaillierter betreut und dokumentiert werden, so dass hier mehr AML-Übergänge erkannt werden können.

Umgekehrt stand den Analysen erstmals eine große Kohorte zur Verfügung, die im Lichte der zu einem bedeutend größeren Anteil an bereits verstorbenen Patienten im Kollektiv im Vergleich zu zwei Vorpublikationen, die sich auch ausschließlich mit Niedrigrisiko-MDS Patienten befasst hatten, eine größere Aussagekraft impliziert [17,18]. Dies ist insbesondere für die Niedrigrisiko-MDS Population von Bedeutung, als deren natürlicher Krankheitsverlauf mit langer medianer Überlebenszeit Aussagen über oder den Nachweis von krankheitsassoziierten Todesursachen und Therapieeffekten erschwert.

Diese Arbeit erlaubte erstmals einen deutlich detaillierteren Einblick in den Krankheitsverlauf von MDS Patienten und belegte, dass trotz des Patientenkollektives von älteren Patienten und ungeachtet des MDS-Subtyps der überwiegende Teil krankheitsassoziiert verstirbt, welches den prognosebestimmenden Charakter der

MDS-Diagnose per se hervorhebt und auch für als Niedrigrisiko-MDS eingestufte Erkrankungen die Notwendigkeit therapeutischer Interventionen mit dem Ziel einer Krankheitsmodifikation unterstreicht [19].

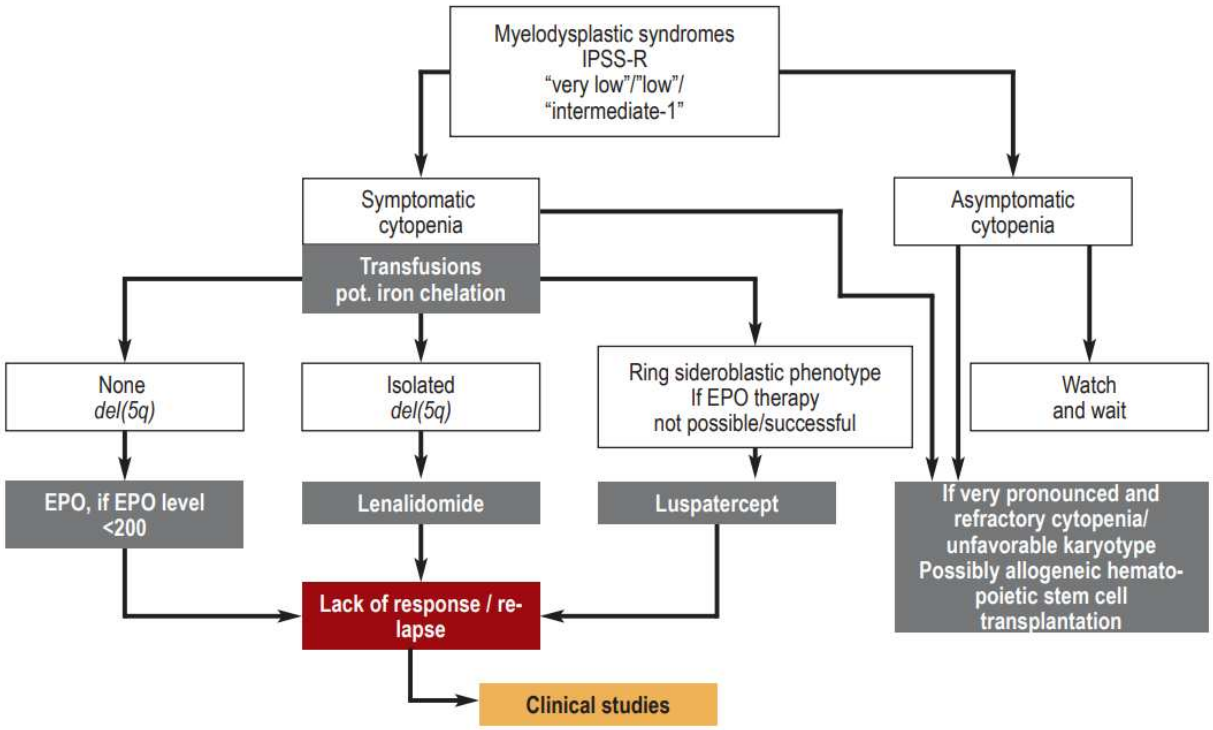
Diese und weitere Ergebnisse meiner Analysen und der hiesigen MDS-Gruppe flossen in die von mir erstellte Arbeit ein, die im deutschen Ärzteblatt International als Übersichtsarbeit veröffentlicht wurde. Insbesondere die Wichtigkeit der obig als essentiell herausgearbeiteten Durchführung von Knochenmarkstanzen zum Diagnosezeitpunkt wurde als Empfehlung im diagnostischen Work Up hervorgehoben. Wir beleuchteten für diese Arbeit alle zum Veröffentlichungszeitpunkt aktuellen Entwicklungen und Erkenntnisse, die sowohl die Diagnostik, aber auch die prognostische Einschätzung von Patienten mit MDS und die neuesten Therapieempfehlungen beinhalteten. Hierzu belegten wir diese Empfehlungen auch mit eigenen Daten des MDS Registers.



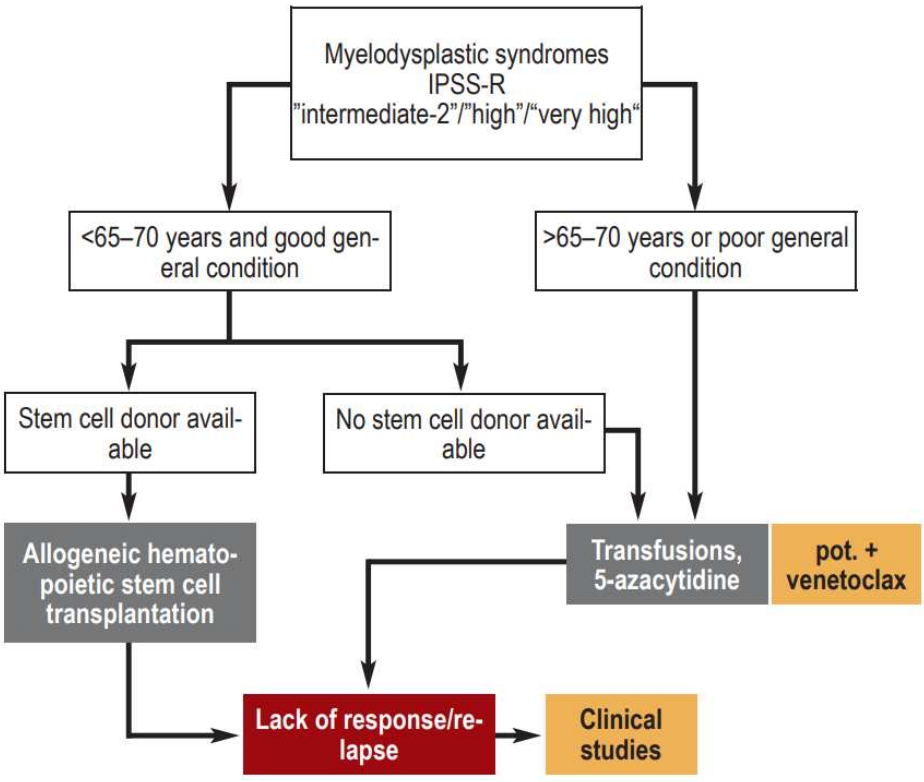
Medianes Gesamtüberleben der Kohorte des MDS Registers anhand der WHO Subtypen. Eigene Abbildung.

Die aktuellsten Klassifikationen WHO 2022 und ICC wurden hier ebenso erläutert wie der Prognosescore IPSS-M, der erstmalig die in MDS mannigfaltig potentiell vorliegenden molekulargenetischen Mutationen in einem robusten Prognosescore mit den bereits etablierten, im IPSS-R eingebrachten Faktoren vereint. Diese Prognosesysteme, ob Klassifikationen oder Prognosescores, haben eklatante Bedeutung zur Charakterisierung des individuellen MDS Patienten in Hinblick auf das weitere Vorgehen nach Diagnosestellung. Hier konnten wir die aktuellsten Therapieempfehlungen für die zwei Gruppen Niedrigrisiko- und Hochrisiko-MDS aufzeigen und insbesondere für die Gruppe der Hochrisiko-MDS die allogene Blutstammzelltransplantation mit der unsererseits bestehenden Empfehlung zur „upfront“-Stammzelltransplantation ohne vorherige Therapie mit beispielsweise HMA

darlegen, auch Konzepte zur Machbarkeit einer potentiell toxischen Therapie im Lichte des herausfordernden Patientenkollektivs mit höherem Lebensalter [20,21].



Therapiealgorithmus für MDS Patienten mit „very low“, „low“ oder „intermediate-1“ Risiko gemäß IPSS-R. Eigene Abbildung.



Therapiealgorithmus für MDS Patienten mit „intermediate-2“, „high“ oder „very high“ Risiko gemäß IPSS-R. Eigene Abbildung.

1.3. Neubewertung von Prognosesystemen bei MDS

Über die Jahre wurden mittlerweile eine Vielzahl von einander sich ablösenden oder auch ergänzenden Klassifikationssystemen und Prognosescores für myelodysplastische Neoplasien publiziert, von denen insbesondere die WHO Klassifikation, aktuell in ihrer neuesten Version der WHO 2022-Klassifikation [6], und der IPSS-R [9] als die sicherlich gebräuchlichsten und bekanntesten gelten. 1982 wurde die erste Klassifikation veröffentlicht, die FAB-Klassifikation [5]. Diese fußte auf dem auch heute noch grundlegenden Parameter des Blastenanteils im Knochenmark und peripheren Blut und nahm eine bis in die heutige WHO-Klassifikation gebräuchliche Gruppierung der MDS in MDS mit normalem Blastenanteil und erhöhtem Blastenanteil bis 20%, sowie 20-29% vor. Heutzutage werden myeloische Neoplasien mit einem Blastenanteil ≥20% als akute Leukämie bezeichnet und sind daher nicht mehr in MDS-Klassifikationen vertreten.

Die erste Weiterentwicklung basierte auf dem Miteinbeziehen der pathognomonischen Dysplasiezeichen im Knochenmark und resultierte in der Publikation der WHO-Klassifikation, die erstmals 2001 [22] und anschließend 2008 [23] und 2016 [24] mit den zu den jeweiligen Zeitpunkten aktuellen Erkenntnissen angepasst veröffentlicht wurden. In den aktuellsten Versionen fanden nun auch zytogenetische Befunde, die nachweislich zu eigenständigen Entitäten mit einem statistisch signifikant differentem Krankheitsverlauf führen, und in 2022 auch histopathologische Befunde Berücksichtigung. Aufgrund der hohen prognostischen Relevanz krankheitsdefinierender Parameter stellen diese Klassifikationen per se starke prognostische Instrumente dar, die eine Einschätzung des medianen Gesamtüberlebens und des Risikos der Entwicklung einer sekundären akuten myeloischen Leukämie zum Erstdiagnosezeitpunkt erlauben.

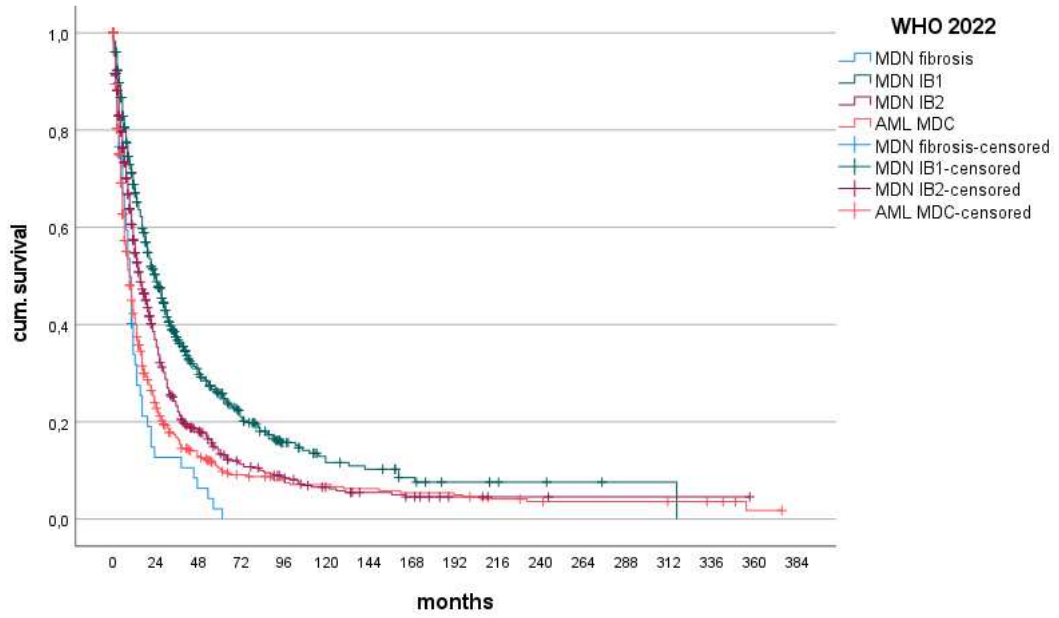
Eigenständige Prognosescores wurden jedoch ebenfalls etabliert. Der bekannteste und weitläufig gebräuchlichste ist der IPSS (International Prognostic Scoring System) [8]. In seiner ersten Version inkludierte der 1997 publizierte IPSS Zytopenien, Zytogenetik und Blastenanteil mit der Generierung von 4 Risikogruppen. 2012 wurde der IPSS-R publiziert, welcher eine Kategorisierung in fünf Risikogruppen vornimmt und neben einer feineren zytogenetischen Zuordnung den jeweiligen Parametern eine andere Wichtung zuteilwerden lässt [9]. Dieser Prognosescore ist bis heute als der Gebräuchlichste im klinischen Alltag anzunehmen. Die aktuellste Version, der IPSS-M [10], wurde 2022 publiziert und beinhaltet erstmals auch molekulargenetische Befunde. Die Kalkulation des individuellen Risikos, welches in nunmehr sechs Gruppen unterschieden wird, ist hier für den Anwender nicht mehr eigenständig vorzunehmen, sondern benötigt einen web-basierten Kalkulator, welcher neben der Abfrage von insgesamt 31 relevanten molekulargenetischen Mutationen auch bei vorigen IPSS bekannte Parameter miteinbezieht. Seine Stärke besteht darin, auch bei nicht vollständigen molekulargenetischen Parametern eine prognostische Aussage

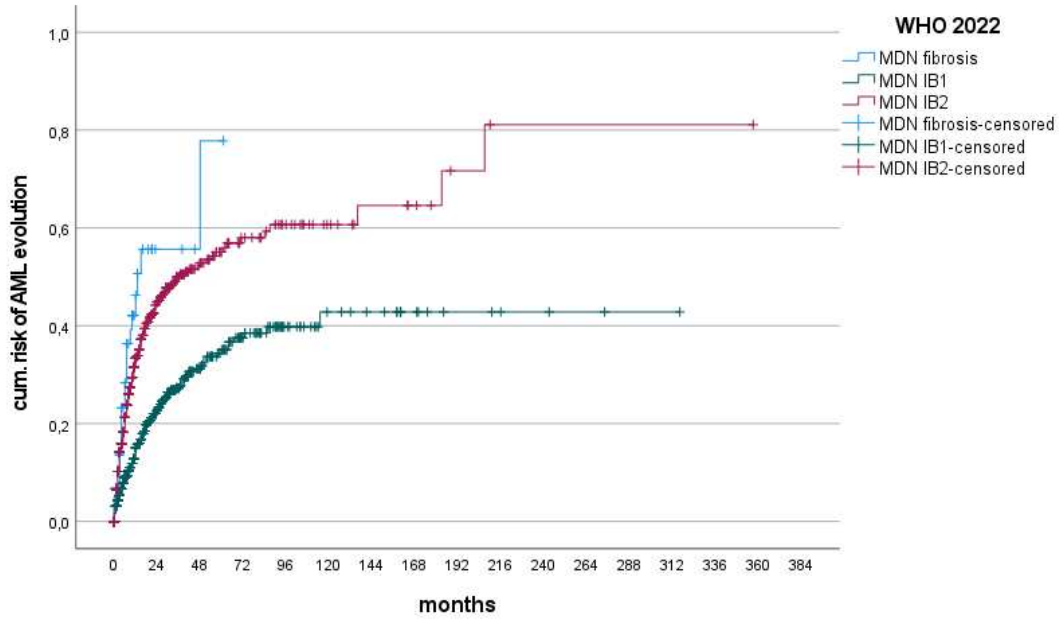
treffen zu können. Durch die Anwendung des IPSS-M gelingt eine noch exaktere prognostische Wertung, nachweislich wurden 46% aus einer IPSS-R Zuordnung restratifiziert, wenn der IPSS-M angewendet wurde. Ein weniger gebräuchlicher Score ist der WPSS, „WHO classification-based Prognostic Scoring System“, welcher eigentlich elegant die beiden aussagestarken Systeme der WHO-Klassifikation und IPSS ineinander vereint [25,26]. So werden über die WHO-Diagnose bereits grundlegende Parameter wie Blastenanteil oder Dysplasie in ein Prognoseinstrument inkludiert und kombiniert mit dem Karyotyp und einem klinischen Parameter, dem Transfusionsbedarf.

In meiner Arbeit zu Prognosebestimmung bei MDS habe ich mich zuletzt mit den aktuellsten Klassifikationen der WHO 2022-Klassifikation sowie der grundlegend neu geschaffenen ICC-Klassifikation [7] beschäftigt, dies im Sinne einer Validierung dieser beider anhand von 5010 Patienten mit MDS und 690 mit AML-MRC des MDS Registers Düsseldorf und um einen Vergleich in der prognostischen Wertigkeit zwischen beiden konkurrierenden Systemen durchzuführen, welcher in der Postulierung einer durch meine Analysen hervorgebrachten fusionierten Klassifikation mündete.

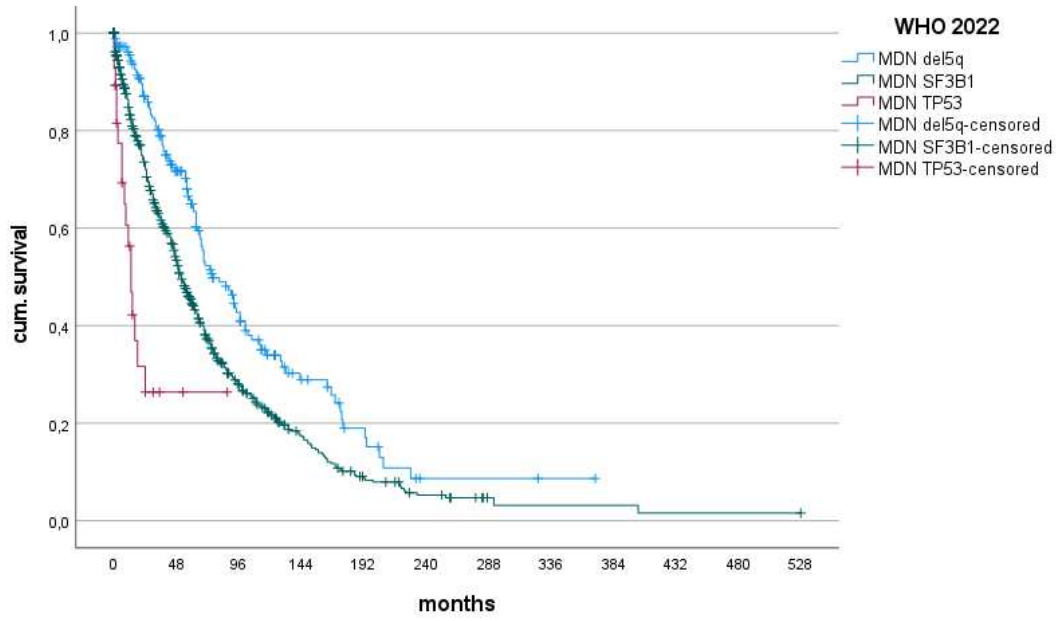
In der aktuellen WHO-Klassifikation wurden gegenüber der WHO 2016-Klassifikation neue Entitäten geschaffen sowie eine Subgruppe, diejenige der MDS-U (unklassifizierbare MDS), entfernt. Die WHO 2022-Klassifikation trägt der zunehmenden Heterogenität, die jedoch höchst prognoserelevant ist, Rechnung und unterscheidet myelodysplastische Neoplasien nun einerseits anhand des Vorhandenseins und Ausmaßes von Dysplasiezeichen, wie bereits beschrieben, und andererseits anhand einer zunehmenden Zahl genetisch definierter Subtypen wie der MDS del(5q), MDS SF3B1 oder TP53-mutierte MDS. Außerdem wurden zwei vollkommen neue Subentitäten geschaffen: MDS mit Fibrose und hypozelluläre MDS. Dieser zunehmend differenziertere Blick auf die große Gruppe der myelodysplastischen Neoplasien erfordert zwar eine immer größer werdende Menge diagnostischer Schritte wie einer Histopathologie und eines molekulargenetischen Panels, zusätzlich zu den bereits bestehenden Diagnostika Zytomorphologie und Zytogenetik, ist allerdings unabdingbar, wenn der prognostischen Relevanz der Parameter Rechnung getragen werden soll.

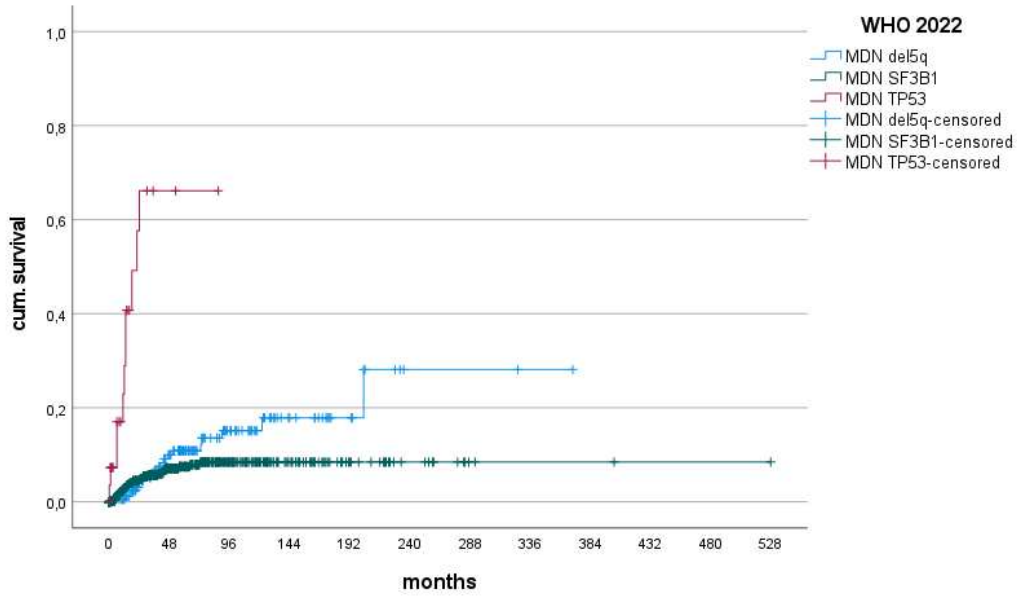
In unserer Kohorte des MDS Registers erlaubte die vorliegende WHO-Klassifikation eine statistisch relevante Trennung der Gesamtgruppe anhand der publizierten Subtypen in MDS Subgruppen mit unterschiedlichem medianen Gesamtüberleben und Risiko der Entwicklung einer sekundären AML. Die in unserer Kohorte erhobenen Werte korrelierten suffizient mit den in der Publikation der WHO-Klassifikation aufgeführten Daten und validierten somit die Daten der Publikation von Khoury et al. in einer großen Kohorte von 5700 Patienten.





WHO-Klassifikation: Medianes Gesamtüberleben und kumulative AML-Entwicklung von Patienten mit erhöhtem Blastenanteil (IB1, IB2, Fibrose) ($p<0.0005$, $p<0.0005$). Eigene Abbildung.

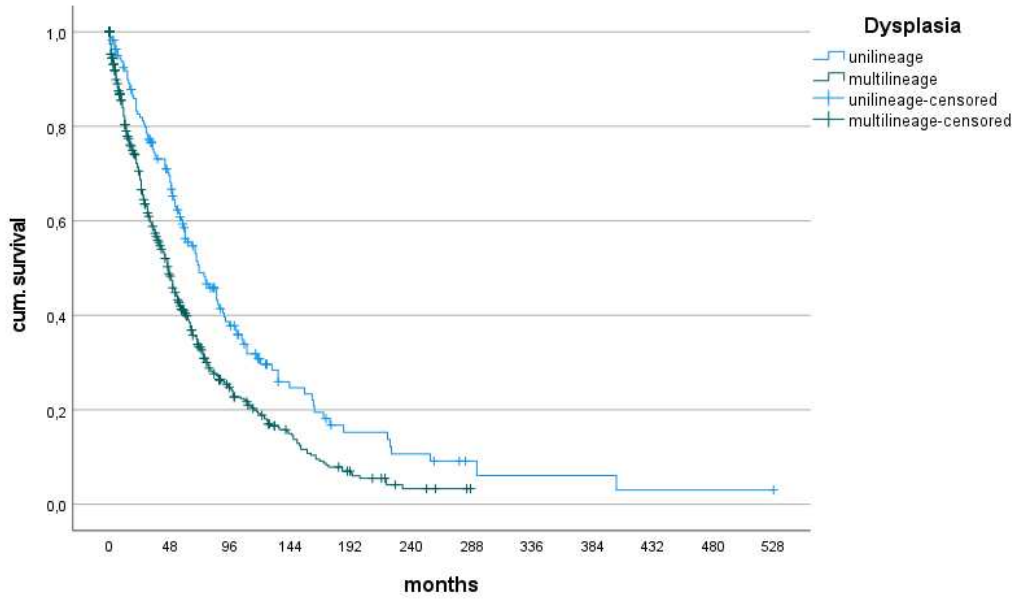




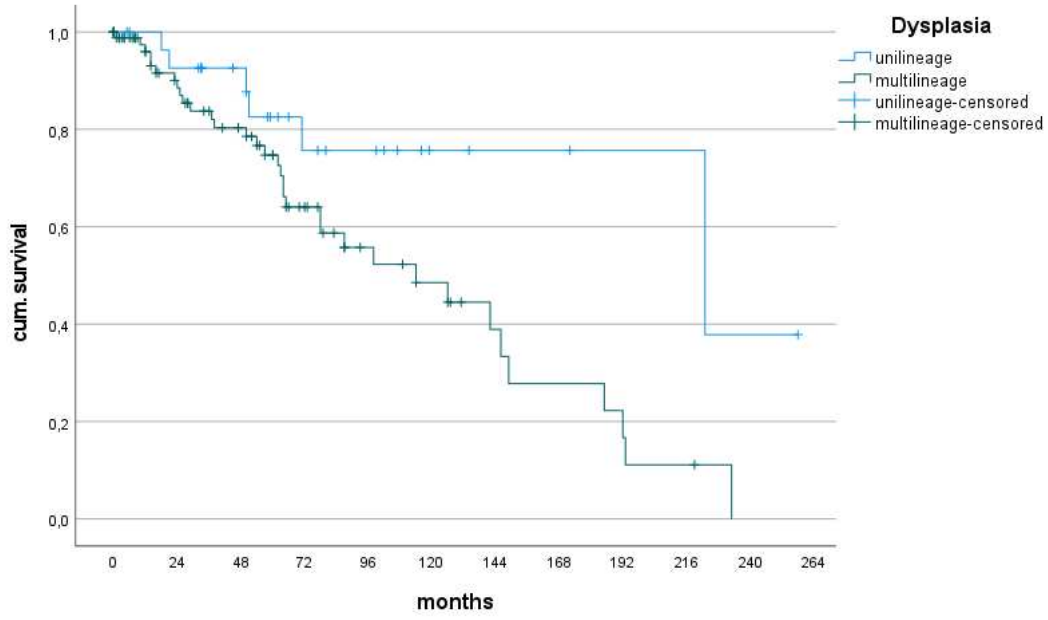
Medianes Gesamtüberleben und kumulative AML-Entwicklung von Patienten mit genetisch definiertem MDS (p<0.00005, <0.00005). Eigene Abbildung.

Das Vorgehen der nun postulierten Subtypen anhand verschiedener Parameter, nämlich morphologischer versus genetischer, geht mit einem potentiellen Überlappen bzw. gleichzeitigem Vorhandensein mehrerer diagnosebestimmender Faktoren in einem Patienten einher und führt zu Unsicherheiten, wie ein Patient in solch einem Fall zu kategorisieren ist. Es ist somit notwendig, ein Hierarchieren der verschiedenen Entitäten bei Überlappung durchzuführen. Hierzu konnte ich aufzeigen, wie eine Wichtung der Faktoren in unserem Patientenkollektiv prognoserelevant vorgenommen werden kann. Ich konnte nachweisen, dass bei gleichzeitigem Vorhandensein einer biallelischen TP53-Mutation und anderen Faktoren eine Eingruppierung in die Entität

MDS-biTP53 vorzunehmen ist, da diese mit der schlechtesten Prognose der MDS-Entitäten einhergeht und diesen Prognoseeinfluss auch mit konkurrierenden Faktoren wie dem Blastenanteil oder Fibrose nicht verliert [27,28]. Ich konnte entgegen einer Publikation von Malcovati et al. über SF3B1-mutierte MDS aufzeigen, dass das Ausmaß der Dysplasie durchaus Prognoserelevanz beibehält, wenn eine SF3B1-Mutation nachweisbar ist [29].



Medianes Gesamtüberleben von Patienten mit SF3B1-Mutation und/oder ringsideroblastischem Phänotyp gemäß Ein- oder Mehrliniendysplasie (p<0.00005, <0.00005). Eigene Abbildung.



Medianes Gesamtüberleben von Patienten mit SF3B1-Mutation gemäß Ein- oder Mehrliniendysplasie ($p<0.04$). Eigene Abbildung.

Das Vorhandensein einer del(5q) und konkurrierenden SF3B1-Mutation zeigte in unseren Analysen keinen Einfluss auf die Wirksamkeit von Lenalidomid, welches für del(5q) zugelassen ist, und keinen Einfluss auf das Progressionsverhalten dieser Patienten, so dass diese Aberration hierarchisch höher einzustufen ist. Das Vorhandensein von Hypozellularität (somit MDS-h) und einer del(5q) oder SF3B1-Mutation sollte zur Einstufung anhand der genetisch definierten Entität führen, der günstige Effekt der Hypozellularität geht somit prognostisch dann verloren.

Es ist somit ratsam, eine Hierarchie wie folgt vorzunehmen: Der Nachweis einer biallelischen TP53-Mutation ist prognostisch ungünstiger als alle anderen Faktoren, gefolgt vom medullären Blastenanteil. Hiernach ist das Vorhandensein einer del(5q) prognosebestimmend sowie nachrangig eine SF3B1-Mutation. Im Falle einer SF3B1-Mutation oder del(5q) würden eine zugleich nachweisbare Chromosom-7-Anomalie oder ein komplexer Karyotyp prognosebestimmend angenommen. MDS-h verlieren ihre günstige Prognose, sobald andere Kofaktoren wie Mutationen hinzukommen.

Eine Validierung der ICC-Klassifikation, welche nahezu zeitgleich und konkurrierend zur WHO 2022-Klassifikation veröffentlicht wurde, gelang mir mithilfe der genannten Kohorte an MDS und AML-MRC Patienten ebenfalls. Die inhaltliche Überlappung der postulierten Entitäten zur WHO 2022 sind allerdings groß, so dass ein Gelingen der Validierung nicht verwundert.

Entgegen der in der ICC-Klassifikation eingeführten Zählung der MDS mit >10% Blasten in eine AML-ähnliche Gruppe MDS/AML zeigte ich jedoch in unseren Analysen konkordant zu bereits vorhandenen historischen Daten eindeutig, dass MDS mit einem Blastenanteil von 10-20% eine statisch signifikant differente Prognose aufweisen zu AML, so dass ein Beibehalten des Grenzwertes von 20% zur AML, wie in der WHO-Klassifikation weiterhin zu finden, gerechtfertigt erscheint.

Schließlich beschäftigte ich mich mit einem Vorschlag zu einer fusionierten Klassifikation dieser beiden Systeme, um den Stärken beider Klassifikationen WHO und ICC Rechnung zu tragen, aber eine Anwendbarkeit im klinischen Alltag und auch im Kontext der Auswertbarkeit zukünftiger klinischer Studien zu erleichtern. Meine Arbeit war die erste, die die WHO 2022- und ICC-Klassifikationen validiert und kritisch kommentiert hat und zudem Vorschläge zu einer Harmonisierung beider Klassifikationen erarbeitet hat.

A) MDS, genetically defined, no AML-defining cytogenetic or molecular finding (NPM1, bZIP CEBPA)

1) **MDS del(5q)**
PB blasts <2%, BM blasts <5%, uni or multilineage dysplasia, del(5q) either isolated or with one other non-chromosome-7 aberration, no biTP53 alteration
- Provisional subtype: with SF3B1/RS
- Provisional subtype: with TP53 monoallelic

2) **MDS with SF3B1/RS**
PB blasts <2%, BM blasts <5%, SF3B1 mutation VAF >2%, uni or multilineage dysplasia, no del(5q) no chromosome 7 aberration, no complex karyotype, no biTP53alteration, no RUNX1 mutation,
Type 1: multilineage dysplasia
a) with SF3B1 mutation
b) without SF3B1 mutation or unknown mutational status
Type 2: unilineage dysplasia
a) with SF3B1 mutation
b) without SF3B1 mutation or unknown mutational status

3) **MDS with biallelic TP53 alteration**
PB blasts <20%, BM blasts <20%, presence of biTP53 alteration

4) **MDS-IB1, MDS-IB-2, MDS-F, with monoallelic TP53 alteration** (VAF >10%)

B) MDS, morphologically defined, no AML-defining cytogenetic or molecular finding (NPM1, bZIP CEBPA)

1) MDS-LB-SLD
PB blasts <2%, BM blasts <5%, unilineage dysplasia, no del(5q), no SF3B1 mutation, ring sideroblasts <15%, no biTP53 alteration, no hypocellularity

2) MDS-LB-MLD
PB blasts <2%, BM blasts <5%, multilineage dysplasia, no del(5q), no SF3B1 mutation, ring sideroblasts <15%, no biTP53 alteration, no hypocellularity

3) Hypoplastic MDS
PB blasts <2%, BM blasts <5%, uni- or multilineage dysplasia, no del(5q), no SF3B1 mutation, ring sideroblasts <15%, no biTP53 alteration, histologically proven hypocellularity

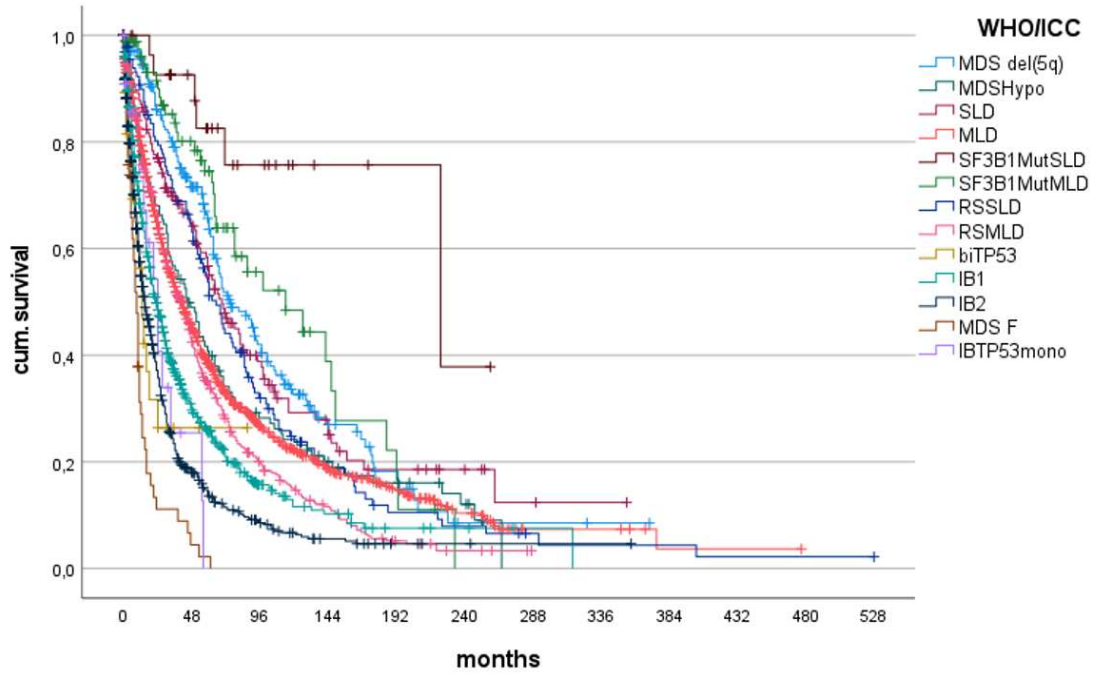
4) MDS-IB1
PB blasts <5%, BM blasts 5-9%, no biTP53 alteration, no TP53 alteration (or VAF <10%)

5) MDS-IB2
PB blasts <19%, BM blasts 10-19%, no biTP53 alteration, no TP53 alteration (or VAF <10%)

6) MDS-F: PB blasts <19%, BM blasts 5-19%, fibrosis Grade 2-3, no biTP53 alteration

Vorschlag für eine fusionierte Klassifikation. Eigene Abbildung.

a



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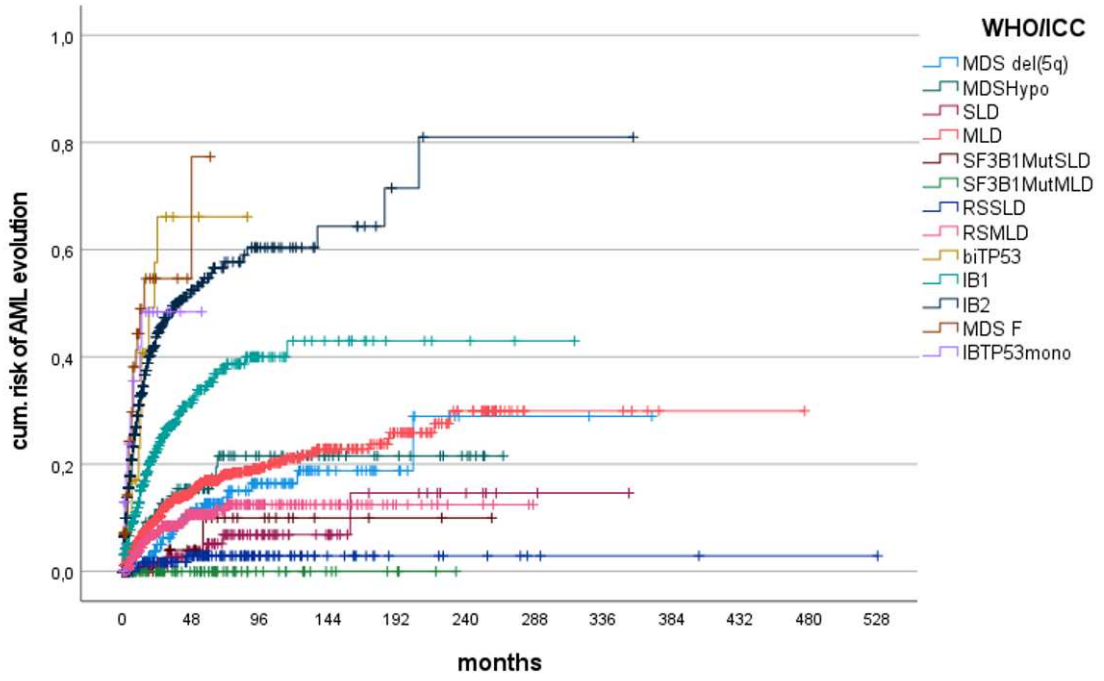


Fusionierte WHO- and ICC-Klassifikation: medianes Gesamtüberleben (a) and kumulative AML-Entwicklung (b) ($p<0.00005$, <0.00005). Eigene Abbildung.

Diese fusionierte Klassifikation behält mehr Elemente der WHO-Klassifikation wie die MDS mit bis zu 20% Blasten anstelle einer MDS/AML Subgruppe, vereint die in beiden Klassifikationen etablierten MDS gemäß (molekular-)genetischen oder morphologisch definierten Subgruppen und verfeinert teils Subgruppen gemäß den in meinen

Analysen erhobenen Daten (zB SF3B1 MLD versus SLD). Ich konnte mithilfe dieser „merged classification“ die Kohorte des MDS Registers signifikant und eindeutig in prognostisch unterschiedliche Subgruppen untergliedern. Eine im weltweiten Gebrauch dominierende oder einheitliche Klassifikation wäre aus unserer Sicht aus den genannten Gründen anzustreben.

2. Prognosebeeinflussung durch Therapien

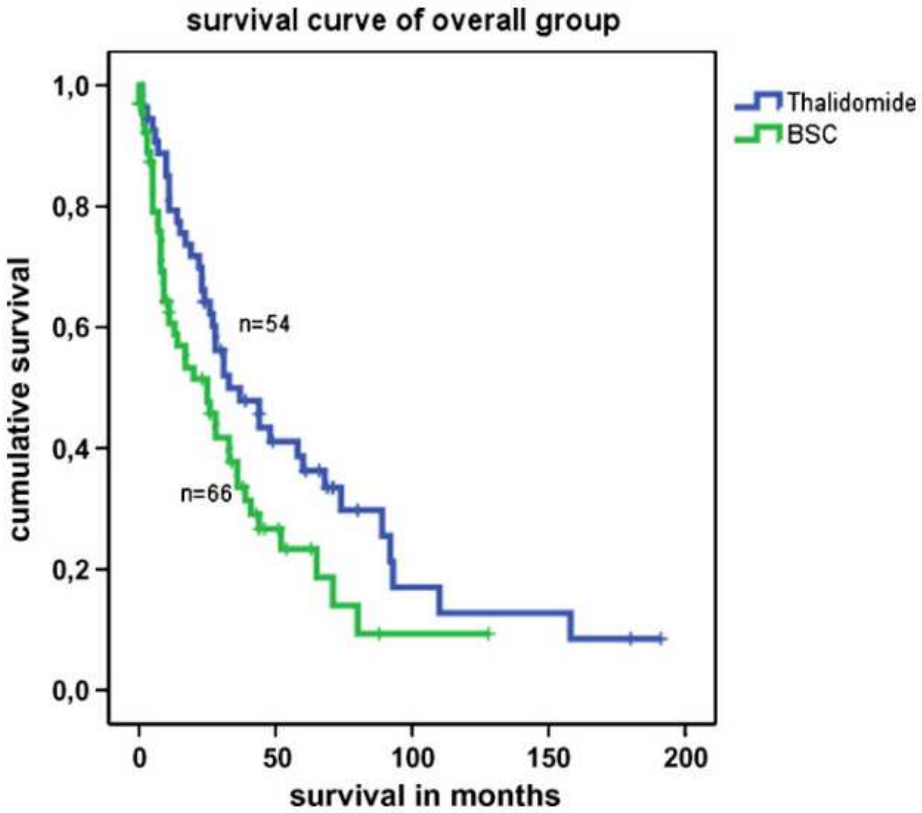
Myelodysplastische Neoplasien umfassen heterogene Krankheitsbilder in Prognose und Krankheitsbiologie, so dass therapeutische Strategien nicht einheitlich für alle MDS festzulegen sind. Für einen Teil der Patienten ist ein rein supportives Konzept mit bedarfsgerechten Bluttransfusionen, Therapien mit Wachstumsfaktoren wie G-CSF oder Erythropoetin und antiinfektiven Prophylaxen ausreichend. Ziel einer solchen Therapie ist die Verbesserung der Lebensqualität. Nichtsdestotrotz stellt sich auch bei sogenannten Niedrigrisiko-MDS die Frage, ob therapeutische Interventionen das Gesamtüberleben, das Risiko einer Entwicklung einer sekundären AML oder auch die Lebensqualität beeinflussen können. In der Vergangenheit wurden mannigfaltige therapeutische Optionen untersucht, dies allerdings zumeist in Phase-I-, Phase-II-Studien oder kleineren Fallstudien. Für Hochrisiko-MDS mit erhöhtem Blastenanteil wurde einst ein den myeloischen Leukämien ähnliches Krankheitsverhalten zugrunde gelegt, bis nachgewiesen wurde, dass konventionelle Chemotherapien keine Verbesserung der Prognose für MDS Patienten mit sich bringen, sondern gar im Gegenteil die Prognose verschlechtern können. Die nach wie vor einzig kurative Therapie, die einen nachgewiesenen Überlebensvorteil mit sich bringt, jedoch eine potentiell signifikante therapieassoziierte Mortalität und Morbidität vorweist, ist die allogene Blutstammzelltransplantation.

Es existieren auch in der heutigen Zeit nur eine geringe Zahl zugelassener Therapieoptionen. Neben der hypomethylierenden Substanz Azacitidin für Hochrisiko-MDS sind lediglich Erythropoetin-α, Luspatercept für transfusionsbedürftige Niedrigrisiko-MDS und Lenalidomid für den spezifischen Subtyp der del5q-mutierten MDS sowie Deferasirox zur Eisenchelation in Deutschland zugelassen [30-37]. Für die Hinzunahme von Venetoclax zu hypomethylierenden Substanzen sind verbesserte Ansprechraten beschrieben, die in den USA auch bereits zur Zulassung der Substanz für die Behandlung von MDS Patienten geführt hat [38,39].

Die neben den erwähnten Therapien innerhalb klinischer Studien oder retrospektiven Analysen untersuchten Therapieansätze definierten das Ansprechen regelhaft anhand der Verbesserung von Blutbildparametern oder dem Transfusionsbedarf. In meiner Arbeit basierend auf Daten des MDS Registers untersuchte ich mittels Matched Pairs Analysen den Einfluss verschiedener Therapieoptionen auf das Gesamtüberleben und das Risiko auf die Entwicklung einer sAML. Die hier untersuchten Therapiemodalitäten umfassten Thalidomid, Valproinsäure, niedrigdosiertes Cytarabin, Antithymozytenglobulin (ATG), konventionelle Chemotherapie und die allogene Blutstammzelltransplantation. Das Register umfasste zum Zeitpunkt meiner Arbeit 3058 Patienten, von welchen 2449 Patienten rein supportiv behandelt worden waren (BSC). Insgesamt erhielten in der Kohorte 55 Patienten Thalidomid, 76 Patienten Valproinsäure, 65 Patienten niedrigdosiertes Cytarabin, 17 Patienten ATG, 172 intensive Chemotherapie und 39 Patienten eine allogene Blutstammzelltransplantation. Für meine Matched Pairs Analysen wurden für jeden Patienten, der eine spezifische Therapie erhalten hatte, je ein definierter BSC-Patient

mittels der Faktoren Alter (+/- 5 Jahre), Geschlecht, Blutbild zum Erstdiagnosezeitpunkt, MDS Subtyp gemäß WHO-Klassifikation, IPSS und IPSS-zytogenetische Risikogruppe zugeordnet. Ich stellte zuvor in einer Subanalyse sicher, dass das Jahr der Erstdiagnose innerhalb dieser Kohorte keinen Einfluss auf die Prognose hatte, so dass dieser Parameter nicht im Matching-Prozess berücksichtigt werden musste. Ein anzunehmender inhärenter Selektionsbias in retrospektiven Analysen muss auch in dieser Arbeit bedacht sein: Für Patienten mit einem ohnehin vergleichsweise langen medianen Gesamtüberleben, in diesem Falle MDS-Niedrigrisiko Subgruppen wie RA, kann es zu einem Selektionsbias kommen, wenn das Intervall zwischen Erstdiagnose und Therapiebeginn hoch ist und so möglicherweise eine Kohorte zustande kommt, die Patienten aufweist mit einer günstigeren Krankheitsbiologie, so dass nicht unmittelbarer Behandlungsbedarf bestand.

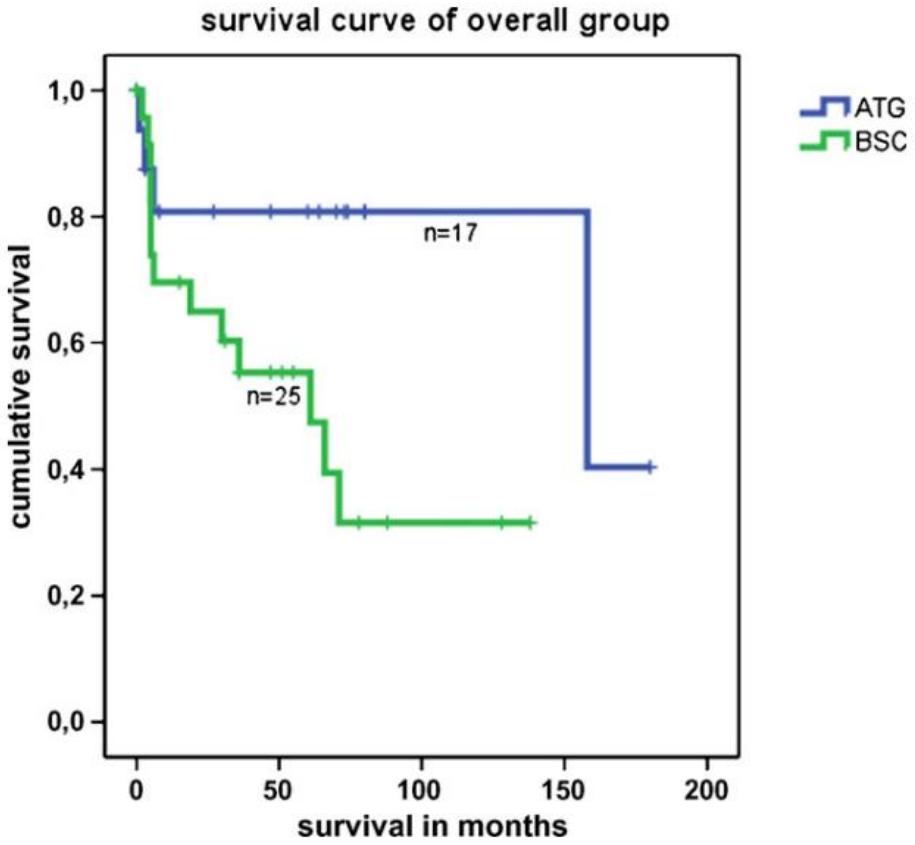
Für die untersuchten Substanzen konnte ich für Thalidomid einen signifikanten Überlebensvorteil für die Gesamtgruppe von 33 Monaten gegenüber 25 Monaten in der rein supportiv behandelten Kohorte zeigen. Dieser Nutzen zeigte sich insbesondere innerhalb der Hochrisiko-MDS gemäß IPSS und auch WHO-Klassifikation (IPSS von 2, WHO Subtyp RAEB I und RAEB II).



Kaplan-Meier-Kurve der Gesamtgruppe von mit Thalidomid versus BSC behandelten Patienten (p=0,0291). Eigene Abbildung.

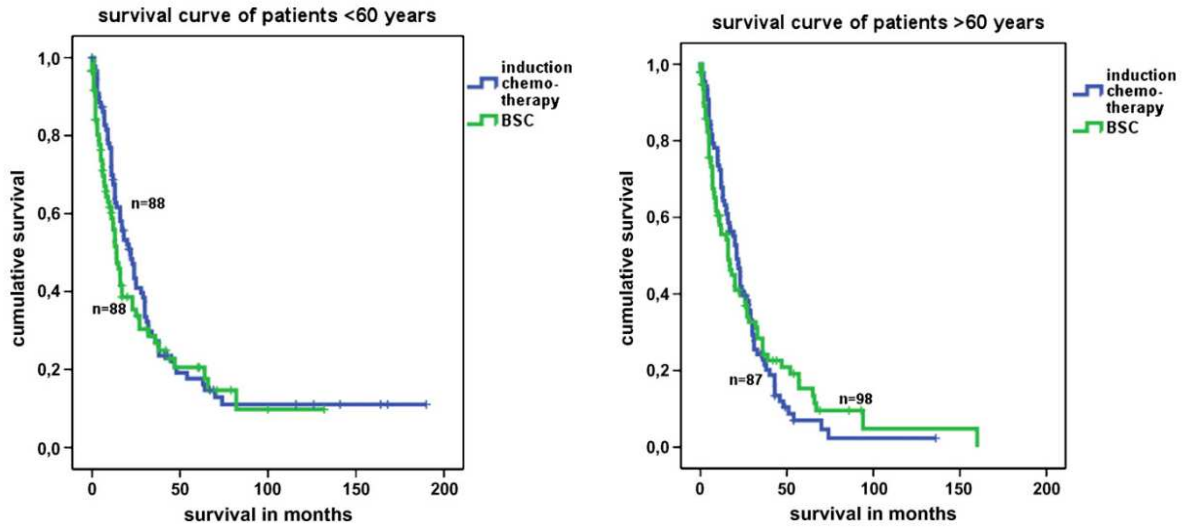
Grenzwertig signifikant konnte ich auch für Valproinsäure einen Vorteil im medianen Überleben von 48 Monaten versus 29 Monaten darlegen. Auch hier war dies vor allen

Dingen für die WHO Subtypen RAEB I und RAEB II zutreffend. Gemessen anhand des IPSS konnte kein Vorteil für bestimmte Subgruppen gezeigt werden. Auch für die Therapie mit dem immunsuppressiven Medikament ATG lag in unserer Kohorte ein Überlebensvorteil für behandelte Patienten vor, dies gar trotz des erwähnten Selektionsbias von einem medianen Intervall von 26 Monaten zwischen Erstdiagnose und Behandlungsinitiation in einer Niedrigrisiko-Kohorte von überwiegend RA oder RCMD Patienten und einem medianen Überleben in den nur mit BSC behandelten Patienten von 61 Monaten.



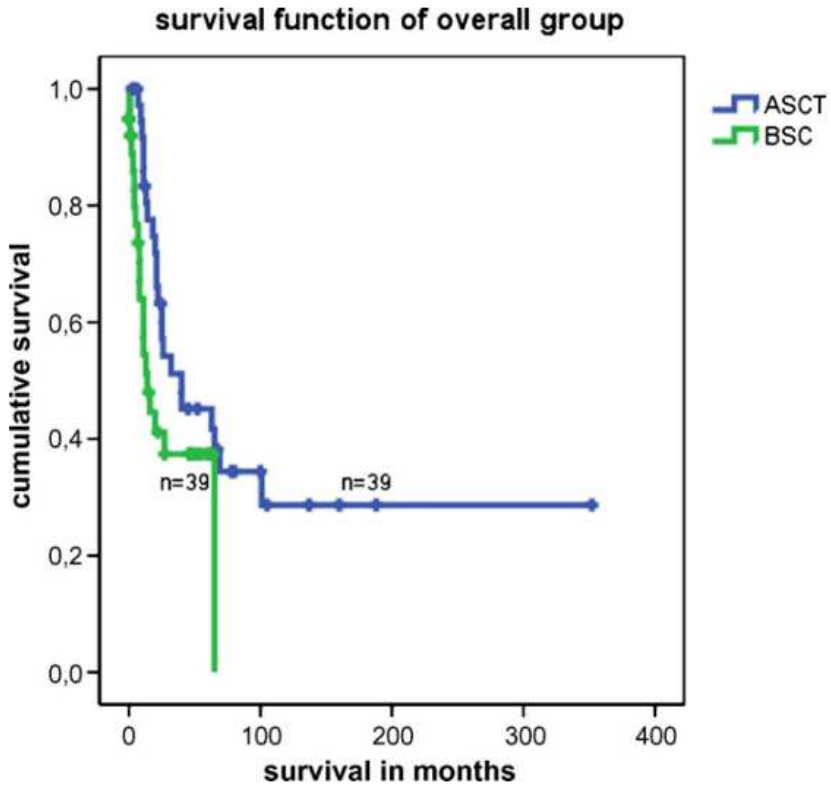
Kaplan-Meier-Kurve der Gesamtgruppe von mit ATG versus BSC behandelten Patienten (p=0,04). Eigene Abbildung.

Sowohl für niedrigdosiertes Cytarabin, als auch für die konventionelle intensive Chemotherapie konnte ich bestätigen, dass eine derartige Therapiemodalität nicht zu einem verbesserten Gesamtüberleben führt, dies auch in Subgruppenanalysen anhand des IPSS oder des Alters.



Kaplan-Meier-Kurve der mit Chemotherapie versus BSC behandelten Patienten, >/<60 Jahre (p=0,307 und p=0,795). Eigene Abbildung.

Die Behandlung mit allogener Blutstammzelltransplantation führte auch in meinen Analysen eindeutig zu einem deutlich besseren medianen Gesamtüberleben unabhängig der WHO Subgruppe und insbesondere in Hochrisiko-MDS wie RAEB I oder RAEB II bzw. anhand des IPSS.



Kaplan-Meier-Kurve der Gesamtgruppe von mit allogener PBSZT versus BSC behandelten Patienten (p=0,04). Eigene Abbildung.

Die auf einer zahlenmäßig umfangreichen und über einen langen Zeitraum erhobenen Daten fußende Arbeit konnte so wertvolle Erkenntnisse über die Wirksamkeit von Therapien bei MDS beitragen, für welche prospektive Untersuchungen zu dem Zeitpunkt kaum vorlagen.

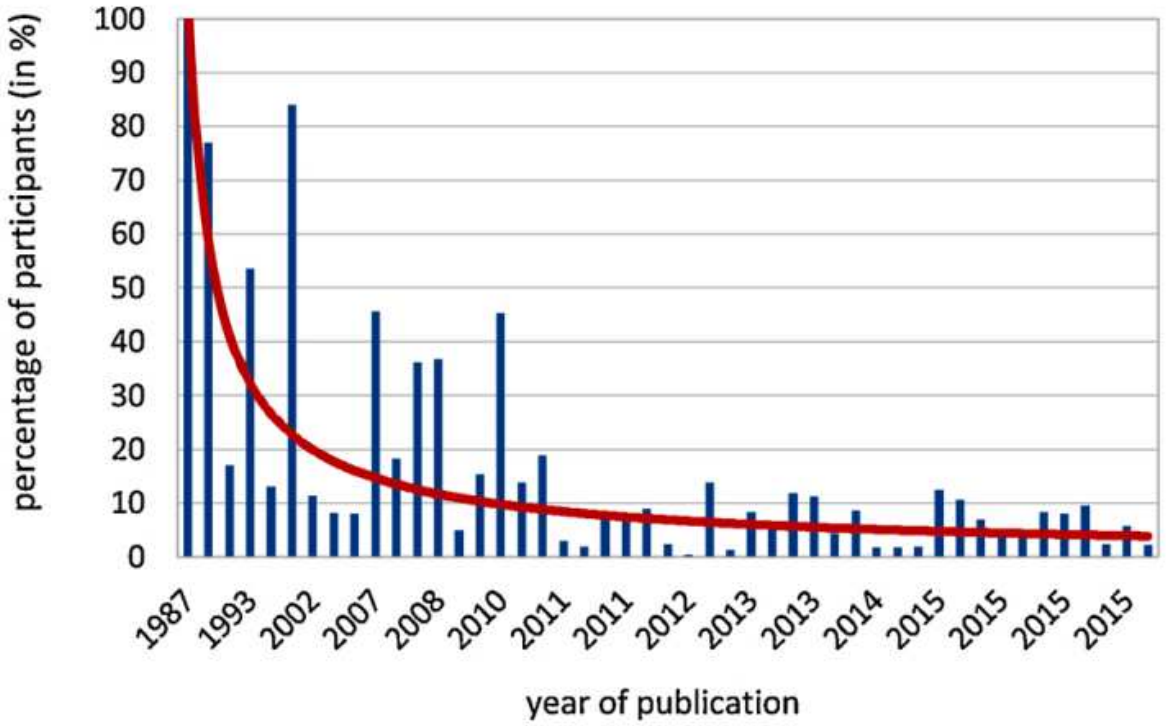
In einer weiteren Arbeit mit dem Fokus auf Prognosebeeinflussung von MDS Patienten durch Therapiemodalitäten befasste ich mich mit klinischen Studien. Wie erwähnt, existieren wenige zugelassenen Therapieoptionen für MDS. Lenalidomid kommt als Substanz nur für transfusionsabhängige Patienten mit Nachweis der 5q-Deletion in Frage, welche nur etwa 5% der MDS-Diagnosen stellen. Die einzig kurative Therapie, die allogene Blutstammzelltransplantation, kann in der MDS-Population von eher älteren und komorbideren Patienten nur circa 10% angeboten werden. Desweiteren existieren Eisenchelation und Erythropoetinsubstitution bei inadäquat niedrigem endogenen EPO-Spiegel für Niedrigrisiko-MDS sowie Azacitin als hypomethylierendes Agens für Hochrisikopatienten. Im Lichte der Tatsache, dass lediglich für einen Anteil von circa 30% von MDS Patienten eine krankheitsmodifizierende Therapie angeboten werden kann, sind klinische Studien weiterhin ein essentieller Bestandteil zur Weiterentwicklung und Optimierung der Prognose von MDS Patienten. Klinischen Studien inhärent ist jedoch das Vorhandensein von sehr spezifischen Ein- und Ausschlusskriterien für die Sicherstellung einer möglichst suffizient auswertbaren homogenen Patientenpopulation. Unser Zentrum hat über die letzten 30 Jahre bis zum Untersuchungszeitpunkt 47 klinische Studien für MDS Patienten durchgeführt bzw. an jenen teilgenommen. Dies waren sowohl sogenannte „IIT“ (investigator initiated trials), als auch von der pharmazeutischen Industrie gesponserte Studien.

In meiner Arbeit wertete ich Patienten des MDS Registers, das zu diesem Zeitpunkt mehr als 7500 Patienten aufwies, hinsichtlich der Akzessabilität von rein supportiv behandelten Patienten in klinische Studien aus und simulierte hierzu, dass das Kollektiv anhand der jeweiligen Ein- und Ausschlusskriterien aller an unserem Zentrum bis zum Untersuchungszeitpunkt angebotenen klinischen Studien auf potentielle Teilnahmefähigkeit geprüft wird.

Die Kohorte umfasste Patienten, die alle zum Einschluss geforderten Grundparameter wie WHO Subtyp, IPSS, relevante Laborwerte, Zytogenetik, Vortherapien und ECOG aufwiesen. Aus dem Register ließen sich so 1809 Patienten für die Simulation extrahieren. Dieses Kollektiv unterschied sich nicht in Hinblick auf Verteilung der WHO Subtypen, Gesamtüberleben und Risiko für Entwicklung einer sAML gegenüber den restlichen Patienten des Registers. Einige in Ein- und Ausschlusskriterien erhobene Parameter wie Einwilligung zu sicheren Kontrazeptionsmaßnahmen lagen systematisch bedingt nicht vor, da sie nicht MDS-spezifisch sind und entsprechend nicht im Register erfasst worden waren. Sie wurden entsprechend in den Analysen nicht berücksichtigt.

Insgesamt waren lediglich 18% der Patienten anhand der geforderten Kriterien für den Einschluss in eine der Studien geeignet. Die Eignung zeigte eine eindeutige Zeitabhängigkeit: Beinahe 70% der Patienten konnte in Studien, die vor dem Jahr 2000

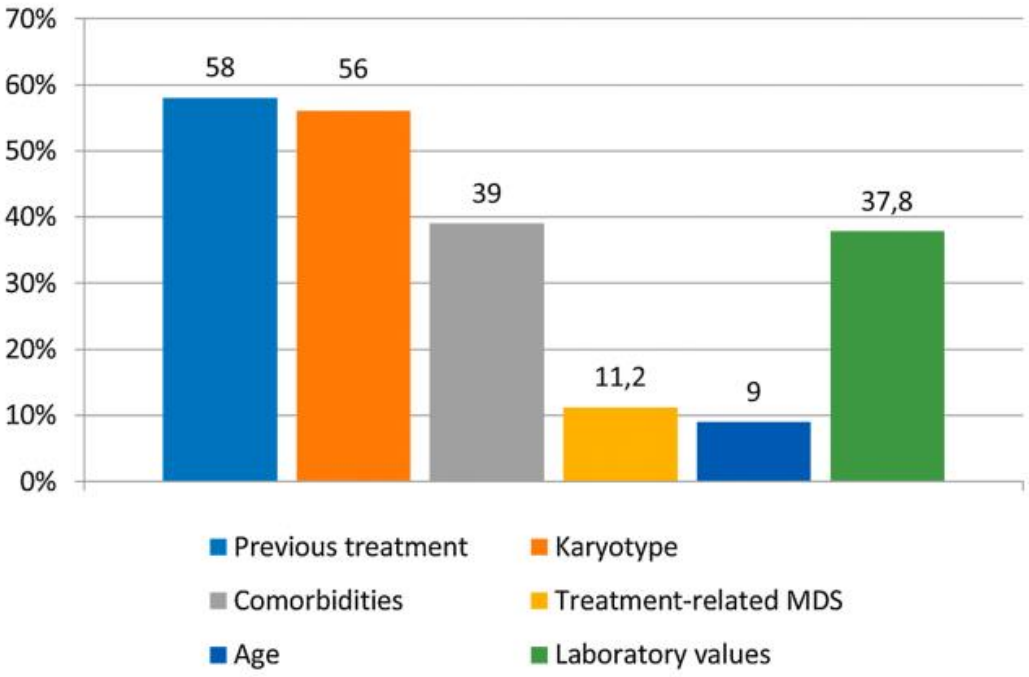
durchgeführt worden waren, fiktiv eingeschlossen werden, 27% in Studien aus den Jahren 2000-2010 und nur noch knapp 7% in Studien ab dem Jahr 2010.



Mittlere Eligibilität in den Jahren 1987-2017 hinsichtlich aller Ein- und Ausschlusskriterien. Eigene Abbildung.

Umgekehrt ermöglichten 60% der 47 Studien den Einschluss von nur 10% der gesamten Kohorte. Prüfer-initiierte Studien, also nicht-kommerzielle Studien, wiesen eine weniger rigide Exklusion von Patienten auf und erlaubten den Einschluss von ca. 25% des Kollektivs versus 16,5% bei Studien der pharmazeutischen Industrie. Ebenso erlaubten Phase-II-Studien einen höheren Anteil an Patienten (21,8%) als Phase-I- (6,2%) und Phase-3-Studien (9,7%).

Ich konnte zeigen, dass die Hauptparameter, die zum Ausschluss eines Patienten der Kohorte führte, das Vorhandensein von Komorbiditäten, von Vortherapien und chromosomale Befunde waren.

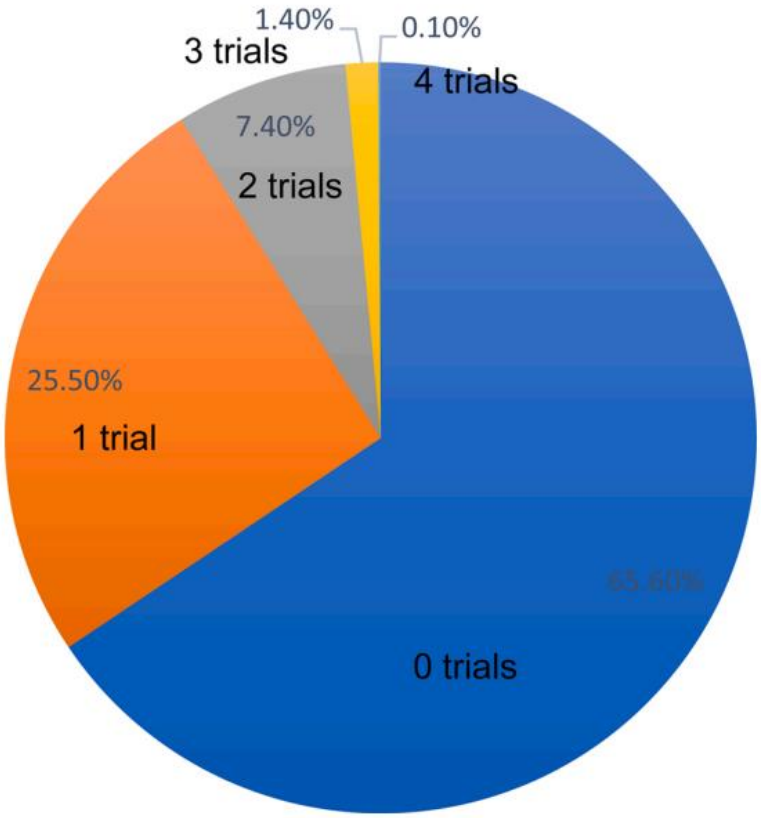


Häufigkeit der hauptsächlichen, zum Ausschluss führenden Kriterien in Prozent. Eigene Abbildung.

Sehr spezifische Studien führten erklärlicherweise zu einem nur sehr geringen Anteil an einschlussfähigen Patienten, so auch die Studie „Lenalidomid-Erhaltungstherapie nach allogener PBSZT“, für die sich lediglich 0,4% der Kohorte eignete.

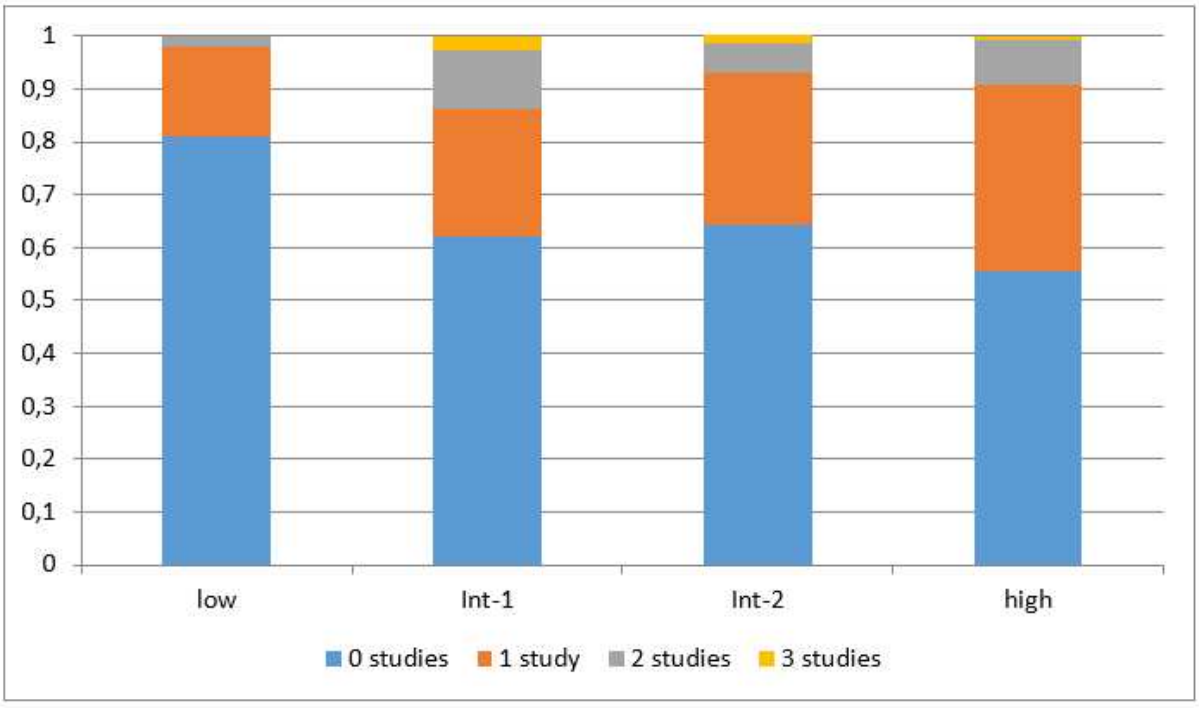
Ich untersuchte des Weiteren, welche Kriterien besonders häufig in Studien verwendet wurden und welche Kriterien den größten Einfluss auf die Eligibilität von MDS Patienten hatten. Allgemeinere Parameter wie Alter wurden verständlicherweise breit implementiert, aber auch Komorbiditäten und Vortherapien waren die am häufigsten verwendeten. Umgekehrt führte der Faktor „Karyotyp“, obwohl in einer geringeren Zahl von nur 11 Studien eingesetzt, zum Ausschluss der größten Zahl an Patienten. Signifikant unterschiedlich war auch der Faktor „sekundäres/therapieassoziiertes MDS“, mit 12,6% einschlussfähigen Patienten mit tMDS versus 37,2% pMDS Patienten.

Ein umgekehrter Blick auf die Daten zeigte, dass, nur gemessen an den Ein- und Ausschlusskriterien, lediglich circa 25% der Kohorte für zumindest eine der im Jahr 2016 offenen 9 klinischen Studien geeignet gewesen wäre, circa 7% für zwei sowie 1,4% für 3 der angebotenen Studien.



Prozentualer Anteil inkludierbarer Patienten in 9 rekrutierende klinische Studien im Jahr 2016. Eigene Abbildung.

Ich konnte zudem zeigen, dass die Wahrscheinlichkeit der Eignung über die Ein- und Ausschlusskriterien mit höherem Risikosubtyp gemäß IPSS zunahm.



Eligibilität gemessen am IPSS Subtyp. Eigene Abbildung.

Der auch in der aktuellen Zeit geringen Zahl an verfügbaren, zugelassenen Substanzen zur krankheitsmodifizierenden Therapie von MDS Patienten steht die Heterogenität der Erkrankung gegenüber, die auch aufgrund zunehmenden Wissens um prognostisch relevante, beispielsweise molekulargenetische Befunde, in den letzten Jahren eher zunimmt. Es liegt somit partiell auch in der Biologie der MDS, dass klinische Studien teils sehr enge Kriterien zum Ein- und Ausschluss definieren müssen, um zB zielgerichtete Therapien nur den wirksamen Subtypen anzubieten, so beispielsweise geltend für Luspatercept, vor allem bei Vorliegen einer SF3B1-Mutation. Umgekehrt zeigen meine Analysen aber auch auf, dass es systematische, nicht krankheitsassoziierte oder aus unserer Sicht modifizierbare Faktoren gibt, die die Zugänglichkeit zu klinischen Studien erschweren. Dies sind insbesondere Komorbiditäten und Vortherapien oder der kategorische Ausschluss sekundärer MDS. Die Gefahr für solch artifiziell homogenisierte Patientenpopulationen in klinischen Studien besteht in der fehlenden Reproduzierbarkeit der Ergebnisse im „real world setting“ [40-42].

Meine Analysen zeigen somit auf, dass klinische Studien nur für einen geringen Anteil an MDS Patienten verfügbar sind. Der Anteil an inkludierbaren Patienten ist womöglich noch geringer anzunehmen, als nicht erhobene Faktoren wie der Patientenwille, die Therapieadhärenz in einem älteren, potentiell weniger mobilen Patientenkollektiv sowie die Verfügbarkeit von Studien deutschlandweit im Vergleich zu einem „centre of excellence“ mit einem entsprechend großen Studienportfolio, auf dem die Daten des Registers beruhen, in dieser Arbeit nicht berücksichtigt werden konnten. Schließlich postulierte ich, dass das uns vorliegende MDS Register ein mögliches sinnvolles Instrument darstellt, um im Rahmen der Planung neuer klinischer Studien potentielle Ein- und Ausschlusskriterien innerhalb der Registerpopulation zu simulieren.

Schlussfolgerung und Ausblick

Prognoseabschätzende Instrumente für myelodysplastische Neoplasien sind nach wie vor und auch besonders bei dieser Erkrankung aus mehreren Gründen hochrelevant:

Zum einen betreffen myelodysplastische Neoplasien vornehmlich ältere Menschen mit einem medianen Erkrankungsalter von circa 70-75 Jahren, so dass insbesondere bei Niedrigrisiko-MDS oder bei relevanter Komorbidität bzw. bei fortgeschrittenem biologischen Alter ein rein supportives Vorgehen vorwiegt. Hier gilt es, möglichst fein herauszuarbeiten, welche Patienten insbesondere mit Niedrigrisiko-MDS doch von einer therapeutischen Intervention profitieren können, sowie umgekehrt, Patienten, für welche jegliche über supportive Maßnahmen hinausgehende Therapien keine Option darstellt, sinnhaft prognostisch einschätzen zu können. Auch unser Blick auf die Todesursachen von MDS Patienten ist in indirektem Sinne prognostisch hoch relevant, zeigt sie doch auf, dass in einem durch Komorbiditäten zunehmend gekennzeichneten Kollektiv von im Mittel älteren Patienten krankheitsassoziierte Todesursachen generell überwiegen und somit die Prognose der Patienten bestimmen, und dies selbst im Niedrigrisiko-Bereich. Dieser Faktor nimmt mit zunehmender Risikokategorie zu. Dies unterstreicht die Wichtigkeit von krankheitsmodifizierenden Therapien, auch für Patienten, die keinen erhöhten Blastenanteil oder eine chromosomale oder molekulare Hochrisikoaberration aufweisen. Durch die den Niedrigrisiko-MDS inhärente vergleichsweise lange mediane Überlebenszeit ist es jedoch schwierig, einen Überlebensvorteil durch Therapieinterventionen aufzuzeigen, welches möglicherweise in der Vergangenheit zur Schlussfolgerung führte, dass ein reines BSC ein ausreichendes Vorgehen für alle Niedrigrisiko-MDS Patienten darstellt.

Zum anderen zeigt sich durch das zunehmende Wissen über die Biologie der Erkrankung, wie heterogen die Prognose innerhalb der Gesamtgruppe von MDS Patienten verläuft, basierend auf molekulargenetischen oder zytogenetischen Aberrationen, aber auch durch weitere Faktoren wie das Vorliegen einer Fibrose oder Zellularität im Knochenmark, deren Bedeutung für myelodysplastische Neoplasien erst in den letzten Jahren herausgearbeitet wurde [27,28,43-49]. Dies ließ sich auch in meiner Arbeit bestätigen, die sich im Detail mit histopathologisch erhobenen Befunden im direkten Vergleich mit zytomorphologischer Befundung beschäftigte. Nebst der Validierung der in der aktuellen WHO Klassifikation berücksichtigten pathologischen Faktoren Fibrose und Zellularität erlaubte meine Arbeit einen feinauflösenderen Blick auf die prognostische Wertigkeit vieler Parameter, wenn sie in Konkurrenz zueinander betrachtet werden und konnte aufzeigen, welche Stärken und Schwächen die jeweilige Methodik mit sich bringt.

Exakt abschätzen zu können, welche Veränderungen und Charakteristika zum Erstdiagnosezeitpunkt eine schlechtere Prognose mit sich bringen, erlaubt, auch Patienten krankheitsmodifizierenden Therapien zu kommen zu lassen, die möglicherweise früher nicht therapiert worden wären, sowie Patienten die Teilnahme an klinischen Studien zu ermöglichen, wenn dies im Rahmen der aktuellen Erkenntnisse sinnhaft erscheint.

Wie ich aufgezeigt habe, nimmt die Zahl an Klassifikationssystemen und Prognosescores, die beide eigenständige prognostische Instrumente darstellen, jedoch über die Jahre zu. Neben der WHO-Klassifikation wurde nun unlängst eine ganz neue Klassifikation, die ICC, publiziert, die in direkter Konkurrenz zur etablierten WHO steht. Daneben existieren IPSS-R und IPSS-M nebeneinander als Prognosescores, welche für den Anwender unterschiedlich zugänglich sind. Der IPSS-M ist ein deutlich komplexeres System, welcher nur mit einem Internet-Tool zu berechnen ist. Auch wenn der IPSS-M mit fehlenden Parametern in der Lage ist, eine prognostische Abschätzung vorzunehmen, ist doch die Nutzung dieses Instrumentes im klinischen Alltag, insbesondere außerhalb des universitären Bereiches, zumindest zu hinterfragen. Der IPSS-R ist nach wie vor ein sehr robuster Score, der auch schnell und mit weniger Parametern eine gute, in unserem Kollektiv mehrfach validierte Abschätzung der Prognose erlaubt. Hier existiert in unseren Augen jedoch nach wie vor eine gewisse Grauzone über die Einschätzung von intermediär-Risiko Patienten in Hinblick auf die Therapieindikation bei Erstdiagnose, und hier insbesondere, ob Patienten, die hierfür geeignet sind, primär eine allogene Blutstammzelltransplantation erhalten sollten. Eine Aufarbeitung der im IPSS-R vorhandenen zytogenetischen Risikostratifizierung innerhalb der „intermediate risk“ Patienten ist aktuell in Publikation befindlich und wird sich dieser Fragestellung nähern.

Eine Einordnung potentiell konkurrierender Systeme und das Vermeiden von „überkomplizierten Strukturen“ ist sicherlich anzustreben, wenn die Heterogenität von MDS ohnehin schon einen immer dezidierteren Blick auf den individuellen Patienten erfordert. Hier werden die jüngsten konkurrierenden Klassifikationssysteme sicherlich noch weitere Einordnung erfahren.

Dass auch nicht zugelassene Therapieoptionen eine das Gesamtüberleben betreffende Wirksamkeit für MDS Patienten aufweisen können, habe ich anhand von Daten des MDS Registers in einer aufwendigen Matched Pairs Analyse für mehrere Substanzen wie Thalidomid, ATG oder auch die allogene PBSZT klar nachweisen können. Dies gilt teils für Subgruppen von MDS Patienten. Umgekehrt konnte ich hierüber bestätigen, dass andere Therapien, wie die intensive konventionelle Chemotherapie, für MDS Patienten als obsolet anzunehmen sind. Dies auch für MDS Patienten mit erhöhtem Blastenanteil IB1 und IB2, die in der ICC-Klassifikation als MDS/AML bezeichnet werden, jedoch offensichtlich nicht wie AML Patienten angesehen werden sollten. Das MDS Register kann auch in Zukunft weiterhin ein hilfreiches Instrument sein, um Therapieversuche oder Fallserien auf ihren prognostischen Einfluss zu untersuchen oder um Daten von klinischen Studien im Sinne von „real world“ Daten zumindest retrospektiv zu validieren oder zu hinterfragen.

Wenn eine Indikation zur therapeutischen Intervention angenommen wird, existieren auch zum heutigen Zeitpunkt noch wenige zugelassene Optionen. Die Bedeutung klinischer Studien ist daher für MDS unstrittig. Jedoch konnte ich erarbeiten, dass die Zugänglichkeit zu klinischen Studien in der Vergangenheit und dies in zunehmendem Maße über die Jahre durch die Ein- und Ausschlusskriterien relevant behindert wird.

Hier erlaubt meine Arbeit die Frage, wie klinische Studien zukünftig möglicherweise besser geplant und gestaltet sein sollten, um MDS Patienten im klinischen Alltag einen breiteren Zugang zu neuen Optionen zu ermöglichen.

Ziel dieser Arbeiten und zukünftiger Projekte ist es somit, der heterogenen Gruppe von Patienten mit myelodysplastischen Neoplasien eine am aktuellen Wissen orientierte und kontinuierlich validierte oder neu entwickelte Behandlung zu ermöglichen, die mit einem in zunehmendem Maße individualisierten Blick auf den einzelnen MDS Patienten eine prognostische Einschätzung vornimmt, um die optimale Therapie oder auch supportive Therapie anbieten zu können. Bestehende Register mit großen Datensätzen wie das MDS Register Düsseldorf, insbesondere im internationalen Austausch und Zusammenschluss, sind neben bewährten Ansätzen der Nutzung großer Datensätze möglicherweise neben der bewährten Methode retrospektiver Analysen zukünftig zunehmend der Ausgangspunkt für KI-basierte Methoden [50-56].

Abkürzungsverzeichnis

AML	Akute myeloische Leukämie
ANC	Absolute Neutrophil Count (Absolute Neutrophilenzahl)
ATG	Antithymozytenglobulin
BSC	Best Supportive Care
CMML	Chronische myelomonozytäre Leukämie
del5q	Verlust eines Teils des Chromosoms 5
ECOG	Eastern Cooperative Oncology Group (Performance Status)
ED	Erstdiagnose
ESA	Erythropoiesis Stimulating Agents
FAB	French American British
G-CSF	Granulozyten Kolonie-stimulierender Faktor
HMA	Hypomethylierende Substanzen
ICC	International Consensus Classification
ICUS	Idiopathic Cytopenia of Unkown Significance
IIT	Investigator Initiated Trials
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System - revised
IPSS-M	International Prognostic Scoring System - molecular
MDS	Myelodysplastische Neoplasien
MLD	Multi Lineage Dysplasia (Mehrliniendysplasie)
MPS	Myeloproliferatives Syndrom
OS	Overall Survival

PBSZT	Allogene Blutstammzelltransplantation
PFS	Progression Free Survival
pMDS	Primäre MDS
RA	Refractory Anemia
RAEB	Refractory Anemia with Excess Blasts
RAEB-T	Refractory Anemia with Excess Blasts in Transformation
RCMD	Refractor Anemia with Multilineage Dysplasia
SAML	Sekundäre akute myeloische Leukämie
SF3B1	Spleißfaktor 3B Untereinheit 1
SLD	Single Lineage Dysplasia (Einliniendysplasie)
tMDS	Therapieassoziierte MDS
UKD	Universitätsklinikum Düsseldorf
WHO	World Health Organisation
WPSS	WHO Based Prognostic Scoring System

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Liste der zusammengefassten Publikationen

Impact on survival of different treatments for myelodysplastic syndromes (MDS).
Nachtkamp K, Kündgen A, Strupp C, Giagounidis A, Kobbe G, Gattermann N, Haas R, Germing U. Leuk Res. 2009 Aug;33(8):1024-8.

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Eligibility for clinical trials is unsatisfactory for patients with myelodysplastic syndromes, even at a tertiary referral center.
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Comparison of cytomorphology and histomorphology in myelodysplastic syndromes (MDS).
Nachtkamp K, Strupp C, Faoro R, Gattermann N, Dietrich S, Germing U, Baldus S. Front Oncol. 2024 Apr 11;14:1359115.

Anhang: Sonderdrucke der zusammengefassten Publikationen

Der Anhang der Publikationen erfolgt mit der freundlichen Genehmigung der Verlage.

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Comparison of cytomorphology and histomorphology in myelodysplastic syndromes

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Gold standard for the establishment of the diagnosis of myelodysplastic syndromes (MDS) are cytomorphological features of hematopoietic cells in peripheral blood and bone marrow aspirates. There is increasing evidence that bone marrow histomorphology not only aids in the diagnosis of MDS but can provide additional prognostic information, particularly through assessment of fibrosis and cellularity. However, there is only sparse data on direct comparison between histological and cytomorphological findings within the same MDS patient cohort. Therefore, we performed such an analysis under exceptionally well-standardized conditions. We reexamined biopsy material of 128 patients from the Düsseldorf MDS registry who underwent bone marrow trephine biopsy (in addition to bone marrow aspiration) at the time of diagnosis, addressing the following items: a. Analysis of concordance of diagnoses made by histology and cytomorphology b. Analysis of additional information by histology with regard to the diagnosis and prognosis. The respective biomaterials were available at our institution and had been processed according to unchanged protocols between 1992 and 2010. Fresh histopathological sections were obtained from the tissue blocks, stained under identical conditions and re-assessed by a designated expert pathologist (C.B.) without knowledge of the previous histopathological report or the respective cytomorphological diagnosis. The latter, likewise, was uniformly made by the same expert cytomorphologist (U.G.). Histopathology of bone marrow trephine biopsies reliably captured the diagnosis of MDS. Assignment to the diagnostic WHO subgroup was not entirely concordant with cytomorphology, mainly due to incongruences between the proportion of CD34-positive cells on histopathology and the cytomorphological blast count. Histopathology provided additional diagnostic and prognostic information with high diagnostic and prognostic significance, such as fibrosis. Likewise, histopathology allowed more reliable estimation of bone marrow cellularity.

KEYWORDS

myelodysplastic syndromes, cytomorphology, histopathology, prognosis, WHO2022

Introduction

Myelodysplastic syndromes are a heterogeneous group of clonal stem cell disorders, morphologically defined by dysplastic features of hematopoietic cells and increasing impairment of hematopoietic cell differentiation, recognizable by an elevated proportion of bone marrow blasts in higher-risk MDS (1–7). Disturbed maturation entails functional defects of blood cells, as well as peripheral blood cytopenias (7, 8). MDS also carries the risk of transformation into acute myeloid leukemia (9). Primary myelodysplastic syndromes, which account for about 90% of MDS cases, lack an apparent cause, whereas radiotherapy or noxious agents, such as chemotherapy or organic solvents, are present in the medical history of patients with secondary or therapy related MDS. In rare cases, a familial predisposition to clonal hematopoietic disorders is recognized.

Myelodysplastic syndromes are categorized by considering dysplastic features, blast count, and cytopenias. The diagnosis is usually established by cytomorphology. Despite peripheral blood cytopenia, the bone marrow in MDS is generally hyper- or normocellular.

Since the 1980s, several classifications have been established that separate morphologically discernible, prognostically relevant types of MDS. The FAB classification, published in 1982, was solely based on morphological criteria (10). The WHO classification, first published in 2001, refined the MDS subtypes and was the first to require chromosomal analyses and to include a chromosomal aberration (del5q) as a disease-defining marker. Revised versions were published in 2016 and 2022 (11–14).

While diagnostic criteria for MDS mainly rely on cytomorphological features, some MDS patients may show bone marrow fibrosis, which can only be assessed on histopathology. In addition, histopathology is deemed superior to cytomorphology regarding assessment of bone marrow cellularity.

Our analysis compares cytomorphological and histopathological findings and their degree of conformity in a cohort of MDS cases with respect to diagnostic accuracy and prognostic significance that is unique in terms of uniform preparation of diagnostic samples and lack of interobserver variability.

Materials and methods

We analyzed bone marrow aspirates of 152 MDS patients diagnosed between 1992 and 2010 by central cytomorphology according to the WHO classification (12, 13). Bone marrow trephine biopsies obtained at the time of diagnosis were also available from these patients. Data regarding clinical features, cell counts, and the course of disease were obtained from the Duesseldorf MDS registry. We considered date of birth, gender, time of diagnosis, WHO/FAB subtype, treatment history, and outcome. Data closure/end of follow-up was July 1st, 2012, or date of death. Only a small subset of patients was lost to follow-up. The availability of the abovementioned data set was mandatory for inclusion in the analysis. 128 patients were assessable for further analysis.

The bone marrow trephine biopsy taken at the time of diagnosis was used for preparing new histopathological sections and stains, which were assessed by a single reviewing pathologist (SB) who had no knowledge of the cytomorphological evaluation, apart from the information "patient with myelodysplastic syndrome". Bone marrow biopsies we carried out and processed according to local standards. Immunohistochemical staining with an anti-CD34 antibody was used to visualize immature hematopoietic progenitor cells. Histological slides were routinely stained with hematoxylin-eosin (HE), periodic acid Schiff reagent (PAS), Giemsa, silver impregnation according to Gomori, and iron staining (Berliner-Blau). In addition, the naphthol AS-D chloroacetate esterase reaction was used to highlight neutrophilic granulopoiesis.

The following morphological parameters were assessed by standardized procedures and were evaluated semi quantitatively (Table 1): cellularity of the specimen in comparison to an age-related control cohort, maturation and dysplasia of megakaryopoiesis, cellularity of erythropoiesis and proportion of erythroid cells relative to granulopoietic cells, degree of fibrosis, bone marrow iron content, and percentage of CD34-positive cells in relation to the overall cellularity of the bone marrow. Length, quality, and number of evaluable intertrabecular areas were also assessed.

The correlating cytomorphological findings were taken from the Duesseldorf MDS registry. Cytomorphological assessment was performed according to standard operating procedures as reported by Germing et al. (Table 1) (15). Of note, 20 patients with the diagnosis of RAEB-T according to the FAB classification were included in the analysis.

To ensure homogeneity and comparability, histopathological and cytomorphological diagnoses were always established by the same reviewers, respectively (UG for cytomorphology, SB for histopathology). Statistical analyses were performed using SPSS. Comparison of blast count by cytomorphology versus histology was analyzed by nonparametrical Wilcoxon T-Test. Categorical variables were analyzed using Chi-Square-Test. All procedures were in accordance with the current version of the Helsinki Declaration. Informed consent was obtained from all patients included in the study.

Results

Patient characteristics

Of the 128 patients evaluable, 79.7% had deceased at the time of this analysis, 19.5% were documented alive at the time of data closure and 0.8% were lost to follow up.

Baseline characteristics of the cohort are presented in Table 2a and Table 2b. Patients' MDS subtype according to both WHO 2016 and WHO 2022 classification are shown in Table 2a, Table 2b demonstrates the redistribution of patients from the WHO 2016 to 2022 classification. Median age was 67 years. Median survival time was 16.3 months after diagnosis (0-164.4 months).

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TABLE 1 Morphologic parameters.

morphological parameters assessed by histopathology	
bone marrow cellularity	<40% (hypocellular)
	40-60% (normocellular)
	>60% (hypercellular)
proportion of adipocytes	0-10%
	11-30%
	31-50%
	51-70%
	>70%
percentage of erythropoiesis	0-20%
	21-40%
	41-60%
	61-80%
	>80%
degree of dysplasia of megakaryopoiesis	0= no signs of dysplasia
	1= low to moderate
	2=marked signs of dysplasia
	3=high degree of dysplasia
bone marrow fibrosis	0= no fibrosis
	1= low degree
	2= high degree
	3= very high degree
iron content of reticulum cells	0= no iron/depletion
	1= low to normal amount
	2= increased amount
	3= markedly increased amount
percentage of CD34-positive cells (in relation to total cell count)	<1%
	1-2%
	3-5%
	6-10%
	11-15%
	16-20%
	21-30%

(Continued)

TABLE 1 Continued

morphological parameters assessed by histopathology	
morphological parameters assessed by cytology	
bone marrow cellularity	hypocellular vs normocellular vs hypercellular
Dyserythropoiesis in marrow	percentage of erythropoiesis
	megaloblastoid changes
	multinuclearity
	nuclear budding
	nuclear bridges
	atypical mitoses
	sideroblastosis
	percentage of ringsideroblasts
	PAS positive red precursors
Dysmegakaryopoiesis in marrow	micromegakaryocytes
	mononuclear megakaryocytes
	hypersegmentes megakaryocytes
	multinuclearity of megakaryocytes
Dysgranulopoiesis in marrow	hyperplasia of granulopoiesis
	left shift of granulopoiesis
	medullary blast count
	Auer rods or Auer bodies (POX-staining)
	hypo/degranulation of white precursors
	pseudo-Pelger cells
	nuclear anomalies of granulocytes (hypersegmentation)
	deficiency of myeloperoxidase
	percentage of monocytopoiesis (esterase staining)
Other features	Percentage of lymphoid cells
	percentage of plasma cells
	iron storage

MDS diagnoses were made according to the WHO classification of 2016. 12 patients were diagnosed as MDS-SLD (9.4%), 25 patients as MDS-MLD with or without ring sideroblasts (19.6%), 3 patients (2%) as RARS, 15 patients (11.7%) as RAEB I, and 23 patients (18.0%) as RAEB II. In addition, 21 patients were diagnosed with CMML 0/I (16.4%), and 9 patients (7.0%) with CMML II. 20 patients (15.6%) belonged to the category of AML with myelodysplasia-related changes (the former RAEB-T diagnosis), with 20-30% medullary blasts.

Histopathological analysis

Determinants of the interpretability of histopathological specimens are length of the trephine biopsy, number of evaluable intertrabecular areas, and overall quality of the sample. 53.9% of the trephine biopsies had a length between 0.6 and 1.0 cm, 26.6% had a length of >1.0 cm. Evaluability was assessed by subjective rating. 93% of all specimens were rated at least satisfactory (grade 3 of 6) and were thus evaluated for all parameters. In 9 cases (7.0%) the number of evaluable intertrabecular areas was less than 5. In 93% of all cases, 5-15 evaluable intertrabecular areas could be analyzed.

Median cellularity was 65%. 23.4% of all cases were hypocellular (e.g., bone marrow cellularity <40%), 21.1% normocellular (40-60% bone marrow cellularity), and 55.5% hypercellular (>60%).

Histological versus cytomorphological findings

Medullary blast count/CD34+ cells

In direct comparison, the medullary blast count was underestimated by histopathology regardless of the proportion of blasts seen by cytomorphology (Table 3, p=0.001). For instance, in patients with a cytomorphologically assessed blast count of more than 20% (RAEB-T by definition), histopathology identified less than 5% blasts in 22.7% of these cases. The same was true for a cytomorphological blast count of 10-19%, where histopathology found a normal blast count (<5%) in 43%, and a blast count of 5-9% in 29% of these cases.

Patients with a hypocellular marrow according to histopathology were more likely to present with a cytomorphologically assessed blast count below 5%, whereas hypercellularity correlated with blast counts above 10% (60.7% of patients with 10-19% blasts and 63.6% with ≥20% blasts, respectively). Nevertheless, 46.9% of patients with <5% medullary blasts presented with hypercellular marrow when

TABLE 2A Patients' characteristics according to WHO 2016 and WHO 2022.

	n	
median age (range)	128	67 (23-90)
	n	percent
male	83	65%
female	45	35%
WHO2016		**n=128**
MDS-SLD	12	9.40%
MDS-RS-SLD	3	2.30%
MDS-MLD	18	14.10%
MDS-RS-MLD	7	5.50%
MDS-EB-1	15	11.70%
MDS-EB-2	25	19.50%
AML-MRC (RAEB-T)	18	14.10%
CMML 0,I	21	16.40%
CMML II	9	7.00%
IPSS		**n=89**
low	11	12.40%
intermediate-1	25	28.10%
intermediate-2	26	29.20%
high	27	30.30%

(Continued)

TABLE 2A Continued

	n	
median age (range)	128	67 (23-90)
	n	
median age (range)	128	67 (23-90)
	n	percent
male	83	65%
female	45	35%
WHO2022		n=128
MDS-LB-SLD	10	7.80%
MDS-LB-MLD	10	7.80%
MDS-SF3B1	10	7.80%
MDS-IB1	13	10.20%
MDS-IB2	20	15.60%
MDS-F	7	5.50%
MDS-hypo	10	7.80%
AML-MRC	18	14.10%
CMML I	21	16.40%
CMML II	9	7.00%

TABLE 2B Comparison of patients' distribution between WHO 2016 and WHO 2022.

			WHO 2022										Total
			LB-SLD	LB-MLD	LB-SF3B1	IB1	IB2	MDS-F	MDS hypo	AML-MRC	CMML I	CMML II	
WHO 2016	MDS-SLD	n	10	0	0	0	0	0	2	0	0	0	12
		% who2016	83,3%	0,0%	0,0%	0,0%	0,0%	0,0%	16,7%	0,0%	0,0%	0,0%	100,0%
	MDS-RS-SLD	n	0	0	3	0	0	0	0	0	0	0	3
		% who2016	0,0%	0,0%	100,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	100,0%
	MDS-MLD	n	0	10	0	0	0	0	8	0	0	0	18
		% who2016	0,0%	55,6%	0,0%	0,0%	0,0%	0,0%	44,4%	0,0%	0,0%	0,0%	100,0%
	MDS-RS-MLD	n	0	0	7	0	0	0	0	0	0	0	7
		% who2016	0,0%	0,0%	100,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	100,0%
	MDS-EB-1	n	0	0	0	13	0	2	0	0	0	0	15
		% who2016	0,0%	0,0%	0,0%	86,7%	0,0%	13,3%	0,0%	0,0%	0,0%	0,0%	100,0%
	MDS-EB-2	n	0	0	0	0	20	5	0	0	0	0	25
		% who2016	0,0%	0,0%	0,0%	0,0%	80,0%	20,0%	0,0%	0,0%	0,0%	0,0%	100,0%
	AML-MRC (RAEB-T)	n	0	0	0	0	0	0	0	18	0	0	18
		% who2016	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	100,0%	0,0%	0,0%	100,0%
	CMML 0,I	n	0	0	0	0	0	0	0	0	21	0	21
		% who2016	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	100,0%	0,0%	100,0%

(Continued)

TABLE 2B Continued

			WHO 2022										Total
			LB-SLD	LB-MLD	LB-SF3B1	IB1	IB2	MDS-F	MDS hypo	AML-MRC	CMML I	CMML II	
	CMML II	n	0	0	0	0	0	0	0	0	0	9	9
		% who2016	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	100,0%	100,0%
Total	n	10	10	10	13	20	7	10	18	21	9	128	

Red marked numbers indicate the either most statistically relevant or most strinkingly differing parameters within the comparison of histo- and cytomorphology.

diagnosed. The correlations did not reach statistical significance in our analyses (p=0.767).

Dysplastic features of megakaryopoiesis

Comparing dysmegakaryopoiesis according to histopathology and cytomorphology, there were 44 cases where megakaryopoiesis appeared inconspicuous on cytomorphology but showed at least mild to moderate signs of dysplasia on histopathology (Table 4, p=0.009). Conversely, among 9 cases that appeared normal on histopathology, 8 showed signs of dysplastic megakaryopoiesis on cytomorphological assessment.

Histopathological assessment of cellularity showed a positive correlation with the degree of dysmegakaryopoiesis. Hypercellular marrow was associated with a greater degree of dysplastic features (Table 4, p=0.009). More pronounced signs of dysmegakaryopoiesis, as assessed by histopathology, were also found in higher-risk MDS subtypes according to WHO 2016 that are characterized by elevated blast count as well as greater cellularity.

A high level of dysmegakaryopoiesis was less common in patients with a high degree of fibrosis (Table 4, p<0.00005). This may be due to an increased blast count and less residual normal hematopoiesis, both contributing to a diminished number of assessable megakaryocytes.

Cellularity

Histopathology is the gold standard for assessing bone marrow cellularity. When compared to the histopathology report, cytomorphology tends to overestimate cellularity (Table 5). A hypocellular marrow was diagnosed in 24.4% of cases by histopathology. Within that group, cytomorphology described a normocellular marrow in 44.8%, and even a hypercellular marrow in 48.3% of cases. Normocellularity was generally congruent when the finding of a normocellular marrow on histopathology was taken as the gold standard. Regarding hypercellularity, almost half of the cases diagnosed as hypercellular on histopathology were characterized as normocellular by cytomorphological assessment.

Considering histopathological cellularity in relation to the WHO2016 subgroups, there was hypercellularity in MDS types with increased blast count such as MDS-EB1 (46.7% of cases with MDS-EB1) and MDS-EB2 (40%), and in CMML with (88.9%) or without (85.7%) increased blast count (p<0.01). Inversely, the incidence of hypocellularity decreased in the aforementioned subgroups. In low-blast WHO subtypes the distribution of cellularities was as follows: hypocellular 46,7%, normocellular 40,7%, hypercellular 21,1%.

We observed a trend towards hypocellularity in MDS-RS-SLD (33.3%), MDS-RS-MLD (42.9%), and MDS-MLD (44.4%). A positive correlation, though not statistically significant, was also found between histopathological cellularity and the proportion of medullary blasts as assessed by cytomorphology.

When cellularity assessed by cytomorphology was used to find correlations, no statistically significant results were obtained, in accordance to the abovementioned results of the direct comparison of histopathological and cytomorphological cellularity assessment.

TABLE 3 Comparison of blast percentages assessed by cytomorphology with blast percentage assessed by staining of CD34 by histopathology (p<0.001).

		CD34+ cells by histopathology			
Blast count by cytology					
	0-4%	5-9%	10-19%	20-29%	total
0-4%	32	15	2	1	50
5-9%	14	9	4	1	28
10-19%	12	8	5	3	28
20-29%	5	4	6	7	22
					128

Red marked numbers indicate the either most statistically relevant or most strinkingly differing parameters within the comparison of histo- and cytomorphology.

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TABLE 4 Comparison of assessment of dysmegakaryopoiesis (histology vs cytology) (χ^2 ° 17.0, p=0.009), dysmegakaryopoiesis assessed by histology vs cellularity by histology (χ^2 ° 17.0, p=0.009) and dysmegakaryopoiesis assessed by histology vs degree of myelofibrosis (χ^2 ° 33.2, p<0.00005).

		Dysplasia by histology			
Dysplasia by cytology					
	No	Low-moderate	Marked signs	High degree of dysplasia	total
No	1	21	17	6	45
yes	8	36	30	2	76
					121
Cellularity by histology					
	No	Low-moderate	Marked signs	High degree of dysplasia	total
<40%	6	18	5	1	30
40-60%	1	14	11	1	27
>60%	3	27	34	7	71
					128
Degree of myelofibrosis					
	No	Low-moderate	Marked signs	High degree of dysplasia	total
No fibrosis	5	11	4	0	20
Grade 1	5	40	39	4	88
Grade 2	0	8	7	4	19
Grade 3	0	0	0	1	1
					127

Red marked numbers indicate the either most statistically relevant or most strinkingly differing parameters within the comparison of histo- and cytomorphology.

Erythropoiesis

The proportion of erythropoiesis did not correlate well between cytomorphological and histopathological review. Although histopathology showed superiority regarding overall cellularity assessment, only erythropoiesis diagnosed by cytomorphology showed a statistically significant correlation with cellularity (p=0.019). When assessed by histopathology, there was only a trend towards increased erythropoiesis in hypercellular marrows.

Neither WHO subtype nor medullary blast percentage correlated with the proportion of erythropoiesis in the marrow, irrespective of assessment by histopathology or cytomorphology.

The degree of dysmegakaryopoiesis, on the other hand, showed a trend towards positive correlation with the proportion of erythroid cells, when assessed by histopathology for both attributes. There was no patient with expanded erythropoiesis who did not demonstrate signs of dysmegakaryopoiesis.

WHO diagnosis

As shown in Table 6, we compared the histopathological and cytomorphological diagnoses. There was no case where histopathology did not confirm the diagnosis of MDS. 48% of MDS diagnoses were identical according to WHO type. However, in 56 cases (44%), the WHO type diagnosed by histopathology differed from the WHO type diagnosed by cytomorphology. The main reason was discordant estimation of medullary blast count. 32 patients were diagnosed with at least 5% medullary blasts by cytomorphology

TABLE 5 Cellularity assessed by histology vs cytology (χ^2 ° 4.33, p=0.36).

		Histology		
Cytology				
	<40%	40-60%	>60%	total
hypocellular	2 (18%)	3 (27%)	6 (55%)	11
normocellular	13 (24.5%)	16 (30.2%)	24 (45.3%)	53
hypercellular	14 (25.5%)	8 (14.5%)	33 (60%)	55

(MDS-EB1, MDS-EB2 and RAEB-T), while histopathology reported a normal blast count. Overestimation of blast count by histopathology occurred in 5 cases. In 8 cases, multi- versus unilineage dysplasia was identified as the discrepancy (MDS-SLD versus MDS-MLD, with or without ring sideroblasts). There were no cases where histopathology failed to diagnose CMML, but correlation regarding the distribution among CMML 0, I or II was week, reflecting the tendency of histopathology to underestimate the blast count.

Fibrosis

Evaluating the degree of fibrosis in a bone marrow specimen up to this day remains the preserve of histopathology. A positive correlation was found in our cohort between bone marrow cellularity and the degree of fibrosis. A high degree of fibrosis was predominantly observed in patients with hypercellularity (89.5% of fibrotic cases were hypercellular by histopathology). Similarly, a higher number of patients with a high degree of fibrosis was found in the high-risk subgroups of WHO 2016, namely MDS-EB2 (26.3%), RAEB-T (10.5%) and CMML I/II (31.6%). The same was true when the degree of fibrosis was compared with the percentage of medullary blast count, assessed by cytomorphology (Table 7).

The positive correlation between cellularity and fibrosis may appear counterintuitive, and the result should be interpreted with caution, due to the low number of patients with a high degree of fibrosis (n=20). However, a proportion of higher-risk MDS cases with elevated cellularity and blast counts may indeed have a tendency for fibrosis, which may have been underestimated so far.

Influence of histopathological and cytomorphological findings on overall prognosis

When the entire patient cohort was regrouped according to the blast count assessed by cytomorphology, the blast count showed a trend towards influencing median overall survival, especially in the patient groups with >5% blasts. The lack of statistical significance (p=0.128) is most likely attributable to the small size of the cohort. Regrouping based on histopathological assessment of blast count did not separate the cohort into subgroups with statistically significant different overall survival.

The presence of dysmegakaryopoiesis, identified on histopathology, did not show any prognostic impact, irrespective of the degree of dysmegakaryopoiesis.

Cellularity assessed by histopathology separated the cohort into three groups with different median survival times. A hypercellular marrow was associated with the worst outcome, even though statistical significance was not reached.

The proportion of erythropoiesis, again assessed by histopathology, seemed to influence overall survival when the patient cohort was divided into 5 groups (0-20%, 21-40%, 41-60%, 61-80%, >80%). Patients with 20-40% erythropoiesis showed a trend for the best overall survival. On cytomorphology, this effect had not been detectable. This might reflect the superiority of histopathological assessment already seen with regard to the overall cellularity.

Presence of a high degree of fibrosis as assessed by histopathology translates into an inferior median survival as the degree of fibrosis separates the cohort into different subgroups with a statistically significant prognosis. Based on the degree of fibrosis, the entire patient cohort could be divided into two groups (no or mild signs of fibrosis versus high or very high degree of fibrosis) that showed a statistically significant difference in prognosis (Figure 1). The prognostic impact of fibrosis was also visible in WHO 2016 low-risk subgroups with a blast count <10%. The importance of fibrosis is reflected by the latest WHO classification for MDS, which now includes MDS with myelofibrosis (MDS-f).

Discussion

Although cytomorphological examination of bone marrow aspirates, focusing on dysplastic features and blast counts, represents the gold standard for MDS diagnosis, additional information can be gained through histopathological evaluation of trephine biopsies (1, 2, 14). We compared cytomorphological and histopathological bone marrow analyses under well standardized

TABLE 6 WHO diagnoses, histology vs cytology (χ^2 = 345.4, p<0.00005).

	Histology									
	SLD	SLD RS	MLD	MLD-RS	EB1	EB2	AML MRC	CMML1	CMML2	Total
Cytology										
SLD	11	0	0	0	0	1	0	0	0	12
SLD-RS	0	2	0	1	0	0	0	0	0	3
MLD	4	0	7	5	1	1	0	0	0	18
MLD-RS	2	0	0	4	0	1	0	0	0	7
EB1	5	0	4	0	5	1	0	0	0	15
EB2	7	0	3	0	9	6	0	0	0	25
AML MRC	2	0	1	0	6	3	6	0	0	18
CMML1	0	0	0	0	0	0	0	20	1	21
CMML2	0	0	0	0	0	0	0	8	1	9

Red indicates strongly different findings between histopathology and cytomorphology, brown indicates more slightly different assessments (e.g. IB1 vs IB2).

TABLE 7 Degree of fibrosis vs medullary blast count by cytology (χ^2 * 3.459, p= 0.063).

		Medullary blast count by cytology	
Degree of myelofibrosis			
	0-4%	>4%	total
Grade 0-1	45 (42%)	62 (58%)	107
Grade 2-3	4 (20%)	16 (80%)	20

conditions with regard to the congruence of the MDS diagnoses, typical MDS features such as dysplastic criteria and on the other hand features between both methods that are rather deemed central histopathological features (cellularity, fibrosis). All histopathological evaluations were done by the same expert pathologist (SB), and all cytomorphological diagnoses were made by the same expert hematologist (UG).

Based on the analysis of 128 MDS patients with regard to both cytomorphological and histopathological assessment of the bone marrow we could show that:

a) Histopathology reliably recognizes the presence of MDS but underestimates the blast count and can therefore not correctly classify MDS patients according to WHO classification.

b) On the other hand, cytomorphology cannot reliably assess bone marrow cellularity and tends to overestimate it (3–6). As the new WHO 2022 classification includes hypocellular MDS (MDS-h) (16), hematologists are now obliged to include a bone marrow trephine biopsy in their diagnostic workup of MDS.

c) When comparing the assigned MDS subtype within our cohort by WHO 2016 with the most recent WHO 2022 classification, it shows that 5,5% of patients are reassigned to the newly created subgroup of MDS-f and is constituted by patients with a former subtype of EB-1 and EB-2. Acknowledging this subtype with high prognostic significance, even in lower blast MDS as described above, is only possible when performing histopathologic assessment. All patients with hypocellular MDS, by definition, are patients of the former low blast subgroups MDS-SLD and –MLD. As in our cohort no patient apart from SF3B1 was included with MDS-defining cytogenetic or molecular aberrations such as del(5q) or biallelic TP53 there was no assignment to the respective subgroups by WHO 2022. As we classified patients according to the WHO classification, there is no shift in additional cases classified as AML as we only have cases with IB1 order IB2 and no additional AML cases as proposed in the ICC using a cut-off of more than 10%.

d) Fibrosis is an important prognostic factor in MDS that can only be assessed by histopathology. We found that fibrosis shows a positive correlation with bone marrow cellularity and the medullary blast count. The new WHO 2022 classification pays tribute to the importance of fibrosis by including MDS with myelofibrosis (MDS-f) as one of the MDS subtypes (16).

e) Dysmegakaryopoiesis seems to be another feature that is properly assessed by histopathology. We found that the degree of dysmegakaryopoiesis correlates with cellularity and unfavorable WHO categories and MDS risk groups.

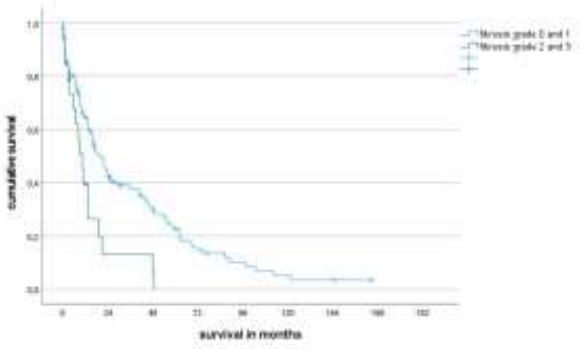

FIGURE 1
Overall survival rates of patients with fibrosis grade 2–3 vs 0–1 (median survival 10 mns vs 20 ms; p=0.004).

We consider histopathology a valuable supplement in the diagnostic workup of MDS. Superiority to a cytomorphologically assessed MDS diagnosis could not be demonstrated, mainly due to its inability to assess subtle morphological features at the level of individual cells except megakaryocytes. Nevertheless, histopathology offers complementary information regarding fibrosis and cellularity that contributes substantially to prognostic assessment. The importance of histopathology is reflected in the new WHO 2022 classification, which includes MDS types (MDS-h and MDS-f) that require histopathology for proper assessment (17).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethikkommission der Medizinischen Fakultät der Heinrich Heine Universität Duesseldorf Votum 3973 Projekt MDS Register. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by- product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

KN: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. CS: Data curation,

Methodology, Validation, Writing – review & editing. RF: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. NG: Data curation, Methodology, Validation, Writing – original draft, Writing – review & editing. SD: Data curation, Methodology, Validation, Writing – review & editing. UG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. SB: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL ARTICLE

Causes of death in 2877 patients with myelodysplastic syndromes

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Abstract Patients with myelodysplastic syndromes face a poor prognosis. The exact causes of death have not been described properly in the past. We performed a retrospective analysis of causes of death using data of 3792 patients in the Düsseldorf registry who have been followed up for a median time of 21 months. Medical files as well as death certificates were screened and primary care physicians were contacted. Death after AML evolution, infection, and bleeding was considered to be clearly disease-related. Further categories of causes of death were heart failure, other possibly disease-related reasons, such as hemochromatosis, disease-independent reasons as well as cases with unclear causes of death. Median age at the time of diagnosis was 71 years. At the time of analysis, 2877 patients (75.9 %) had deceased. In 1212 cases (42.1 %), the exact cause of death could not be ascertained. From 1665 patients with a clearly documented cause of death, 1388 patients (83.4 %) succumbed directly disease-related (AML (46.6 %), infection (27.0 %), bleeding (9.8 %)), whereas 277 patients (16.6 %) died for reasons not directly related with myelodysplastic syndromes (MDS), including 132 patients with cardiac failure, 77 non-disease-related reasons, 23 patients with solid tumors, and 45 patients with possibly disease-related causes like hemochromatosis. Correlation with IPSS, IPSS-R, and WPSS categories showed a proportional increase of disease-related causes of death with increasing IPSS/IPSS-R/WPSS risk category. Likewise, therapy-related MDS were associated with a higher percentage of disease-related causes of death than primary MDS. This reflects the increasing influence of the underlying disease on the cause of death with increasing aggressiveness of the disease.

Keywords Myelodysplastic syndromes · Causes of death · Prognosis

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Introduction

Patients with myelodysplastic syndromes (MDS) present with very heterogeneous courses of their diseases, ranging from mild anemia and a relatively good prognosis to severe cytopenia as well as increasing marrow blast percentage with significant loss of life expectancy. The prognosis of MDS patients is primarily dependant on disease-specific characteristics, i.e., the medullary blast count and chromosomal findings. Besides that, transfusion dependency [1], comorbidities [2–4], as well as low cell counts [5–9] are parameters that predict an unfavorable course of the disease [9]. Low cell counts potentially may lead to signs of bleeding and/or infections and comorbidities associated with potentially life-threatening conditions lead to a poor prognosis as well. Up to now, data on the causes of deaths in patients with myelodysplastic syndromes are sparse. A study from Texas is the only one that presents data on causes of death in a subset of patients ($n = 273$) [10]. In this study, we aimed at a better description of causes of death using the large database of the Duesseldorf MDS Registry, comprising 3792 patients.

Materials and methods

Between 1969 and 2014, 3792 patients with myelodysplastic syndromes were diagnosed at our hospital and included in our MDS Registry. Procedures are in accordance with the current version of the Helsinki Declaration. Informed consent was obtained from all patients for being included in the study. All bone marrow smears were examined by the same investigator(s) (CA and/or UG). Morphological diagnosis was made according to the FAB and current WHO 2008 classification [11, 12]. We maintained the differentiation between RCMD and RCMD-RS as proposed by the WHO 2001 classification [12]. Patients with the former MDS type of RAEB-T, as well as patients with a mixed myelodysplastic/myeloproliferative neoplasms (RARS-T, CMML I, and CMML II), were also analyzed. Patients were followed for survival and leukemic progression through December 31, 2014. The median time of follow-up was 21 months (0–449). As the initial karyotype at the time of diagnosis was available in only 1682 patients of the entire cohort, the IPSS, IPSS-R, and WPSS [2] could be described in a subset of 41.8 % (IPSS), 39 % (IPSS-R), and 26.2 % (WPSS) of the cohort, respectively.

We aimed at an exact description of the cause of death in all patients who died within the observation period. The cause of death of patients who died at our clinic was documented following the patient files and the death certificate. Patients who were not treated at our institution were followed up by contacting their primary care physicians and the hospitals where the patient had died. Again, we tried to assess the exact cause of death by the death certificates and patient files. The collection of causes of death of patients who died at home was more complicated, as the certificate of deaths were not available in many cases and the description of the cause of death often was vague. Cases where the exact cause of death was not known were grouped as "unknown cause of death."

To shed light on the group of patients with inconcise data on the exact causes of death, we performed comparative analyses with regard to MDS risk categories and the site of primary medical attendance (University clinic versus surrounding regional sites).

We grouped the well-described causes of death into different categories:

(1) Disease-related causes of death

   a. Death after development of an acute myeloid leukemia
   b. Infection
   c. Bleeding

(2) Causes of death, not necessarily related to the disease

   a. Congestive heart failure
   b. Other non-disease-related causes of death
   c. Other possibly disease-related causes of death

Outcome and leukemic evolution were calculated in months from date of diagnosis to date of the respective event. Categorical variables were analyzed by frequency tables; continuous variables were described via median (range). Time-to-event curves were calculated by the Kaplan-Meier method. Log-rank test was used for univariate comparisons. X^2 test was employed for univariate comparison cross tabulation. A p value <0.05 was considered as statistically significant. Statistical analyses were performed using SPSS for Windows (Version 22, SPSS Inc. Chicago, IL).

Results

Patient characteristics

Within the observation period, 2877 patients had deceased. Details of patient characteristics with regard to gender, age, WHO subtype, IPSS score, etc. are presented in Table 1. Median survival time of the entire cohort of deceased patients was 18 months (0–292). Seven hundred seventy-six patients (27.0 %) developed AML (medullary blasts >30 %). The actuarial risk of AML evolution 2 and 5 years after diagnosis was 28.9 and 46.9 %.

Causes of death (COD)

Within the observation period, 2877 patients (75.9 %) of all patients had died. The exact cause of death could be described in 1665 patients, whereas in 42.1 % of this cohort the exact date of death but not the exact cause of death could be assessed. For the description of the causes of death, we therefore limited the analyses of those 1665 patients.

Within the group of patients where the exact cause of death could not be ascertained, there was a statistically significant higher proportion of MDS subgroups with less than 5 % blasts at the time of diagnosis (62 versus 39.5 %). The overall survival of the cohort with an unknown cause of death showed was longer when compared to the 1665 patients with a well-documented cause of death (23 versus 16 months, $p<0.001$).

Stratified by the IPSS, the same distribution pattern was evident with 66.1 % of the cohort with an unknown cause of death in low or intermediate-1 subgroups versus 44.5 % in patients with a documented cause of death. The proportion of patients with an IPSS score available, though, was significantly lower in the first cohort (33.9 versus 44.2 %), mainly because low-risk MDS patients often were not karyotyped in the past.

The site of medical attendance is also part of the documentation within the MDS registry Duesseldorf. Patients are stratified between primary medical attendance at our University clinic and outpatient clinics or other sites in the region of North-Rhine Westfalia. When stratifying between these

Table 1 Correlation of different patient- and disease-related parameters with causes of death in percentages

		AML	Infection	Bleeding	Cardiac insufficiency	Non-disease-related	Other disease-related	*P* value
Overall group		46.6 %	27.0 %	9.8 %	7.9 %	6.0 %	2.7 %	
WHO 2008 ($n=1665$)	RCUD ($n=68$)	33.8 %	23.5 %	10.3 %	10.3 %	14.7 %	7.4 %	<0.00005
	RARS ($n=89$)	11.2 %	31.5 %	10.1 %	21.3 %	21.3 %	4.5 %	
	RCMD ($n=321$)	40.5 %	31.2 %	9.0 %	6.9 %	9.0 %	3.4 %	
	RSCMD ($n=139$)	31.7 %	36.7 %	10.8 %	11.5 %	5.8 %	3.6 %	
	5q− ($n=35$)	48.6 %	22.9 %	0.0 %	14.3 %	11.4 %	2.9 %	
	RAEB I ($n=216$)	43.5 %	31.5 %	9.3 %	6.0 %	5.6 %	4.2 %	
	RAEB II ($n=310$)	55.5 %	22.6 %	11.0 %	6.1 %	2.3 %	2.6 %	
	CMML I ($n=151$)	33.8 %	34.4 %	14.6 %	11.3 %	4.6 %	1.3 %	
	CMML II ($n=55$)	54.5 %	20.0 %	16.4 %	7.3 %	1.8 %	0.0 %	
	RAEB-T ($n=254$)	77.6 %	13.0 %	6.7 %	2.0 %	0.8 %	0.0 %	
	Unclassifiable ($n=5$)	60.0 %	40.0 %	0.0 %	0.0 %	0.0 %	0.0 %	
	RARS-T ($n=22$)	22.7 %	45.5 %	4.5 %	22.7 %	4.5 %	0.0 %	
IPSS ($n=740$)	Low ($n=87$)	44.8 %	29.9 %	5.7 %	9.2 %	5.7 %	4.6 %	<0.00005
	Int-1 ($n=245$)	52.2 %	29.8 %	8.2 %	2.9 %	3.3 %	3.7 %	
	Int-2 ($n=189$)	72.5 %	19.0 %	4.2 %	1.1 %	0.0 %	3.2 %	
	High ($n=219$)	78.1 %	12.3 %	8.2 %	1.4 %	0.0 %	0.0 %	
IPSS-R ($n=660$)	Very low ($n=30$)	40.0 %	30.0 %	6.7 %	3.3 %	10.0 %	10.0 %	<0.00005
	Low ($n=134$)	44.0 %	32.8 %	8.2 %	7.5 %	5.2 %	2.2 %	
	Intermediate ($n=176$)	63.1 %	24.4 %	4.5 %	1.7 %	2.3 %	4.0 %	
	High ($n=144$)	72.9 %	18.8 %	5.6 %	1.4 %	0 %	1.4 %	
	Very high ($n=176$)	78.4 %	13.6 %	5.1 %	0.6 %	0 %	2.3 %	
WPSS ($n=459$)	Very low	32.3 %	41.9 %	0.0 %	12.9 %	9.7 %	3.2 %	<0.00005
	Low	47.0 %	27.3 %	9.1 %	7.6 %	7.6 %	1.5 %	
	Intermediate	55.1 %	22.4 %	8.2 %	3.1 %	5.1 %	6.1 %	
	High	63.4 %	26.9 %	6.5 %	0.0 %	0.5 %	2.7 %	
	Very high	75.6 %	15.4 %	6.4 %	1.3 %	0.0 %	1.3 %	
Age (years) ($n=1665$)	<80	50.6 %	26.3 %	9.2 %	6.4 %	4.8 %	2.7 %	<0.00005
	>80	23.9 %	30.8 %	13.0 %	16.6 %	13.0 %	2.8 %	
Gender ($n=1665$)	Male	47.2 %	27.1 %	9.2 %	7.7 %	5.9 %	2.9 %	0.920
	Female	45.7 %	26.8 %	10.6 %	8.2 %	6..2 %	2.5 %	
Primary/therapy-related MDS ($n=1637$)	pMDS	46.0 %	26.9 %	9.8 %	8.5 %	6.2 %	2.6 %	0.428
	tMDS	47.3 %	31.0 %	11.6 %	3.1 %	3.9 %	3.1 %	
Hb (g/dl) ($n=1605$)	<7	41.3 %	29.4 %	14.7 %	6.9 %	6.0 %	1.8 %	0.141
	>7	46.5 %	26.9 %	9.3 %	8.4 %	6.0 %	2.9 %	
Platelets ($\times 10^6/\mu l$) ($n=1589$)	<10	43.8 %	21.9 %	15.6 %	6.3 %	9.4 %	3.1 %	0.815
	>10	46.0 %	27.4 %	9.9 %	8.2 %	5.8 %	2.7 %	
ANC (/μl) ($n=1439$)	<800	57.8 %	24.2 %	10.6 %	2.8 %	2.5 %	2.2 %	<0.00005
	>800	40.4 %	28.6 %	10.7 %	10.9 %	7.0 %	2.4 %	

two cohorts, more patients treated in Duesseldorf could be documented with a known cause of death. Nevertheless, the primary site of medical treatment had no effect on the outcome of patients. Probably due to a higher proportion of long-term surviving patients in consequence of a higher ratio of allogeneic transplantations in the cohort of patients treated in the University Clinic Duesseldorf, the median survival differed between patients treated in Duesseldorf and in the surrounding sites for patients with a known cause of death in favor of Duesseldorf patients despite a higher proportion of high-risk MDS subtypes by WHO classification in the cohort of patients treated in Duesseldorf (18 versus 14 months, $p=0.01$). Comparing known versus unknown causes of deaths and substratifying by site of primary medical attendance, the

median survival of patients with an unknown cause of death was longer irrespective of the site of primary medical care (22 versus 23 months for patients with an unknown cause of death treated in Duesseldorf versus surrounding sites, $p=0.232$). This cohort had a higher percentage of lower-risk MDS subgroups by WHO which might explain the difference in the overall outcome. The percentage of patients primarily treated in Duesseldorf increased over the time period of 45 years.

Four hundred forty-nine (27.0 %) patients died due to infection, 163 patients (9.8 %) succumbed to bleeding, and 776 patients (46.6 %) died in succession of developing AML, resulting in a total of 1388 patients (83.4 %) who died directly disease-dependent. One hundred thirty-two patients (7.9 %) died due to congestive heart failure, 100 (6.0 %) due to other non-disease-related causes, including solid tumor diseases, and 45 patients (2.7 %) succumbed to other disease-related causes.

To shed light on the exact cause of death within the group of patients that had succumbed to AML, we could clarify in a subset of 283 patients that 72.1 % died as a result of an infection, 21.6 % succumbed to bleeding complications, and in 6.4 % of these patients, congestive heart failure lead to death.

In a next step, we correlated the causes of death with patient- and disease-related parameters. Table 1 presents the results.

Age as a patient-related factor played a statistically relevant role with regards to the distribution of causes of death. Patients aged below 80 years succumbed to disease-related causes in a majority of cases, especially to AML. For patients aged over 80 years, non-disease-related causes and refractory heart insufficiency gained importance with a percentage of about 14 % of all causes of death within this group, probably due to age-related comorbidities. Gender did not have an impact on causes of death.

It becomes evident that patients with therapy-related MDS tend to succumb to a disease-related cause of death as compared to patients with a primary MDS, although statistical significance was not reached (89.9 versus 82.7 %, $p=0.08$).

When analyzing leukocyte, granulocyte, and thrombocyte counts at the time of diagnosis and correlating death due to infection or bleeding with these parameters, we were not able to demonstrate an increase in infection-related causes of death

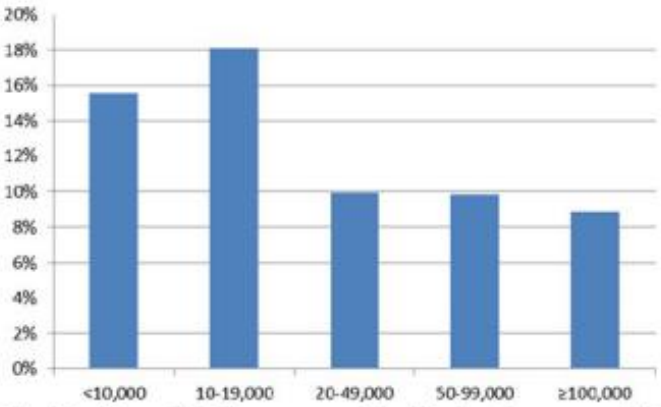

Fig. 2 Incidence of bleeding as a cause of death by thrombocyte count (/μl)

in patients with lower leukocyte or granulocyte counts at the time of diagnosis. Nevertheless, decreasing ANC levels correlated strongly with an increase in disease-related causes of death (see Fig. 1, $p<0.0001$).

This might be explained by a number of cases classified as AML-related cause of death where, in fact, infection leads to death. We therefore subanalyzed the cohort of patients that succumbed to AML. Within the subset of patients that died due to AML evolution and with further data on the exact cause of death, there was a statistically significant increase of cases that died due to infection in patients with ANC levels below 1000/μl (ANC >2000, 51 %; ANC 1000–1999, 52 %; ANC 500–999, 61 %; ANC 0–499, 63 %; $p=0.029$).

The incidence of bleeding as a cause of death correlated in that platelet levels below 20,000/μl was associated with a significantly higher incidence of bleeding than thrombocyte levels above this threshold (see Fig. 2, $p=0.041$).

With regard to hemoglobin levels at the time of diagnosis, the threshold of 10 g/dl applied in the IPSS separates two patient cohorts with a statistically significant incidence of disease-related causes of death (Hb >10, 78 % disease-related deaths; Hb <10, 75 %; $p=0.004$).

When analyzing thresholds of 9, 8, or 7 g/dl, the difference reached no significance (Hb-threshold 9 g/dl, $p=0.112$; Hb-threshold 8 g/dl, $p=0.09$; Hb-threshold 7 g/dl, $p=0.337$). Interestingly, none of the abovementioned thresholds was able

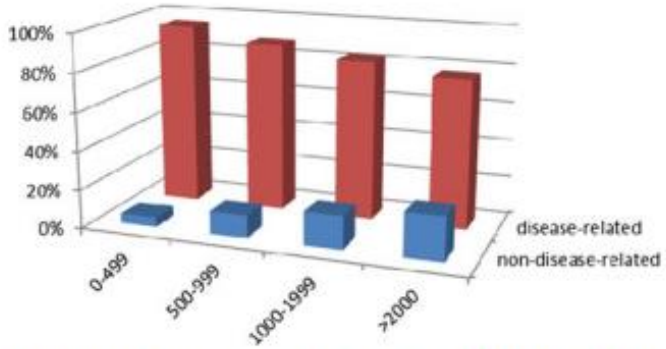

Fig. 1 Incidence of disease-related causes of death by ANC levels (/μl)

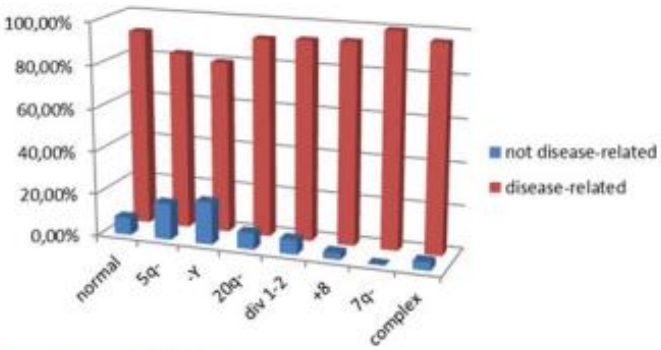

Fig. 3 Causes of death by karyotype

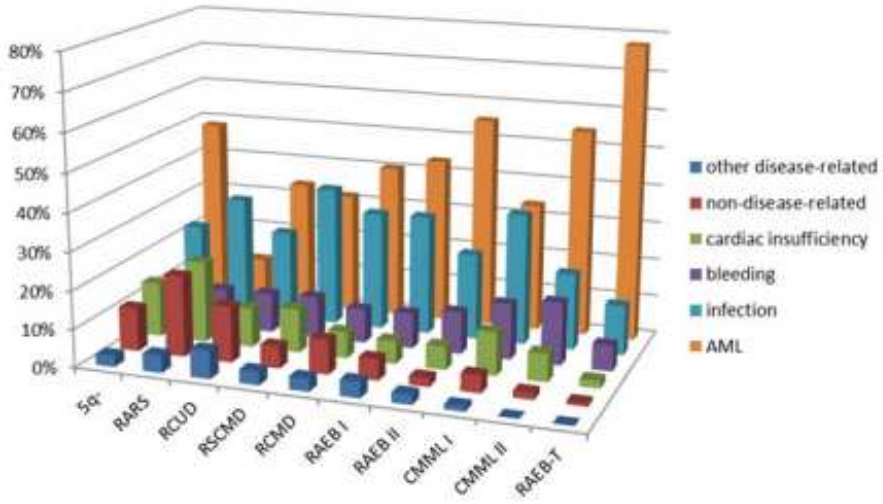

Fig. 4 Causes of death by WHO subgroup

to statistically significantly discriminate between death due to congestive heart failure and other causes of death.

Karyotype as a disease-related factor did not have a statistically significant influence on the cause of death in our MDS cohort when contrasting normal versus any type of abnormal karyotype. In spite of this finding, a subanalysis of the specific genetic alterations known in MDS could demonstrate a higher incidence of non-disease-related causes of death within the subgroups of del(5q) and loss of chromosome Y (see Fig. 3, $p < 0.0001$).

We restratified the existing karyotype information within the MDS registry according to the new IPSS-R cytogenetic risk categories. The causes of death within the patient cohort with cytogenetic information available ($n = 734$) show a trend towards a higher incidence of AML evolution within "High Risk" and "very High Risk" categories by IPSS-R cytogenetic risk groups (50 and 62.3 % for risk groups "Very Good" and "Good" versus 66.9 and 74.2 % for "Intermediate," "Poor," and "Very Poor" risk groups), though statistical significance for the overall analysis was not reached ($p = 0.056$).

When analyzed by the risk stratification according to the IPSS, an increasing incidence of disease-related causes of death with increasing risk group becomes evident.

There were striking differences between the WHO types, IPSS, IPSS-R, and WPSS risk groups with decreasing median survival, increasing rate of progression, and mortality from unilineage dysplastic types to multilineage dysplastic types and blastic types (RAEB I /II, CMML I/II, RAEB-T). Patients' causes of death within higher-risk subgroups tended towards AML as the main cause of death. Infection as cause of death was found in a relative constant percentage within the WHO or IPSS/IPSS-R subgroups (Figs. 4, 5, and 6).

When differentiating between disease-relation and disease-unrelated causes of death, patients with higher-risk MDS by IPSS, IPSS-R, or WPSS as well as patients with therapy-related MDS succumbed to disease-related causes of death in an increasing incidence (Fig. 7). Nevertheless, MDS patients succumb to disease-related causes of death in a clear majority of cases, regardless of the risk category.

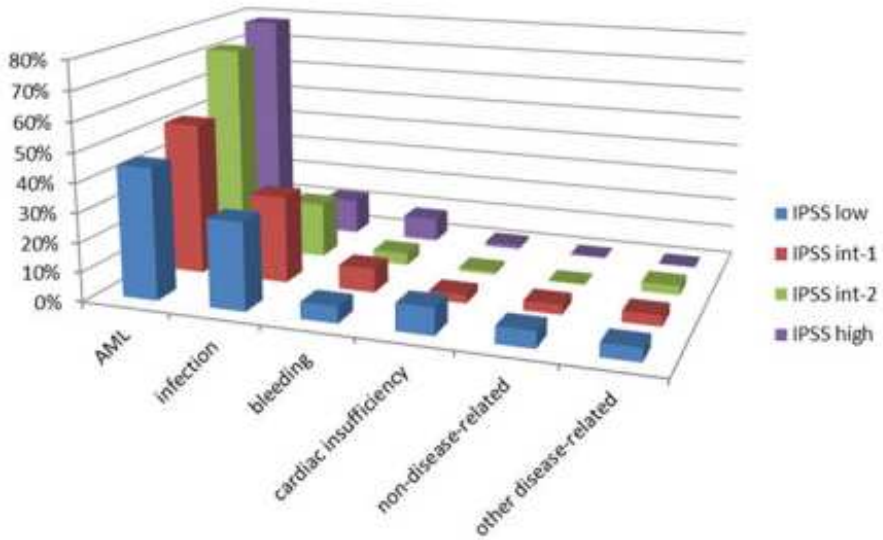

Fig. 5 Causes of death by IPSS

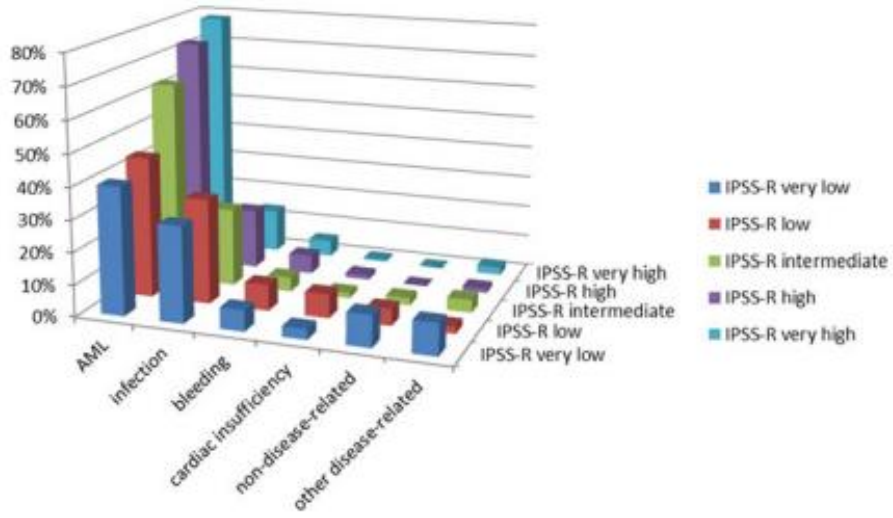

Fig. 6 Causes of death by IPSS-R

Discussion

Assessing causes of death in patients with myelodysplastic syndromes, we performed statistical analyses on patients of the MDS registry Duesseldorf. After correlating disease-related versus non-disease-related causes of death in subgroups of MDS patients according to, e.g., WHO or IPSS and IPSS-R, we also tried to analyze in detail the impact of different patient-related characteristics, such as age, cell counts, or karyotype, on the type of cause of death. These analyses were impeded by a large number of patients of the registry that were documented as unclear cause of death. Acquisition of data on the exact causes of death is often difficult due to insufficient information on the death certificate or the difficulty to obtain information on patients that died outside of the University Hospital of Duesseldorf, primarily at home.

Our data show that a majority of MDS patients succumb directly disease-related and mostly due to development into acute myeloid leukemia, infections, or bleeding. In addition, we were able to further clarify the exact cause of death in patients who developed AML in the course of their disease by exceeding the threshold of 20 % in the marrow or peripheral blood. Of 776 patients that died after the development of AML, a more detailed characterization was possible in 283 patients (36.5 %) as described in the "Results" section. Compared to the literature, our cohort demonstrated a higher percentage of patients dying after AML development. This may be due to the fact that the follow-up procedures of patients in the Duesseldorf MDS registry include a very rigid hematological follow-up by repeat differential counts and marrow examination. We potentially might therefore have detected more AML evolutions as has been described in the literature up to now. Furthermore, disease-related causes of death become more frequent in high-risk MDS subtypes regarding WHO subtype, IPSS, IPSS-R, and WPSS, but also in younger patients, as age-related comorbidities that lead to non-disease-related causes of death gain importance with increasing age, especially within low-risk MDS subgroups and within patients with primary MDS [13]. Our data within the registry supports the clinical fact that determining of causes of deaths is more difficult in low-risk MDS patients (see above mentioned data of the "Results" section). The characterization of low-risk MDS patients remains a challenge for the fact that a longer median survival time makes demonstrating a benefit by

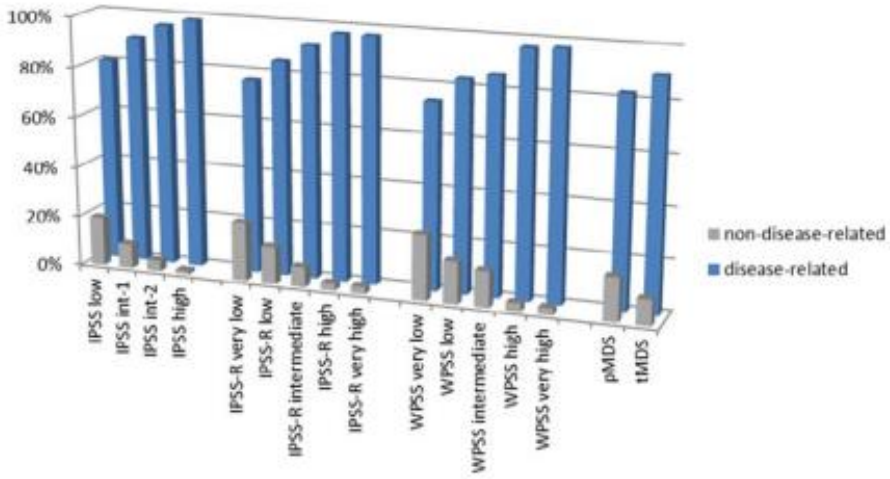

Fig. 7 Disease-relation of causes of death by IPSS, IPSS-R, WPSS, p/tMDS

therapeutic intervention difficult and the determination of the exact cause of death is often not possible, partly by follow-up difficulties when patients' supervision was continued in an outpatient setting after the initial diagnosis was made in the University clinic.

As therapy-related MDS often belong to high-risk categories, causes of death within patients with tMDS are mostly disease-related as well. The frequency of the exact cause of death within the therapy-related causes nevertheless did not differ between patients with primary versus therapy-related MDS in our analysis.

Blood counts at the time of diagnosis do not in general have an impact on causes of death. Patients with low leukocyte or granulocyte levels at the time of diagnosis did not show a higher incidence of death due to infection, irrespective of the absolute cell counts. Nevertheless, disease-related causes of death showed a higher frequency with decreasing absolute neutrophil count. Likewise, within the group of patients with AML as main cause of death, infection as exact cause of death gained importance with decreasing ANC levels. The inability to demonstrate this finding in the overall factor "infection" may be explained by (a) patient numbers and (b) difficulties in defining the exact leading cause of death in everyday clinical work. On the other hand, we could demonstrate a clear increase in bleeding as cause of death within the group of patients with low thrombocyte levels [14]. Presence of anemia, in our analyses, did not translate into higher numbers of deaths due to cardiac insufficiency but showed a higher incidence of disease-related causes of death. Low hemoglobin levels therefore probably represent a higher degree of hematopoietic insufficiency and a higher aggressiveness of the disease rather than a standalone risk factor for death due to cardiac events.

With regard to karyotype, the analysis of the specific genetic alterations had a statistically relevant impact on a higher incidence of non-disease-related causes of death in patients with 5q− syndrome and loss of chromosome Y on one side and a very high incidence of disease-related causes of death in patients with 7q−, trisomy 8, and multiple alterations on the other side, which well reflects the characteristics of the natural course of the disease for low- and high-risk karyotype groups. Gender as a patient-related factor did not have an impact on the causes of death in our analysis.

To our knowledge, only one further analysis with a smaller patient population of 273 patients focusing solely on low-risk MDS patients was published by Dayyani et al. which demonstrated a comparable distribution of disease-related versus non-disease-related causes of death [10].

In the recent publication of de Swart et al. regarding the validation of the IPSS-R in patients with lower-risk MDS of the EUMDS registry, a lower proportion of 43 % of low-risk patients deceased disease-related as compared to our data (50 % for IPSS low and intermediate 1 risk), assuming that in the ELN cohort patients with an unknown cause of death were included [15]. When subtracting patients with an unknown cause of death in our analyses, the proportion of patients with a disease-related cause of death rises up to 90.8 %. We discussed the probable documentary bias for our analyses in the "Results" section, and when considering the disease biology of low-risk MDS, it seems reasonable that low-risk MDS patients succumb to non-disease-related causes of death more frequently which could also be demonstrated in our data. Comparability of the results of the validation cohort with our analyses is impaired due to the different patient characteristics. In our overall cohort, firstly the distribution pattern of risk subgroups includes a higher percentage of high-risk MDS patients. Secondly, a higher proportion of patients had deceased at the time of our analyses, regardless of MDS risk group (76 versus 31 % in the de Swart publication) which might uncover a clearer view on low-risk MDS patients with a follow-up time long enough to demonstrate disease-related causes of death due to, e.g., progression of the disease. The most frequent causes of deaths are comparable, infection being the leading cause of death in a similar percentage in both publications (27 versus 20 %).

In summary, myelodysplastic syndromes represent a deleterious disease associated with causes of death that are directly related to the hematopoietic insufficiency which, in its impact on the prognosis, in most cases overrides the possibly underlying effects of comorbidities on the outcome of patients.

Given the considerable dominance of disease-related causes of death in MDS patients, even in low-risk MDS categories, treatment modalities therefore should aim at an improvement of cell counts, respectively the betterment of hematopoietic insufficiency, and at the prevention of disease progression into acute myeloid leukemia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Review Article

Myelodysplastic Syndromes

New Methods of Diagnosis, Prognostication, and Treatment

Kathrin Nachtkamp, Guido Kobbe, Norbert Gattermann, Ulrich Germing

Summary

Background: Myelodysplastic syndromes (MDS) are malignant diseases arising from hematopoietic stem cells. Their overall incidence is 4 cases per 100 000 persons per year, and they are usually diagnosed when evaluating cytopenia. The median survival time is three years. Myelodysplastic syndromes take a variable course; one-quarter of patients go on to develop acute leukemia.

Methods: This review is based on publications retrieved by a selective search of the literature from 2013 to 2022, including relevant guidelines, in the PubMed database. The time period was chosen to reflect developments since the publication of the latest EHA guidelines in 2013.

Results: The gold standard of diagnosis is cytomorphology of the blood and bone marrow, supplemented by banding cytogenetics, histomorphology, and somatic mutation analyses. The new classification proposed by the WHO incorporates the molecular and cytogenetic findings. The Molecular International Prognostic Scoring System (IPSS-M), which takes somatic mutations into account, is now available as an aid to prognostication. Quality of life evaluation with standardized instruments is helpful in many ways. Low-risk patients are treated supportively with erythrocyte transfusions and iron chelation therapy. Erythropoietin-a can be given to patients whose erythropoietin level is less than 200ng/mL, lenalidomide to those with a 5q deletion, and luspatercept to those with an SF3B1 mutation. High-risk patients should be evaluated as early as possible for allogeneic hematopoietic stem cell transplantation with curative intent. 5-azacytidine improves outcomes in patients for whom stem cell transplantation is not suitable.

Conclusion: Once a precise diagnosis has been established, new prognostic instruments such as the IPSS-M enable risk-adapted treatment based on the biological aspects of the patient's disease as well as his or her age and comorbidities.

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With an incidence of approximately 4 cases per 100 000 persons per year, myelodysplastic syndromes (MDS) are among the most common malignant diseases arising from stem cells. The incidence increases significantly with age. MDS are caused by genetic mutations that occur randomly and accumulate with age or are related to radiation or chemotherapy. The median age at onset is 70 to 75 years.

In the majority of cases, the etiology of the disease is unknown. However, it has been shown that patients diagnosed with clonal hematopoiesis of indeterminate potential (CHIP) based on somatic mutations, typically of the DNMT3A, TET2 and ASXL1 genes, are at a higher risk of developing MDS of about 0.5 to 1% per year. Prevalence increases with age and is estimated to be 10% at age 80 years and older. It is also known that germline mutations are more common in MDS than previously thought, in particular among younger adults (1–3). The disease is caused by genetic alterations of hematopoietic stem cells. Progressive loss of differentiation and maturation results in functional impairment of blood cells, especially of platelets and granulocytes (4–7). In many cases, this is associated with an increase in immature malignant precursor cells and an approximately 30% risk to develop acute myeloid leukemia (AML) within two years (8). Disease progression may also occur on the chromosomal level (9, 10). Besides cytomorphology, the diagnostic work-up should always include bone marrow histology, banding cytogenetics, and molecular testing for somatic mutations. Myelodysplastic syndromes take a variable course. While life expectancy is almost normal in some patients, there are also patients who develop acute leukemia within a few months and/or die from infections or hemorrhages. Thus, besides a precise diagnosis, the best possible estimation of the expected course of the disease is also relevant, as it is the basis for treatment planning. The Revised International Prognostic Scoring System (IPSS-R) or, if information about somatic mutations is available, its advanced version, the Molecular International Prognostic Scoring System (IPSS-M), is used for this purpose. Our review is based on publications retrieved by a selective search of the literature from 2013 to 2022 to reflect new developments since the last guidelines of the European Hematology Association (EHA), such as the updated WHO classification, the IPSS-molecular and new drug

BOX 1

Diagnosis of myelodysplastic syndromes/neoplasms (12, 15)

Peripheral blood (mandatory)

- White blood cell count; possibly <4000/µL
- Platelet count, possibly <100 000/µL
- Hemoglobin, almost always <12 g/dL in females, <13.5 mg/dL in males
- Reticulocyte count; usually—but not always—reduced
- Manual differential blood count (neutrophil granulocyte count, signs of dysplasia, blast percentage)
- LDH U/L (levels above normal are indicative of an unfavorable prognosis)
- Ferritin µg/L, possibly elevated
- Erythropoietin level, often increased
- Blood typing, in case transfusions are required
- **Not mandatory:** HLA typing and CMV status, if eligible for allogeneic stem cell transplantation
- **Not mandatory:** WT1 expression (if >50 indicative of a poor prognosis)

Bone marrow (mandatory)

- Cytology with staining for iron, POX and esterase staining (extent of dysplasia, blast percentage)
- Histology of a trephine biopsy (cellularity, fibrosis)
- Chromosomal analysis with analysis of 25 metaphases (chromosomal aberrations); complemented by FISH, in individual cases
- Mutation analyses (important genes: TP53, MLL, ETV6, IDH2, CBL, SF3B1, JAK2, ASLX1, RUNX1, SRSF2, U2AF1, DNMT3A, ZRSE2, EZH2, NRAS, KRAS, PDGF-a/b)
- **Not mandatory:** immunophenotyping

FISH, fluorescence in situ hybridization (FISH); human leukocyte antigen; LDH, lactate dehydrogenase; WT1, Wilms' tumor 1

approvals. From the 8876 hits, original articles, pivotal clinical studies and consensus reviews were selected, also taking into account guidelines of the German Society of Hematology and Medical Oncology (DGHO) and NCCN guidelines. Clinical relevance for physicians practicing in Germany was the criterion for selection.

Diagnosis

Patients often present with symptoms of anemia or hemorrhage or incidental abnormal routine blood count results (*Box 1*). An initial differential diagnostic evaluation to exclude iron, vitamin B12 and folate deficiencies, as well as hemolysis, among others, should be followed by special hematological tests. A normal routine blood count with differential makes bone marrow stem cell disease unlikely (11–13). Bone marrow stem cell disease must be assumed especially in patients with bi- or pancytopenia. Besides deficiency anemias and hemolysis, key differential diagnoses include toxic bone marrow damage, immune-mediated cytopenia (immune thrombocytopenia/hemolysis), aplastic anemia, hereditary bone marrow diseases, paroxysmal nocturnal hemoglobinuria, but also acute myeloid leukemia and primary myelofibrosis. It is important to take past exposure to mutagenic agents, such as chemotherapy, radiotherapy and radioiodine therapy, into account, as these increase the risk of stem cell disease. Approximately 10% of patients have therapy-related MDS. It is important to take the occupational history into account, especially in elderly patients, because in the case of exposure to benzene, for example as a painter/finisher or petrol pump attendant, MDS may be regarded as an occupational disease. The first step should be a microscopic examination of the blood to evaluate single cell morphology, since signs of granulocytic dysplasia, such as hypogranulation or pseudo-Pelger–Huët cells, may be indicative of MDS. Bone marrow cytology and bone marrow histology are mandatory. Bone marrow cytology by definition shows at least 10% cells with impaired differentiation/maturation in one, but in most cases two or all three myeloid cell lines (14). Chromosomal analysis is required for diagnostic and prognostic reasons.

Table 1 shows the proposals of the current WHO classification. What is new is that two groups of MDS types are distinguished. One group is classified according to morphology—in this case primarily using the blast percentage which is relevant for prognostication, but MDS with bone marrow fibrosis is now also included in this group due to its prognostic significance (15, 16). The second group is classified on the basis of molecular cytogenetics. In this group, specific genetic alterations determine how the disease is classified. These changes include MDS with deletion (5q), with SF3B1 gene mutation and with bi-allelic TP53 alterations (17–18). The same classification applies to therapy-related MDS (19). Another international group has proposed a similar classification that less clearly sets out the distinction of MDS from acute leukemias (20).

All defined subgroups carry prognostic significance (extent of blast excess, fibrosis, dysplasia signs, and genetic alterations). On the one hand, their relevance results from the extent of bone marrow insufficiency with increased risk of infections and bleeding, and on the other hand, from factors that increase the risk of AML development/progression of the disease (21). Consequently, there are significant differences in prognosis between these subgroups (16–18) (*Figure 1*).

Thus, more than ever before, close cooperation between cytomorphology, genetics, and pathology is required in the diagnostic workup. The preparation of an integrated report on the findings with comments, taking into account all the methods used, is crucial to ensure the treating hematologist has comprehensive information available.

Prognostication

In advanced MDS in particular, the major causes of death—i.e., infection, hemorrhage, and development of acute myeloid leukemia—are directly related to the disease (21). Numerous biological (e1) and patient-related

TABLE 1

Classification of myelodysplastic syndromes (MDS) as proposed by the WHO (15)

	Blast percentage	Banding cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated deletion (5q)	<5% bone marrow; <2% blood	Deletion (5q) isolated, or with 1 other abnormality except monosomy 7 or deletion (7q)	SF3B1 possible
MDS with low blasts and SF3B1 mutation*[1]		No deletion (5q), no monosomy 7, no complex aberrant karyotype	*SF3B1*
MDS with biallelic TP53 inactivation	Any	Typically complex aberrant	or more TP53 mutations, or 1 mutation plus evidence of copy number loss of TP53.
MDS defined by morphology*[2]			
MDS with low blasts	<5% bone marrow; <2% blood		
MDS, hypoplastic*[3]			
MDS with excess blasts			
MDS with excess blasts-1	5–9% bone marrow and/or 2–4% blood		
MDS with excess blasts-2	10–19% bone marrow and/or 5–19% blood		
MDS with fibrosis	5–19% bone marrow; 5–19% blood		

*[1] Detection of ≥ 15% ring sideroblasts can substitute for detection of an SF3B1 mutation
*[2] ≥ 10% signs of dysplasia in at least one cell line
*[3] ≤ 25% bone marrow cellularity, age-adapted –

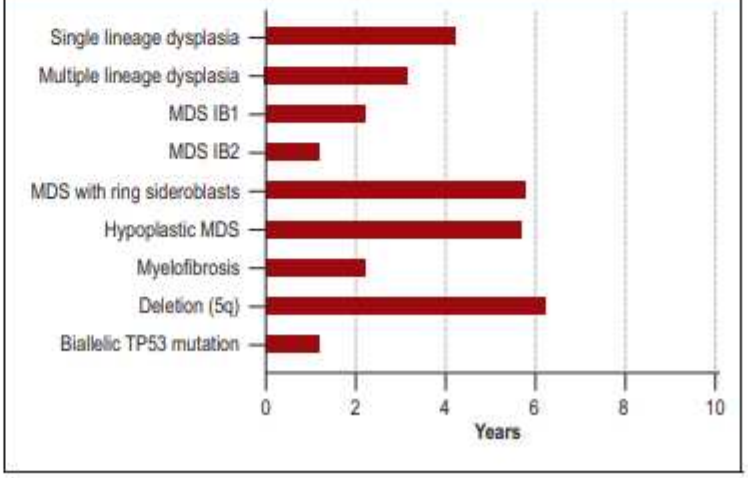
(22) prognostic parameters have been identified and prognosis scores have been developed (23–25). Over the last decade, the Revised International Prognostic Scoring System (IPSS-R) has proven to be a robust prognostication tool (*eTable 1, eFigure 1, eFigure 2*) (26, e2). This score is based on the extent of cytopenia, bone marrow blasts and chromosomal findings; it defines five risk groups. What is new is the additional consideration of results of mutation analyses obtained in the Molecular International Prognostic Scoring System (IPSS-M) in addition to the IPSS-R. The IPSS-M is a regression model solely designed for web-based use; it divides the patients into six categories that are distinct from one another. When weighting somatic mutations, their prognostic significance is taken into account, as well as the number of mutated genes (*eTable 2*). The more complete the information on mutations, the more accurate the prognostic predictive power of the model. Based on 2957 patients, this score was developed with substantial involvement of German MDS centers. As a general rule, most mutations—with the exception of the SF3B1 mutation—have an unfavorable impact on prognosis. This means that such patients must be assigned to a higher risk category and, consequently, may need the therapy indicated for this risk group. In light of the above, screening for somatic mutations is mandatory and the IPSS-M should be used whenever possible and deemed appropriate, taking into account the higher median age of the patient population and the assessed fitness for treatment.

Care and treatment

Initially, a watch-and-wait approach or supportive treatment are indicated for a large proportion of MDS patients who are not classified as high-risk MDS at the time of first diagnosis. Supportive interventions include replacement of blood products, prevention and treatment of infections and, where necessary, erythropoietin replacement therapy.

Especially for low-risk MDS, standardized instruments for quality of life assessment are valuable

FIGURE 1



Mean survival time according to WHO subtype in years; MDS, myelodysplastic syndrome

BOX 2

Parameters used to apply the IPSSmoL and entered into the web-based calculator

Data on bone marrow blasts, platelets, hemoglobin, chromosomal risk group, number of TP53 mutations, and loss of TP53 heterozygosity are mandatory; additional data make the estimation of the model more robust and valid. The IPSS-M is used to calculate the risk groups "very low", "low" , "moderate low", "moderate high", "high", and "very high".

Clinical parameters

- Bone marrow blasts in % (mandatory)
- Platelets × 100 000/µL (mandatoty)
- Hemoglobin g/dL (mandatory)
- Neutrophils × 100 000/µL
- Age

Chromosomal findings (according to the IPSS-R)

Mandatory:

Very good (−Y, del [11 q])
Good (normal, del [5q], del [12p], del [20q], double clone with del [5q] except chr 7)
Intermediate (del [7 q], + 8, + 19, i[17 q], other single or double independent clones.)
Poor (- 7, inv[3]/t[3q]/del [3 q], double clone with –7/del [7q], complex [3 aberrations])
Very poor (complex >3 aberrations)

Molecular cytogenetic findings

Mandatory:

- Number of TP53 mutations (0 versus 1 versus 2 or more)
- Loss of heterozygosity of TP53 (yes or no)
- MLL-PTD (mutated versus not mutated versus unknown)
- FLT3 (ITD or TKD) (mutated versus not mutated versus unknown)

Genes with individual weighting

Mandatory:

- ASXL1 (mutated versus not mutated versus unknown)
- CBL (mutated versus not mutated versus unknown)
- DNMT3A (mutated versus not mutated versus unknown)
- ETV6 (mutated versus not mutated versus unknown)
- EZH2 (mutated versus not mutated versus unknown)
- IDH2 (mutated versus not mutated versus unknown)
- KRAS (mutated versus not mutated versus unknown)
- NPM1 (mutated versus not mutated versus unknown)
- NRAS (mutated versus not mutated versus unknown)
- RUNX1 (mutated versus not mutated versus unknown)
- SF3B1 (mutated versus not mutated versus unknown)
- SRSF2 (mutated versus not mutated versus unknown)
- U2AF1 (mutated versus not mutated versus unknown)

Facultative:

Number of mutations among the following genes (is calculated)

- BCOR (mutated versus not mutated versus unknown)
- BCORL1 (mutated versus not mutated versus unknown)
- CEBPA (mutated versus not mutated versus unknown)
- ETNK1 (mutated versus not mutated versus unknown)
- GATA2 (mutated versus not mutated versus unknown)
- GNB1 (mutated versus not mutated versus unknown)
- IDH1 (mutated versus not mutated versus unknown)
- NF1 (mutated versus not mutated versus unknown)
- PHF6 (mutated versus not mutated versus unknown)
- PPM1D (mutated versus not mutated versus unknown)
- PRPF8 (mutated versus not mutated versus unknown)
- PTPN11 (mutated versus not mutated versus unknown)
- SETBP1 (mutated versus not mutated versus unknown)
- STAG2 (mutated versus not mutated versus unknown)
- WT1 (mutated versus not mutated versus unknown)

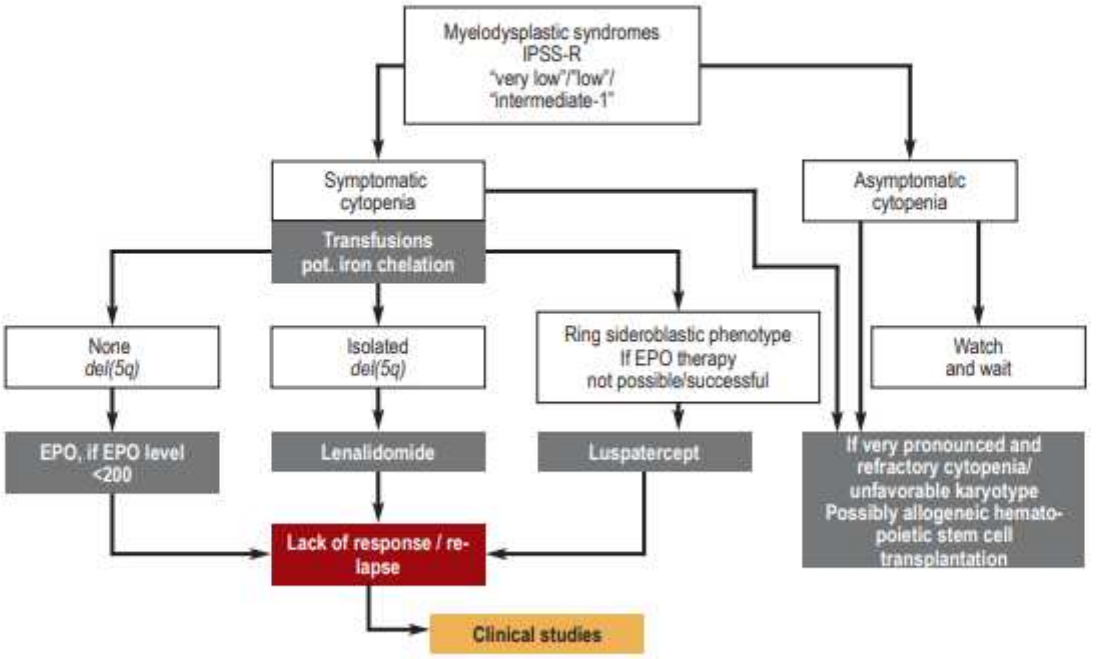
tools that also allow the treating physician to evaluate treatment success and burden, including supportive interventions. Moreover, quality-of-life-associated factors, such as fatigue, were found to have prognostic relevance. MDS-specific scoring systems (QOL-E, QUALMS) have been developed in addition to well-validated quality-of-life (QoL) instruments, such as the EQ-5D or EORTC-QLQ-C30, but still require further intensive validation (28).

Since over 80% of those affected receive regular supportive red blood cell transfusions over the course of their disease and the human body lacks the ability to excrete iron, transfusion-related iron overload is common and may result in heart failure, cardiac arrhythmias, and other organ damage (29). Therefore, if serum ferritin levels exceed 1000 ng/mL and the patient is transfusion-dependent, chelation therapy should be started to at least mitigate iron overload toxicity. The only available phase III study on iron chelation showed an improvement in prognosis with such therapy (e5, e6). In addition, blood counts improved in about 10–15% of patients and infections were found to be delayed (e7, e8).

Based on data from a double-blind multicenter randomized controlled phase III study, epoetin-α was approved for transfusion-dependent patients without excess blasts and endogenous erythropoietin levels <200 ng/mL. 85% and 68% of MDS patients with moderate transfusion requirements, classified as "very low risk" and "low risk", respectively, according to IPSS-R, respond to this treatment after a few weeks and may remain transfusion-free for years with therapy (e9, e10).

Transfusion-dependent patients with isolated deletion (5q) and no excess blasts can be treated with lenalidomide, an immunomodulatory agent. The only prospective multicenter phase II study evaluating this indication, the LE-MON-5 trial, showed that

FIGURE 2



Therapy algorithm for patients with myelodysplastic syndrome and very low, low, or intermediate risk: approved = gray (erythropoietin-alpha, Exjade, lenalidomide, luspatercept)
EPO, erythropoietin

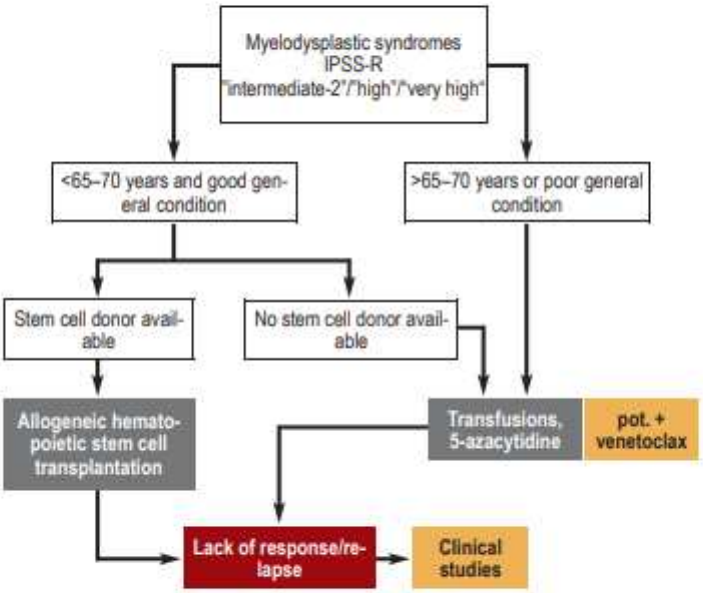
approximately two-thirds of patients become transfusion-free within four months (30) and that lenalidomide does not promote progression to AML. During the median follow-up period of 20 months, 73% of these patients did not require transfusion. Determining clone size by fluorescence in situ hybridization (FISH) in peripheral blood significantly helped to establish molecularly guided therapy (31) and to allow long breaks in therapy once transfusion-free status was achieved. Prior to initiation of therapy, screening for TP53 mutation should be performed, as in these cases a more aggressive course of the disease may be observed.

Luspatercept, a TGF-β ligand trap, has recently been approved for the treatment of transfusion-dependent patients without excess blasts but with a ring sideroblastic phenotype and/or detection of an SF3B1 mutation. It achieves transfusion-free status in 40% of patients. The agent was evaluated by the German MDS Study Group in a multicenter phase II study (32, e11). Thrombopoietin analogs may be used on a case-by-case basis for patients with thrombocytopenia to avoid transfusions of platelet concentrates and to reduce the risk of bleeding, in line with phase II data (e12–e13). Similarly, immunosuppressive therapy with anti-thymocyte globulin (ATG) can be used to improve hematopoiesis in patients with hypoplastic MDS on a case-by-case basis (e14).

Numerous new substances are being evaluated in clinical trials (www.D-MDS.de) (e15). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only therapy with curative potential. If an HLA-identical sibling or unrelated donor can be identified, allogeneic stem cell transplantation is performed after prior conditioning chemotherapy, which is bone marrow toxic and destroys the patient's own diseased hematopoietic stem cells, with the goal of achieving a graft-versus-leukemia (/MDS) effect through the transplanted immune system. Apart from acute toxicity and the risks associated with the aplasia phase after chemotherapy (especially infections, bleeding), the risk of immune diseases, which constitute a distinct clinical entity as graft-versus-host disease (GvHD), and the risk of an MDS relapse are the main factors in the further course of the disease.

When establishing the indication for allogeneic hematopoietic stem cell transplantation (alloHSCT), it is important to include disease factors as well as patient and therapeutic factors in the decision-making process. Since alloHSCT is still associated with high toxicity and consequently significant treatment-related morbidity and mortality (2-year non-relapse mortality rate of 16%) (33), primarily patients with high-risk MDS should be evaluated for this type of treatment. In individual cases, patients classified as low risk according to IPSS-R/M may also benefit from alloHSCT, if they are exposed to a high risk due to severe thrombocytopenia or neutropenia (35). It is important to note that, while alloHSCT is the only hope of cure for patients with high-risk MDS, genetic

FIGURE 3



Therapy algorithm for patients with myelodysplastic syndrome and intermediate risk (int-2), high risk or very high risk: approved gray (5-azazytidine,9 allogeneic stem cell transplantation)

TABLE 2

Most important side effects of treatment options for patients with myelodysplastic syndrome

Substance/therapy	Most important side effects
Erythropoietin	– Hypertension
Iron chelation	– Renal failure – Gastrointestinal intolerance
Lenalidomide	– Deterioration of blood count – Thrombosis – Polyneuropathy
Luspatercept	– Fatigue – Gastrointestinal intolerance – Hypertension
TPO analogs	– Thrombotic/thromboembolic events – Headache
Anti-thymocyte globulin	– Allergic reactions – Immunosuppression
Hypomethylating substances	– Blood count deterioration – Infection – Local reactions with s.c. administration
Venetoclax	– Blood count deterioration
Allogeneic peripheral hematopoietic stem cell transplantation	– Life-threatening infections/hemorrhage – Graft-versus-host disease – Toxicity of therapy

factors and/or somatic mutations, such as RUNX and TP53, which are associated with an unfavorable prognosis, still have an impact on prognosis even after alloHSCT, because post-transplant relapses are significantly more likely among those patients—for example, 61% in the 5-year estimate (33, 34).

Rather than age, comorbidities such as organ failure or chronic infections, are critical factors driving treatment-related mortality in patients with alloHSCT. Older patients are typically treated with a conditioning regimen, i.e. chemo-/immunotherapeutic agents +/- total body irradiation (TBI) administered in preparation for transplantation. In this setting, a less intensive regimen is used to reduce treatment-related mortality (TRM). In retrospective studies, however, reduced-intensity conditioning was usually associated with an increased likelihood of relapse (e16). In the absence of myeloablative conditioning, especially high-risk patients relapse significantly more frequently. Consequently, conditioning therapy should be chosen to be as intensive as is deemed acceptable in the individual patient (33, 36).

The transplant process itself consists of an intensive early phase of about six weeks, during which patients are cared for in a specialized transplant unit, and a later outpatient monitoring phase of about two years, also with close support in a specialized center. During this late phase, impending complications, such as graft-versus-host disease and infections, should be detected and treated as early as possible, and the success of therapy should be continuously monitored for minimal residual disease by means of complex diagnostic tests (for example, molecular genetic analyses). The fact that MDS relapse after alloHSCT can be successfully treated in 29–71% of cases by early therapy with hypomethylating agents and donor lymphocytes highlights the relevance of minimal residual disease monitoring (37, 38).

Pre-transplant induction chemotherapy or 5-azacytidine therapy to reduce malignant cells has long been considered indispensable, but frequently achieves disease stabilization at most (e17, e18). Studies have shown that this strategy often selects resistant MDS clones that later cause resistant relapses (e19, e20). In addition, more than 30% of these patients develop complications or experience disease progression during pre-transplant therapy, rendering transplantation impossible. Therefore, it is justified in patients with stable MDS disease to adopt an observation-only approach during the donor search and then perform an early, primary alloHSCT (39). Retrospective studies showed that post-transplant relapses can be treated very successfully, especially in this setting (9).

If a patient is not eligible for allogeneic stem cell transplantation, the hypomethylating agent 5-azacytidine can be used. In a randomized controlled phase III study, a survival benefit of about ten months was observed with 5-azacytidine treatment (e21). About half

of the patients respond to this treatment at least with an improvement in blood counts, and in some cases also with a reduction in blast percentage. A minimum treatment duration of 4–6 months is required. Patients with good response should continue 5-azacytidine treatment to stabilize its success. Unfortunately, as yet, no robust disease biology-related predictive parameters are known that would allow prediction of treatment success (e22). Various mechanisms of resistance can lead to a loss of efficacy over the course of treatment (e23). Adding the bcl-2 inhibitor venetoclax, already approved for acute myeloid leukemia (AML), appears to improve speed/duration of response, remission rate, and prognosis in patients with high-risk MDS (e24).

New agents and combination therapies are currently undergoing clinical trials in patients with high-risk MDS (CPX351, venetoclax, magrolimab, sabatolimab, etc.).

Treatment of high-risk patients with classical induction chemotherapy, as used in AML, can no longer be recommended because remission rates are low, remission duration is short, and long-term outcomes are extremely disappointing (e25). *eFigure 3* shows the survival curves of high-risk patients (IPSS-R risk groups "intermediate", "high" and "very high") by treatment. Patients receiving supportive therapy alone have a mean survival of only 18 months; therapy with 5-azacytidine improves prognosis by a median of six months, but only those who could undergo alloHSCT have a significantly better long-term prognosis.

Figure 2 and *Figure 3* show updated treatment algorithms for patients with low risk and high risk, respectively; *Table 2* highlights important side effects. It is useful to perform a detailed diagnostic work-up, including a molecular genetic analysis, to be able to offer the most appropriate therapy to each individual patient, considering new prognostic tools (IPSS-M) and in some cases new targeted treatment strategies. Over the course of the disease of an individual MDS patient, the indication for treatment may change or existing therapies may be switched. Moreover, approved treatment options are often exhausted over the course of the disease. These patients, in particular, can benefit from being seen in an MDS center, where new agents or combination therapies are being evaluated in clinical trials. We go to great lengths to design studies that address the clinical needs of as many patients as possible. Unfortunately, inappropriate inclusion and exclusion criteria mean that only a minority of patients are eligible for participation in a great number of clinical trials (40). The German MDS study group coordinates clinical trials for this purpose. In addition, there is close cooperation between the centers, numerous hospitals, medical care centers (MVZs) and hematology practices within the framework of the MDS registry funded by German Cancer Aid and the MDS Biobank in Düsseldorf which provides data and material for numerous scientific projects.

Conflict of interest statement

N.G. received financial support from Takeda. For his participation on Advisory Boards, he received honoraria from Novartis and BMS. He received lecture fees from BMS and Novartis. He received congress fees from Abbvie.

U.G. received lecture fees from Celgene, Novartis, BMS, Janssen, and Abbvie. He received consultancy fees from Celgene.

G.K. received honoraria from MSD, Pfizer, Amgen, Novartis, Gilead, BMS-Celgene, Abbvie, Biotest, Takeda, Eurocept, Jazz, Medac, and Eurocept. He received lecture fees from MSD, Pfizer, Amgen, Novartis, Gilead, BMS-Celgene, Abbvie, Biotest, Takeda, Eurocept, and Jazz.

K.N. received lecture fees from Jazz.

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► Supplementary material

eReferences, eTables, eFigures:
www.aerzteblatt-international.de/m2023.0005

Supplementary material to:

Myelodysplastic Syndromes

New Methods of Diagnosis, Prognostication, and Treatment

by Kathrin Nachtkamp, Guido Kobbe, Norbert Gattermann, and Ulrich Germing

Dtsch Arztebl Int 2023; 120: 203–10. DOI: 10.3238/arztebl.m2023.0005

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eTABLE 1

Definition of the Revised International Prognostic Scoring System (IPSS-R) (26)

	0	0.5	1	1.5	2	3	4
Karyotype	*1		*2		*3	*4	*5
Blasts (%)	≤ 2		> 2 ≤ 5		5–10	> 10	
Hb concentration (g/dL)	≥ 10		8 ≤ 10	< 8			
Platelets (/nL)	≥ 100	50 ≤ 100	< 50				
Neutrophils (/nL)	≥ 0.8	< 0.8					

Risk score	Points	Median survival (years)
"very low risk"	≤ 1.5	9.00
"low risk"	2–3	5.63
"intermediate risk"	3.5–4.5	2.63
"high risk"	5–6	1.28
"very low risk"	> 6	0.85

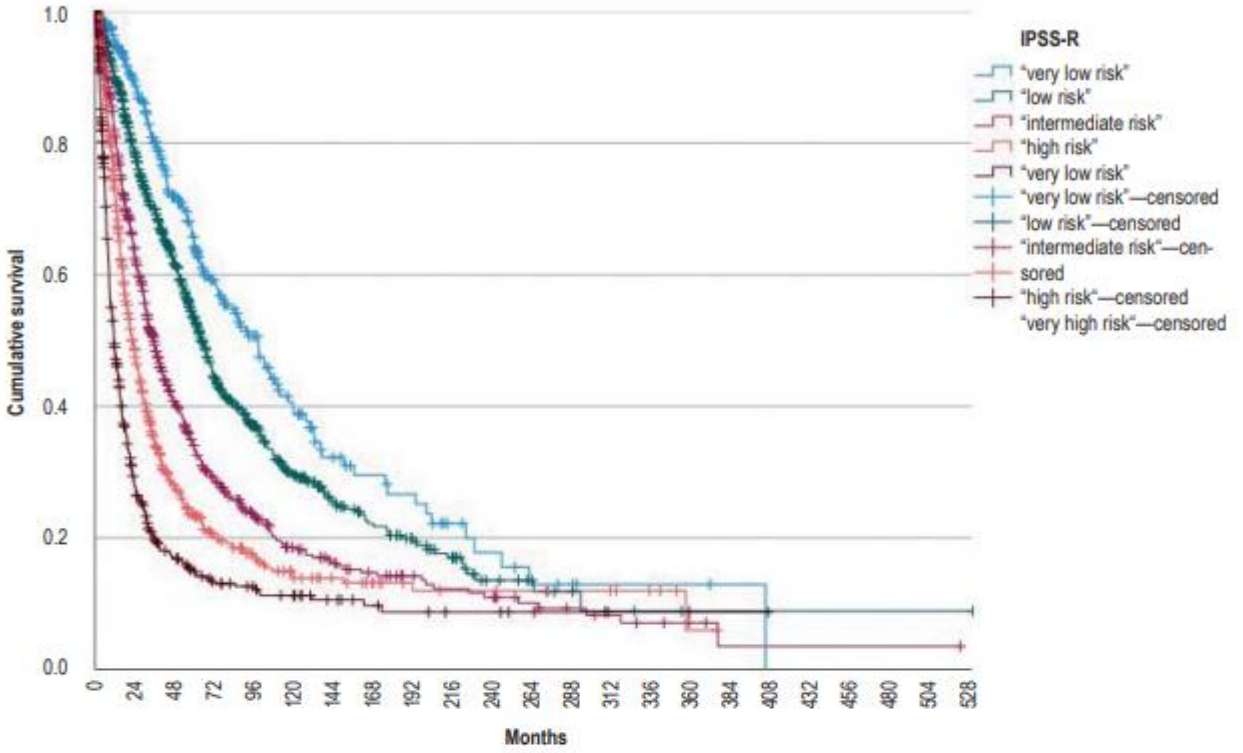
*1 Very good (–Y, del[11q])
*2 Good (normal, del[5q], del[12p], del[20q], double clone with del[5q] except chromosome 7)
*3 Intermediate (del[7q], +8, +19, i[17q], other single or double clones)
*4 Poor (-7, inv(3)/t(3q)/del(3q), double clone with –7/del(7q), complex with max. 3 aberrations)
*5 Very poor (complex with more than 3 aberrations)

eTABLE 2

Important somatic mutations in myelodysplastic syndromes

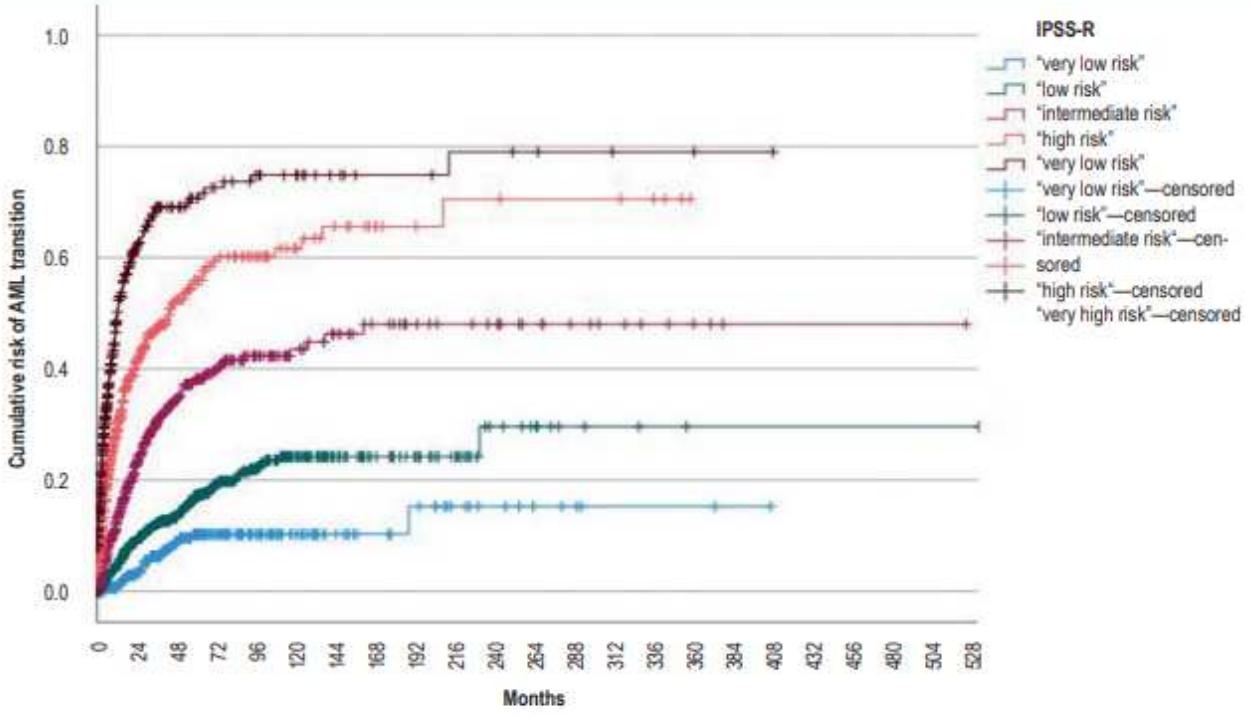
Function	Gene	Prognosis	Approx. percentage
Splicing	*SF3B1*	Good	15–30%
	SRSF2	Poor	5–10%
	USAF1	Poor	5–10%
	ZRSR2	Indifferent	5%
Transcription factor	*RUNX1*	Poor	5–10%
	TP53	Poor	5–10%
	BCOR	Poor	5%
	ETV6	Poor	3%
Methylation	*DNMT3A*	Poor	5–10%
	TET2	Indifferent	15–25%
Histone modification	*IDH1/IDH2*	Indifferent	5%
	ASXL1	Poor	10–20%
	EZH2	Poor	3–5%
	MLL	Poor	3%
Signaling	*NRAS/KRAS*	Poor	5–10%
	CBL	Poor	5%

eFIGURE 1



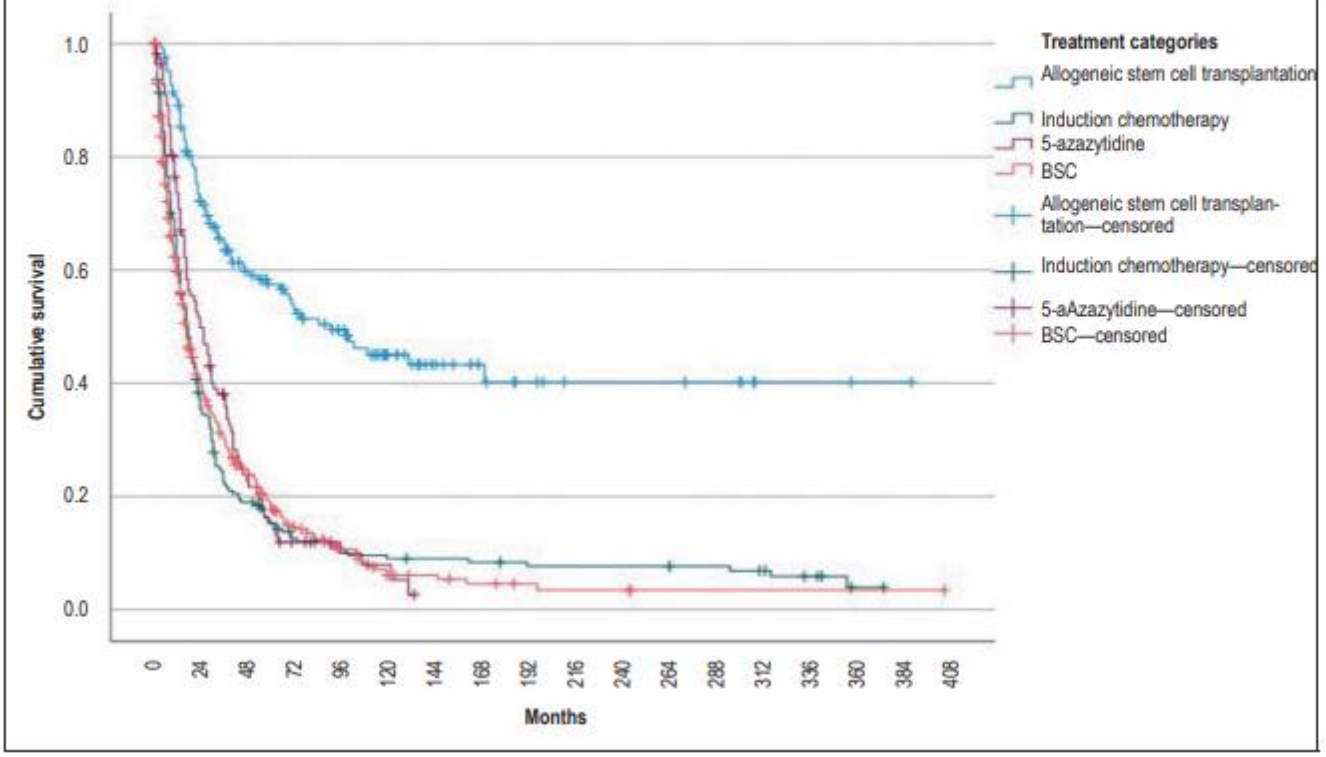
Survival curves of the different risk groups according to the IPSS-R. Mean survival of all patients 34 months, mean survival of IPSS-R risk groups: blue: "very low": 98 months, green: "low": 61 months, red: "intermediate": 31 months, orange: "high": 23 months, brown: "very high risk": 10 months, $p<0.00005$, (n= 2694, data from the Düsseldorf MDS Registry).

eFIGURE 2



Cumulative risks for AML transition of the various risk groups according to IPSS-R, blue: "very low": green: "low", red: "intermediate", orange: "high", brown: "very high", $p<0.00005$ ($n = 2694$, data from the Düsseldorf MDS Registry). AML, acute myeloid leukemia; MDS, myelodysplastic syndromes

eFIGURE 3



Survival curves of patients with "intermediate", "high" and "very high risk" after IPSSR, according to therapy, mean survival time of all patients 20 months, mean survival time with "best supportive care" 18 months, with induction chemotherapy 18 months, with therapy with 5-azacytidine, 24 months and with allogeneic stem cell transplantation 96 months, $p<0.0005$ (n = 887, data from the Düsseldorf MDS Registry). BSC, best supportive care; MDS, myelodysplastic syndromes

Questions on the article in issue 12/2023:

Myelodysplastic Syndromes

cme plus+

New Methods of Diagnosis, Prognostication, and Treatment

The submission deadline is 23 March 2024. Only one answer is possible per question.
Please select the answer that is most appropriate.

Question 1

In what age range is the median age of onset for myelodysplastic syndromes?

a) 40–45 years
b) 50–55 years
c) 60–65 years
d) 70–75 years
e) 80–85 years

Question 2

Elevation of which of the following blood parameters (from peripheral blood) may indicate the presence of myelodysplastic syndrome/myelodysplastic neoplasia?

a) White blood cell count
b) Hemoglobin
c) Ferritin
d) Reticulocyte count
e) Platelet count

Question 3

From what percentage of cells with signs of impaired differentiation or maturation in bone marrow cytology is the diagnosis of MDS assumed by definition?

a) 5%
b) 10%
c) 20%
d) 35%
e) 70%

Question 4

For which genotype does the text describe the option of treatment with lenalidomide?

a) Isolated deletion 5q
b) Isolated SF3B1 mutation
c) Isolated TP53 mutation
d) Isolated NRAS mutation
e) Isolated deletion KRAS

Question 5

Median survival is less than 2 years for which of the following WHO subtypes of MDS?

a) MDS IB1
b) Deletion 5q
c) Hypoplastic MDS
d) MDS with ring sideroblasts
e) Biallelic TP53 mutation

Question 6

Of the following genes, which is an exception in that it is associated with a comparatively favorable prognosis according to the IPSS-M score?

a) NRAS
b) RUNX1
c) USAF1
d) SF3B1
e) CBL

Question 7

In which situation does the text recommend starting chelation therapy?

a) Whenever a transfusion therapy is started
b) In patients with serum ferritin levels >1000 ng/mL
c) In patients with erythropoietin replacement therapy
d) In patients treated with luspatercept
e) In patients with low red blood cell count

Question 8

In the article, the use of which drug is described to improve prognosis in patients with high-risk MDS who are not eligible for allogeneic stem cell therapy?

a) Lenalidomide
b) Sabatolimab
c) Gefitinib
d) 5-azacytidine
e) Tamoxifen

Question 9

According to the text, what percentage of patients with MDS have therapy-related MDS?

a) approx. 0.5%
b) approx. 5%
c) approx. 10%
d) approx. 20%
e) approx. 35%

Question 10

In the text, which substance is mentioned for the treatment of SF3B1 mutations?

a) Lenalidomide
b) Luspatercept
c) Exjade
d) Tamoxifen
e) Cisplatin

LETTER OPEN

Check for updates

MYELODYSPLASTIC NEOPLASM

The new WHO 2022 and ICC proposals for the classification of myelodysplastic neoplasms. Validation based on the Düsseldorf MDS Registry and proposals for a merged classification

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TO THE EDITOR:

After the French–American–British (FAB) group first described different types of myelodysplastic neoplasms (MDS) in 1982, refined classifications of MDS were proposed by the WHO in 2001, 2008 and 2016, defining minimal diagnostic criteria for MDS [1]. In 2021, a new approach was taken by focusing on genetic aberrations and integrating morphologic features that had not been harnessed previously [2]. In parallel, an international working group independently proposed another refined classification of myeloid neoplasms (international consensus classification, ICC) [3]. The large data base of the Düsseldorf MDS Registry has repeatedly served to validate MDS classifications [4–6]. This we used to validate both classifications in terms of clinical applicability and prognostic impact.

5010 patients in the Düsseldorf MDS Registry diagnosed between 1982 and 2021 as well as 690 patients with acute myeloid leukemia (AML) and myelodysplasia-related changes were used as a comparator for the WHO 2022 category of MDS-IB2. For all patients, central cytomorphological review was performed in our laboratory according to the criteria of the different WHO classifications. It was therefore not difficult to assign cases to the newly proposed categories. In the observation period until Dec 31, 2022, 63% of the patients died, 20.3% developed AML, and 5% were lost to follow-up.

Median age at diagnosis was 71 years (18–104) in the overall study population. Median age was significantly lower in patients diagnosed as MDS with fibrosis (MDS-f) and MDS del(5q). 44% were females. 355 patients (6.2%) were diagnosed as myeloid neoplasm post cytotoxic therapy.

Supplementary Table 1 presents clinical, haematological, and genetic characteristics of the WHO MDS subtypes. The lowest blood cell counts were seen in MDS-f. Remarkably, hematopoietic insufficiency was more pronounced in MDS-f than in MDS-IB1 and MDS-IB2.

Patients with ring sideroblasts (RS) were found in all WHO-defined subtypes but, by definition, mainly in the *SF3B1*-mutated group. The highest percentage of complex karyotypes was detected in MDS-bi*TP53*, followed by MDS-f. *TP53* mutations were, apart from MDS-bi*TP53* patients, also found as monoallelic aberration in all other MDS types, particularly in MDS-f. The highest percentage of peripheral blasts was seen in MDS-bi*TP53* and MDS-f.

There was a clear difference regarding hematopoietic insufficiency and the detectability of chromosomal aberrations between single- and multilineage dysplasia. This difference was also found in patients with RS and/or *SF3B1*-mutation (Supplementary Fig. 1/3A).

Increasing marrow blast percentage and karyotype complexity correlated with the likelihood of AML-progression and the poorest median survival and was highest in MDS-bi*TP53* and MDS-f. Six hundred ninety patients diagnosed as AML-MRC presented with the lowest blood cell counts, the highest percentage of PB blasts, but less complex karyotypes compared to MDS-bi*TP53* and MDS-f.

Supplementary Table 2 shows the prognostic significance of defining parameters used in WHO 2022 in terms of OS and risk of AML development. Figure 1A–D demonstrates the respective Kaplan–Meier curves. Supplementary Fig. 3A presents further prognostic analyses of MDS types.

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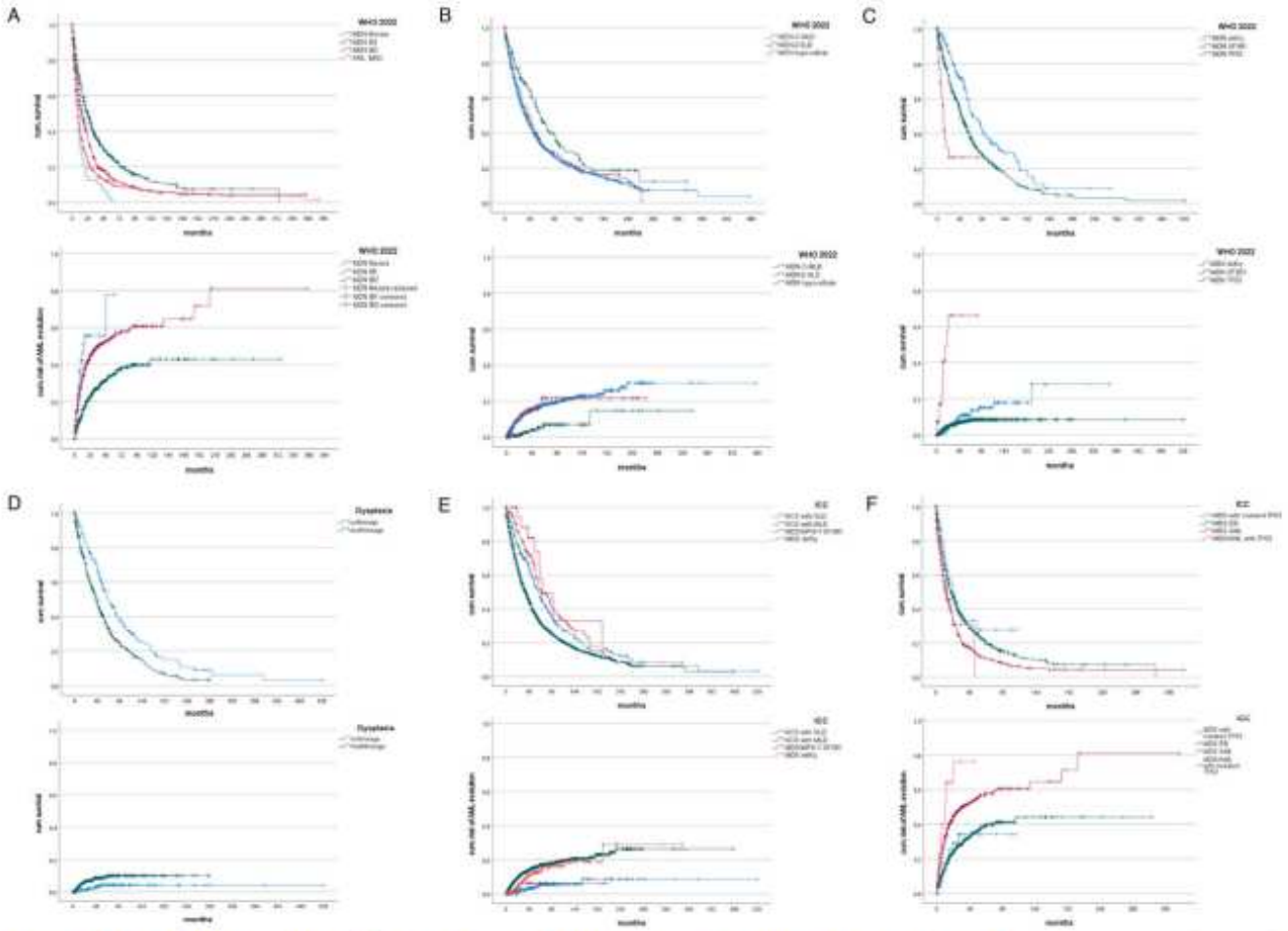

Fig. 1 OS and risk of AML evolution of selected MDS subgroups according to WHO 2022 and ICC. A WHO 2022: Overall survival and cumulative AML evolution of patients with increased blasts (IB1, IB2, fibrosis) ($p < 0.0005$, $p < 0.0005$). **B** WHO 2022: Overall survival and cumulative AML evolution of patients with low blast count (SLD, MLD, hypocellular MDS) ($p = 0.006$, p0.002). **C** Overall survival and cumulative AML evolution of patients with genetically defined MDS ($p < 0.00005$, <0.00005). **D** Overall survival and cumulative AML evolution of patients with SF3B1 mutation and/or ringsideroblastic phenotype according to lineage dysplasia ($p < 0.00005$, <0.00005). **E** ICC: Overall survival and cumulative AML evolution of patients less than 5% medullary blasts ($p < 0.00005$, <0.00005). **F** ICC: Overall survival and cumulative AML evolution of patients more than 4% medullary blasts ($p < 0.00005$, <0.00005).

Fibrosis grade 2 or 3 was identified in 11% of patients with MDS-IB1/-IB2. Although the database of patients with reliable information on fibrosis was substantially smaller than the entire cohort, the median OS estimates for MDS-IB1 (20 months), MDS-IB2 (17 months), and MDS-f (9 months) were very similar to the respective estimates in the entire cohort.

Multivariate analyses of the prognostic parameters used in the WHO 2022 classification demonstrated, within the restricted database of patients with stringent applicability of WHO and ICC, *TP53* mutational status and multilineage dysplasia were independently associated with poor outcome. We then analysed patients lacking data on fibrosis and cellularity. Again, *TP53* mutation immediately appeared in the regression model, followed by marrow blast percentage and karyotype according to IPSS-R, indicating that these parameters are independently associated with a poor outcome (Supplementary Table 3).

In Supplementary Table 4, clinical, haematological, and genetical characteristics of the different ICC subgroups are given. The del(5q) group was almost identical with the respective WHO type. The *SF3B1* group was significantly smaller, since patients with RS without known *SF3B1* mutation status were allocated to NOS-SLD and NOS-MLD, enlarging those groups. MDS-IB2 according to the WHO 2022 classification corresponded to MDS/AML in the ICC. Patients harbouring a *TP53* mutation were categorized separately. Not surprisingly, these patients more often presented with a complex karyotype. MDS with mutated *TP53* showed the highest cumulative risk of AML development and the poorest survival. Interestingly, median OS and risk of AML did not differ significantly between MDS with mutated *TP53* and MDS/AML with mutated *TP53*. Figure 1E, F presents the Kaplan–Meier curves for OS and AML development.

Supplementary Fig. 2A/B illustrates how patients formerly classified according to WHO 2016 are re-distributed among the new WHO 2022 classification and ICC.

The proposed WHO 2022 classification of MDS requires complex diagnostics but offers a very useful update of morphologically or genetically defined subtypes with prognostic impact. The first definition of a purely molecularly defined MDS type, namely MDS-bi*TP53*, was not triggered by a genotype-phenotype correlation but solely by prognostic considerations, partly due to the highest risk of progression to acute leukemia [7–9]. This genetically defined MDS type is thus clinically justified. To identify these patients, chromosomal analysis is always required, preferentially supplemented by fluorescence in-situ hybridization. Importantly, biallelic *TP53* alteration can only be recognized if next-generation sequencing is performed.

The WHO developed additional morphologically defined MDS types. MDS-f has been introduced, which includes patients from the former MDS-EB1 and -EB2 groups and is characterized by younger age at diagnosis, a preponderance of males, and more

A

Type	Median survival	progression to AML %
A) Genetically defined:		
1) MDS del(5q):	76	12
2) MDS SF3B1/RS		
Type 1: multilineage dysplasia		
a) with SF3B1 mutation	114	2
b) without SF3B1 mutation	40	8
Type 2: unilineage dysplasia		
a) with SF3B1 mutation	223	2
b) without SF3B1 mutation	65	6
3) MDS with biallelic TP53 alteration:	12	39
4) MDS-IB1, MDS-IB-2, MDS-F with monoallelic TP53 alteration	14	36

Type	Median survival	progression to AML %
B) Morphologically defined:		
1) MDS-LB-SLD	69	4
2) MDS-LB-MLD	41	11
3) MDS, hypoplastic	45	13
4) MDS-IB1	24	19
5) MDS-IB2	15	32
6) MDS-F	9	37

B

MDS, genetically defined, no AML-defining cytogenetic or molecular finding (NPM1, bZIP CEBPA)

1) **MDS del(5q)**
PB blasts <2%, BM blasts <5%, uni or multilineage dysplasia, del(5q) either isolated or with one other non-chromosome-7 aberration, no biTP53 alteration
- Provisional subtype: with SF3B1/RS
- Provisional subtype: with TP53 monoallelic

2) **MDS with SF3B1/RS**
PB blasts <2%, BM blasts <5%, SF3B1 mutation VAF >2%, uni or multilineage dysplasia, no del(5q) no chromosome 7 aberration, no complex karyotype, no biTP53alteration, no RUNX1 mutation,
Type 1: multilineage dysplasia
a) with SF3B1 mutation
b) without SF3B1 mutation or unknown mutational status
Type 2: unilineage dysplasia
a) with SF3B1 mutation
b) without SF3B1 mutation or unknown mutational status

3) **MDS with biallelic TP53 alteration**
PB blasts <20%, BM blasts <20%, presence of biTP53 alteration

4) **MDS-IB1, MDS-IB-2, MDS-F, with monoallelic TP53 alteration** (VAF >10%)

MDS, morphologically defined, no AML-defining cytogenetic or molecular finding (NPM1, bZIP CEBPA)

1) **MDS-LB-SLD**
PB blasts <2%, BM blasts <5%, unilineage dysplasia, no del(5q), no SF3B1 mutation, ring sideroblasts <15%, no biTP53 alteration, no hypocellularity

2) **MDS-LB-MLD**
PB blasts <2%, BM blasts <5%, multilineage dysplasia, no del(5q), no SF3B1 mutation, ring sideroblasts <15%, no biTP53 alteration, no hypocellularity

3) **Hypoplastic MDS**
PB blasts <2%, BM blasts <5%, uni- or multilineage dysplasia, no del(5q), no SF3B1 mutation, ring sideroblasts <15%, no biTP53 alteration, histologically proven hypocellularity

4) **MDS-IB1**
PB blasts <5%, BM blasts 5-9%, no biTP53 alteration, no TP53 alteration (or VAF <10%)

5) **MDS-IB2**
PB blasts <19%, BM blasts 10-19%, no biTP53 alteration, no TP53 alteration (or VAF <10%)

6) **MDS-F**
PB blasts <19%, BM blasts 5-19%, fibrosis Grade 2-3, no biTP53 alteration

Fig. 2 Merged classification for MDS. A Median survival and proportion of AML transformation of MDS types according to the merged MDS classification. **B** Proposals for a merged MDS classification.

pronounced cytopenias. Since hematopoietic insufficiency is severe, prognosis is poor. This has been consistently demonstrated [10, 11] and our own data corroborate these findings. MDS-f can only be diagnosed if a bone marrow biopsy is performed.

This is also mandatory to recognize hypocellularity. Schemenau [12] and Nachtkamp [13] demonstrated that cytomorphology is inferior to histopathological assessment. MDS with hypocellularity has not yet been associated with cytogenetic or molecular features but the clinical observation of a relatively good prognosis and a chance to respond to immunosuppressive therapy justifies recognition as a separate MDS type.

These two histopathological features are not intended as overruling criteria. An overlap of genetically and morphologically defined subtypes is unavoidable. Accordingly, a hierarchy of classification criteria is implicit in the WHO classification. The overruling criterion is biallelic *TP53* mutation, followed by the medullary blast percentage. Next-level criteria in low-blast MDS are del(5q) and *SF3B1* gene mutations. Del(5q) weighs heavier than *SF3B1*, as was the case in 10% of patients with del(5q) in our study population.

While the WHO 2022 classification maintains single- vs. multilineage dysplasia as an optional criterion in MDS with low blast count, this criterion has been abandoned in MDS with *SF3B1* mutation as Malcovati [14] reported this distinction lacked prognostic impact. In contrast, our data indicate prognostic relevance if all patients with ≥15% RS are included, irrespective of *SF3B1* mutation status. In our cohort we had a considerable number of such cases with long-term follow-up. We found that MLD-RS has a significantly worse prognosis because, in contrast to SLD-RS, it includes patients with marked thrombocytopenia and/or granulocytopenia with a higher risk of disease-related complications, but also with a higher risk of AML evolution as shown in Fig. 1D.

Validating the ICC in our patient population, ICC-defined MDS types are also clearly distinguishable in terms of prognosis. The ICC subdivides an MDS/AML group according to *TP53* status, which is comprehensible because of the prognostic impact of *TP53* alterations, particularly if biallelic [9]. The difficult question of where MDS ends and where AML begins is handled by the ICC through introducing MDS/AML (10–19% blasts). However, all larger studies show that MDS-IB2 have a better prognosis than patients with >19% blasts and may indeed include long-term survivors [15]. The term MDS/AML according to the ICC may imply that patients in this group must be treated like patients with AML. We think that this would be misleading and could trigger harmful therapy decisions, thus support maintaining the 20% blast cutoff to define AML.

In our view, a disadvantage of the ICC is its omission of histopathology, namely cellularity and fibrosis. Aforementioned results underscore that they should receive appropriate attention.

Dealing with two competing MDS classifications is somewhat cumbersome and complicates the design and comparability of clinical trials. A situation hampering progress in clinical research should be remedied. We would like to suggest how a merger might be possible. A few adaptations regarding the classification criteria may harness the strengths of both classifications as outlined in Fig. 2B. Applying the merged classification to our cohort yielded good separation in terms of OS and risk of AML transformation (Fig. 2A/Supplementary Fig. 3B).

The Düsseldorf MDS Registry demonstrates both classifications categorize genetically and morphologically well-defined subtypes with prognostic relevance. We postulate the WHO 2022 classification offers clearer definitions and, by including histopathology, addresses features of MDS possibly having been underestimated so far and requiring further analysis regarding their molecular causes. Finally, our proposals for a merger may help to develop a re-unified MDS classification that could foster clinical research by facilitating the design and comparability of clinical trials.

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AUTHOR CONTRIBUTIONS

KN and UG designed the study, performed statistical analyses and wrote the manuscript. KN, NG and UG performed development of methodology and writing, review and revision of the paper. MV collected data and performed statistical analyses. JB performed statistical analyses. CS, AK, DH, CG, BH, BB, AG, CA, SB, WH, MP, PV, ML, MS, MR, RS, OK, KG, AK, FS, SD and GK collected data. DH, CG, BH and BB provided genetical analyses. MS and MR provided histopathological data. All authors read and approved the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Impact on survival of different treatments for myelodysplastic syndromes (MDS)

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ABSTRACT

Therapies for myelodysplastic syndromes (MDS) often achieve hematological responses but their impact on overall survival has generally not been evaluated. The Duesseldorf MDS Registry allowed us to perform matched-pair analyses to assess a possible survival benefit of treatment with thalidomide, valproic acid, low-dose Ara-C, antithymocyte globulin (ATG), induction chemotherapy, or allogeneic stem cell transplantation (allo-SCT). For all treatment modalities, lengthening of survival was restricted to certain subgroups of patients. With the exception of allo-SCT, MDS treatment was generally palliative. Recently, epigenetic treatment with demethylating agents proved to be the first therapy that can significantly prolong survival in patients with higher-risk MDS.

1. Introduction

Based on morphological findings in the blood and bone marrow as well as results of cytogenetic analysis, the World Health Organization (WHO) has defined eight types of MDS [1–3]. Our current knowledge regarding their prognosis is based on the course of disease in patients receiving best supportive care only [2]. If therapy goes beyond BSC, patients require individualized, risk-adapted decisions weighing aggressiveness of disease type against possible treatment-related toxicity. However, the prognostic impact of various treatment approaches needs further clarification [4–9] because clinical trials, with few exceptions, usually concentrated on hematological improvement and/or decreased transfusion needs [10–18].

Significantly prolonged survival was demonstrated by three prospective randomized trials of epigenetic treatment in patients with high-risk MDS. In comparison to BSC, epigenetic treatment with 5-azacytidine or decitabine achieved an increase in median survival between 4 and 9.5 months [4–7]. Phase-III-studies of similar quality are not available for many other treatment modalities used in MDS. On the basis of the Duesseldorf MDS Registry, which included more than 3000 patients since its opening in 1982, we performed a matched-pair analysis to compare best supportive care with a variety of other treatments, namely thalidomide, valproic acid, low-dose Ara-C, antithymocyte globulin (ATG), cytotoxic chemotherapy, and allogeneic stem cell transplantation following myeloablative conditioning.

2. Patients and methods

The Duesseldorf MDS Registry currently features a total of 3058 patients, 2449 of whom received BSC only, which included transfusion of red blood cells and/or platelets, antibiotic, antifungal, and antiviral agents, as well as administration of erythropoietin in patients with inadequate endogenous Epo levels.

The following drugs and treatment modalities were evaluated: thalidomide ($n = 55$), valproic acid ($n = 76$), low-dose Ara-C ($n = 65$), immunosuppressive treatment with antithymocyte globulin (ATG) ($n = 17$), intensive chemotherapy ($n = 172$), and allogeneic blood stem cell transplantation ($n = 39$). For the matching procedure, the following parameters were taken into account: age (±5 years), gender, blood cell counts, WHO type, International Prognostic Scoring System (IPSS) category, and IPSS cytogenetic risk group. Patients without karyotype analysis at the time of diagnosis were matched according to the Duesseldorf Score [19]. Matching was performed without weighing the year in which the diagnosis of MDS was made, since the natural course of MDS showed no significant difference between 1970 and 2005.

We are aware of the problem of choosing appropriate matching partners for patients with a long interval between diagnosis and start of therapy. Such patients may have a rather benign type of disease. This potential selection bias is particularly relevant for low-risk MDS, whereas patients with high-risk MDS who are candidates for intensive chemotherapy usually start such treatment within four weeks after diagnosis.

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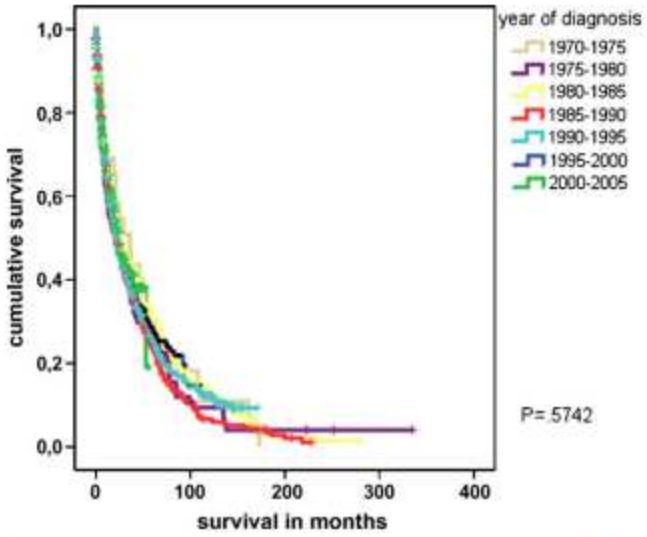

Fig. 1. Cumulative survival of BSC patients between the years 1970 and 2006.

If, for example, the median survival is 24 months in patients receiving best supportive care only, a median interval of 12 months before onset of specific therapy in one of the treatment groups would be highly suggestive of selection bias, because approximately 50% of patients potentially eligible for the treatment under consideration would no longer be alive at the time of possible treatment initiation. To facilitate the interpretation of our results, we provide the median time between diagnosis and therapy for each treatment group.

In a first step, each specific treatment was evaluated by comparing the median survival of the entire group of patients receiving the respective treatment with the median survival of a group of matched patients receiving BSC only. Subsequently, the evaluation was refined by splitting each treatment group into lower-risk MDS and higher-risk MDS. Lower-risk refers to IPSS low and intermediate-1 (named 0 and 1) or WHO types RA, RARS, RCMD and RCMD-RS; higher-risk refers to IPSS intermediate-2 and high (named 2 and 3) or WHO types RAEB I and RAEB II. If a group consisted of at least 12 patients it was further subdivided according to karyotype. Results of cytogenetic analyses were available in 76% of patients receiving specific therapy, compared to 26% of patients receiving BSC only. The probability of survival was estimated using the product limit method (Kaplan–Meier). Patients in this study were followed up until July 31st, 2007 with a median time of follow-up of 29 months.

3. Results

Cumulative survival curves of patients receiving BSC were compared regarding 5-year-intervals between 1970 and 2005. Fig. 1 shows no significant change in the natural course of disease, with median survival times varying between 51 months in the first observation period and 33 months in the latest 5-year-interval. We therefore concluded that the year of diagnosis did not confound the accuracy of the matching. Essential patient characteristics are given in Table 1. For all treatments evaluated, matching parameters showed no significant difference between treatment and control (BSC) group.

3.1. Thalidomide

Fifty-five patients started thalidomide after a median of 17 months (range: 0–141) following diagnosis of MDS. Thalidomide was given over a median of 9 months (range: 0.4–38) at a dosage between 100 and 800 mg per day. The median survival of patients receiving thalidomide was 33 months, compared to 25 months in patients receiving BSC only. The difference was statistically significant ($p = 0.0291$, Fig. 2). No difference was noted for the risk of AML transformation. Interestingly, lower-risk patients (according IPSS or WHO) showed no significant survival benefit, whereas higher-risk patients lived significantly longer with thalidomide treatment than with best supportive care. For instance, thalidomide treatment in patients with an IPSS of 2 was associated with a median survival of 57 months, compared to 10 months in the BSC group ($p = 0.0015$). The benefit of thalidomide was less apparent but still significant when patients diagnosed with RAEB I and RAEB II were grouped together (31 vs 8 months, $p = 0.021$). It should be noted that exclusion of patients who started thalidomide later than 12 months after diagnosis did not change the outcome of the survival analysis.

Table 1
Distribution of WHO and IPSS subgroups within treatment groups.

WHO type	Thalidomide	VPA	ATG	Chemotherapy	ASCT
RA	4	5	5	6	2
RSCMD	13	16	2	13	2
RARS	1	1	0	0	0
RCMD	19	31	12	22	6
5q-Syndrome	3	1	1	0	0
RAEB I	12	15	1	29	8
RAEB II	12	13	1	76	11
CMML I	3	5	1	10	1
CMML II	1	1	0	10	0
RAEB-T/sAML	2	6	0	110	9
Total	70	94	23	276	39
IPSS					
Low	12	20	7	7	0
Intermediate 1	30	34	13	52	11
Intermediate 2	17	17	2	73	14
High	8	8	0	114	11
Total	67	79	22	246	36

3.2. Valproic acid (VPA)

Seventy-six patients received valproic acid as an HDAC inhibitor. The medication achieved trough levels of 80–120 μg/l. Patients treated with VPA lived significantly longer (median: 48 months) than patients receiving BSC only (median: 29 months, $p = 0.0325$, Fig. 3). A median time of 17 months elapsed before VPA was started. The median duration of VPA treatment was 8 months (range: 0.3–30). When patients were classified according to IPSS there was no significant survival difference between VPA and BSC. When focusing on RAEB I, or RAEB I plus RAEB II, survival was significantly longer for patients treated with valproic acid (RAEB I: 48 vs 25 months, $p = 0.0421$; RAEB I plus RAEB II: 46 vs 22 months, $p = 0.019$).

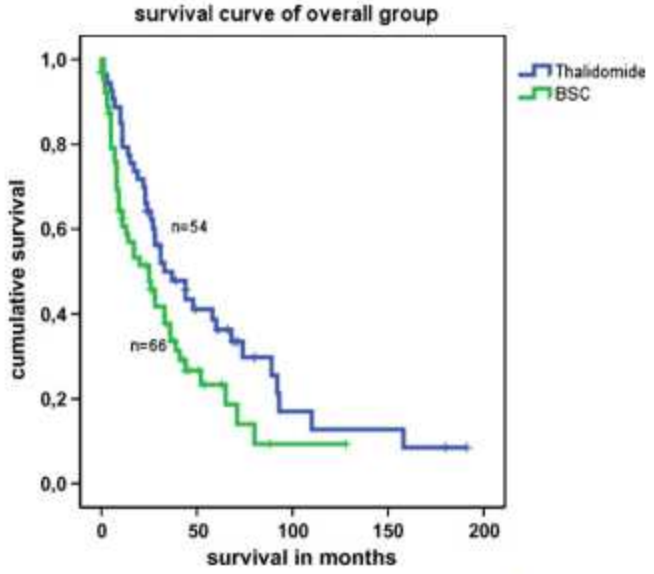

Fig. 2. Cumulative survival of the overall group treated with thalidomide.

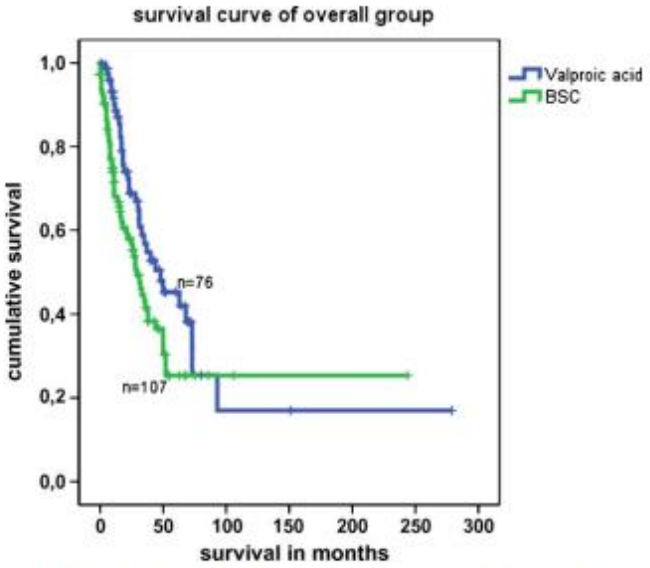

Fig. 3. Cumulative survival of the overall group treated with valproic acid.

If the analysis was confined to patients who started treatment less than 12 months after diagnosis ($n = 22$), no survival difference was detected between those receiving VPA and those receiving BSC. This is an example of the above-mentioned problem of a selection bias that is hard to avoid in retrospective matched-pair analyses.

3.3. Antithymocyte globulin (ATG)

Patients receiving ATG constituted a relatively heterogeneous group including 15 patients with RA/RCMD, one patient with RAEB, and one patient with CMML. Treatment was initiated at a median of 26 months after diagnosis. Median survival for the entire group of 17 patients was 158 months, compared to 61 months in the group of matched BSC patients ($p = 0.04$, Fig. 4).

3.4. Low-dose Ara-C

The decision to initiate treatment with low-dose Ara-C was made after a median of 7 months following the diagnosis of MDS.

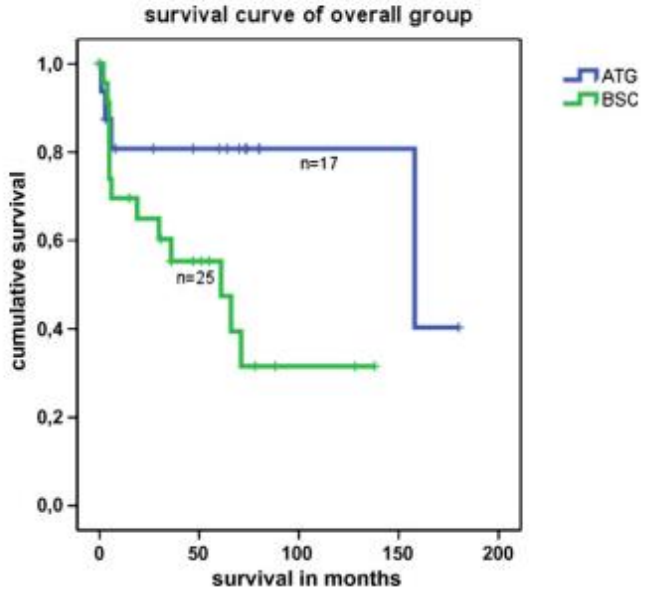

Fig. 4. Cumulative survival of the overall group treated with ATG.

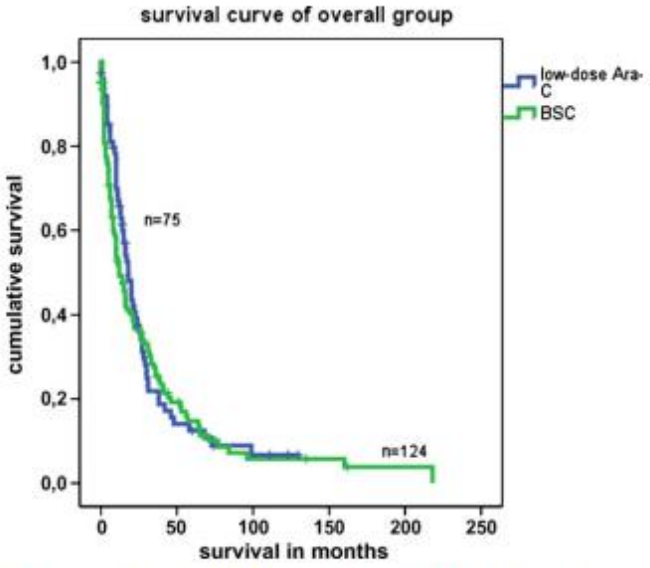

Fig. 5. Cumulative survival of the overall group treated with low-dose Ara-C.

For the entire group of patients who received low-dose Ara-C at a median dose of 20 mg per day over a median time of 2 months, survival did not differ significantly from that of patients receiving BSC only (18 vs 12 months, $p = 0.5348$, Fig. 5). This was also true if the evaluation was restricted to patients who started treatment within 3 months after diagnosis. Neither was there a difference in patients belonging to the low-risk group. Only patients classified as IPSS 2 or 3 had a significantly longer survival if they received low-dose Ara-C instead of BSC (18 vs 7 months, $p = 0.0294$).

3.5. Induction chemotherapy

In general, the aforementioned therapies represent palliative treatment, which explains why the interval between diagnosis and treatment varied a lot. In contrast, the decision to embark on intensive cytotoxic chemotherapy was made relatively early following a confirmed diagnosis of MDS, i.e. within 1 month in our patient population. Therefore, selection bias is less likely than for the other treatment groups. In the entire group of 261 patients there was no significant survival difference between intensive chemotherapy and BSC (21 vs 14 months, $p = 0.36$). In light of this finding a detailed description of chemotherapy regimens appears unnecessary. Patients usually received one or two cycles of Ara-C combined with an anthracycline.

Since only a few patients with low-risk MDS received intensive chemotherapy, statistical evaluation of further prognostic factors was confined to the high-risk group ($n = 205$). As far as age is concerned, chemotherapy in patients younger than 60 was associated with a median survival of 22 months, which was not significantly different from the 14 months observed in matched patients who received BSC only ($p = 0.3068$, Fig. 6). The same was true for patients older than 60 (21 vs 16 months, $p = 0.7946$, Fig. 7). There was no marked difference in terms of leukemic transformation, which implies that induction chemotherapy did not significantly decrease the risk of progression to AML in patients with high-risk MDS.

3.6. Allogeneic stem cell transplantation (ASCT)

Thirty-nine patients, mostly belonging to the intermediate-2 or high-risk category (10 RCMD/RSCMD, 8 RAEB-I, 11 RAEB-II, 9 RAEB-T, and 1 CMML-I), were treated with allogeneic stem cell transplantation. The group as a whole derived a significant survival benefit (49 vs 14 months, $p = 0.04$, Fig. 8) compared to BSC patients. This effect was even more pronounced (65 vs 8 months, $p = 0.0017$)

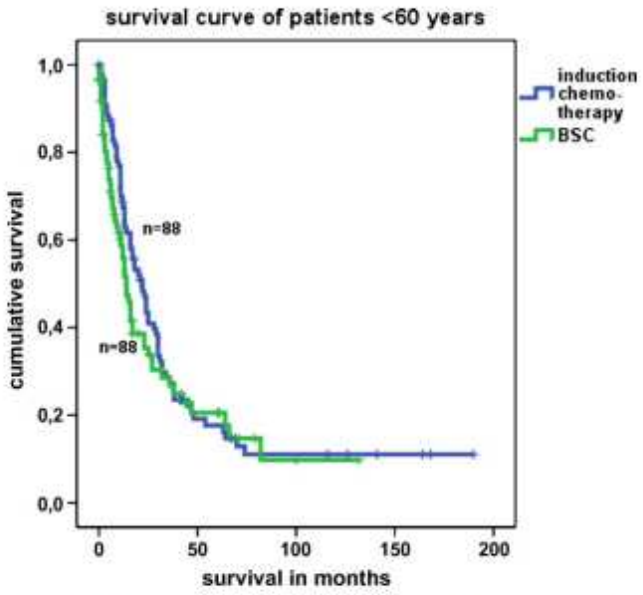

Fig. 6. Cumulative survival of patients aged under 60 years receiving induction chemotherapy.

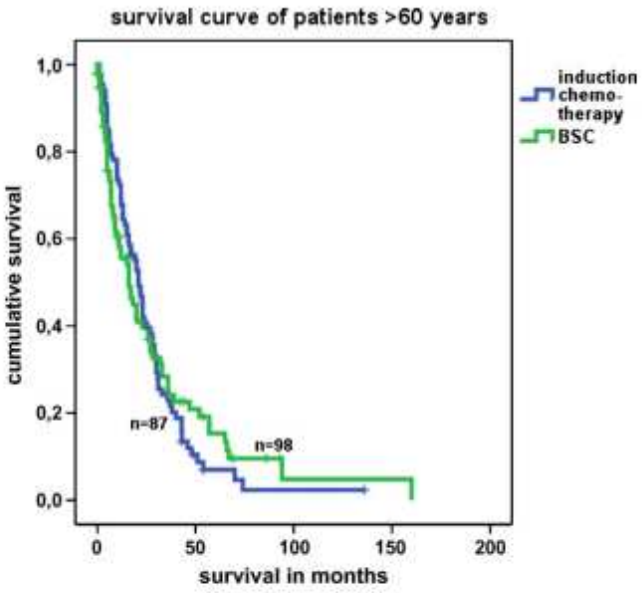

Fig. 7. Cumulative survival of patients aged over 60 years receiving induction chemotherapy.

in patients with an IPSS of 2 or 3. Accordingly, there was also a survival benefit from allo-SCT in the combined group of patients with RAEB-I, RAEB-II, and RAEB-T patients (32 vs 8 months, $p = 0.0008$) as well as the RAEB-I plus RAEB-II group (40 vs 8 months, $p = 0.001$). RAEB-I patients had the best prognosis (101 months with allo-SCT vs 27 months with BSC; $p = 0.0446$).

4. Discussion

Trying to assess the survival benefit of different treatment approaches in MDS we performed a matched-pair analysis on the basis of 3058 patients entered into our registry since 1982. This relatively large data base may permit a meaningful evaluation of drugs that have not been investigated within prospective randomized phase-III-studies. Some of the treatments have been studied at our center in phase-II-trials, including thalidomide, valproic acid, ATG, and intensive chemotherapy.

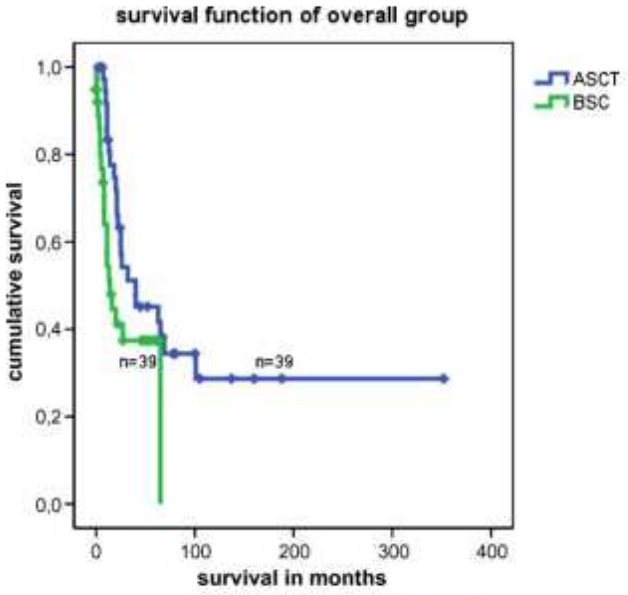

Fig. 8. Cumulative survival of the overall group receiving allogeneic transplantation.

For matched-pair analysis, we considered erythropoietin treatment to be part of best supportive care. There was only a small group of patients with endogenous EPO levels low enough to be considered for EPO treatment ($n = 71$). Accordingly, the number of patients receiving EPO solely was very small.

The survival probability of patients receiving BSC remained unchanged over about three decades, which is a sobering result that, on the other hand, allowed us to draw on a large cohort of match partners. Even though our matching criteria were relatively rigid, we were able to identify an appropriate counterpart for each of our patients in the various treatment groups. Accordingly, treatment groups and BSC patients showed no statistically significant differences regarding the matching criteria, i.e. age, gender, hematological parameters at diagnosis, and classification according to IPSS or WHO. Follow-up and patient care in our outpatient department were equally thorough in the treatment and BSC group. When matching was completed we focused our analysis on a single endpoint, namely length of survival after a confirmed diagnosis of MDS.

For the low-toxicity regimens like valproic acid, thalidomide or ATG, it turned out that patients receiving this kind of treatment showed significantly longer survival than their matched partners receiving best supportive care only. However, we soon realized that in patients treated with VPA the survival benefit disappeared if the intervall between diagnosis and start of therapy was taken into account. This observation prompted us to reconsider the other treatment groups as well. It was interesting to see that thalidomide achieved a survival benefit irrespective of treatment being initiated earlier or later than 12 months after diagnosis. On the other hand, low-dose Ara-C or intensive chemotherapy do not appear to prolong survival in the majority of patients. These unfavourable results are unlikely to be attributable to selection bias. We have previously shown that only a small minority of high-risk patients achieve complete remission translating into long-term survival [20]. We also suggested that chemotherapy should mainly be used in patients with a good-risk karyotype. In patients with an unfavourable risk profile, intensive chemotherapy will probably be substituted by epigenetic treatment with hypomethylating agents in the near future.

At the time of this writing 41.3% of low-risk MDS patients are still alive. It is therefore conceivable that we may have underestimated, for unknown reasons, the treatment benefit in this group, irrespective of the treatment applied.

In summary, we have demonstrated that various types of treatment may improve hematological parameters or may even achieve remissions in MDS, without necessarily producing a significant prolongation of survival. This conclusion does not negate the beneficial effects of improved blood counts on the patients' quality of life.

Although we still lack a thorough understanding of the disease mechanisms involved in MDS, we should try to pursue patient-tailored treatment, similar to risk-adapted stratification of patients with AML which is based on cytogenetic and molecular genetic findings. However, it will take much time and effort to identify predictive factors that may guide clinical decision making in MDS. Such guidance is particularly desirable in the context of very demanding treatment modalities like allo-SCT.

Conflict of interest

None.

Acknowledgements

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Eligibility for clinical trials is unsatisfactory for patients with myelodysplastic syndromes, even at a tertiary referral center☆

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ABSTRACT

Participation in clinical trials may allow patients with MDS to gain access to therapies not otherwise available. However, access is limited by strict inclusion and exclusion criteria, reflecting academic or regulatory questions addressed by the respective studies. We performed a simulation in order to estimate the average proportion of MDS patients eligible for participation in a clinical trial. The simulation drew upon 1809 patients in the Düsseldorf MDS Registry whose clinical data allowed eligibility screening for a wide range of clinical trials. This cohort was assumed to be alive and available for study participation. The simulation also posited that all MDS trials (n = 47) conducted in our center between 1987 and 2016 were open for recruitment. In addition, study activities in the year 2016 were analyzed to determine the proportion of patients eligible for at least one of the 9 MDS trials open at that time.

On average, each clinical trial was suitable for about 18 % of patients in the simulation cohort. Conversely, 34 % of the patients were eligible for at least one of the 9 clinical studies in 2016. Inclusion/exclusion criteria of studies initiated by the pharmaceutical industry excluded more than twice the fraction of patients compared with investigator initiated trials (potential inclusion of 10 % vs. 21 %, respectively). Karyotype (average exclusion rate 58 %), comorbidities (40 %), and prior therapies (55 %) were the main reasons for exclusion. We suggest that in- and exclusion criteria should be less restrictive, in order to meet the needs of the real-life population of elderly MDS patients.

1. Introduction

Disease-modyfing treatment options for patients with myelodysplastic syndromes are sparse. Iron chelation, hypomethylating agents (HMA), lenalidomide for patients with isolated del(5q), and erythropoietin-α for low risk patients with an endogenous EPO level < 200 mU/mL are the only approved therapies at present. Iron chelation and erythropoietin-α can be useful for transfusion-dependent and/or symptomatic low-risk MDS patients with anemia, lenalidomide is a good option for about 5% of MDS patients, namely those diagnosed with transfusion-dependent MDS del(5q), and a response to HMAs can be expected in about the half of the patients with high-risk MDS [1]. Less than 10 % of all MDS patients undergo allogeneic stem cell transplantation. Consequently, a large proportion of about 68 % of all MDS patients cannot be offered effective treatment in addition to best supportive care. Therefore, novel treatment options must be developed through clinical trials. These are usually designed for specific subsets of MDS patients. In the past, the international prognostic scoring system (IPSS) [2] has often been used to define study populations, including either low- and intermediate 1-risk or intermediate 2- and high-risk patients. Compounds offered to low- and intermediate 1-risk patients usually aim at ameliorating cytopenias and thereby improving quality of

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life, whereas clinical trials for intermediate 2- and high-risk patients mainly try to prolong life expectancy.

Inclusion criteria take into account the characteristics of the investigational medicinal product, the risk category of the patient's disease and, certain biological and clinical parameters. Clinical trials in the field of MDS are either initiated by the pharmaceutical industry, often in collaboration with MDS centers (pharma trials) or are set up by academic centers as investigator-initiated trials (IIT).

Patients who cannot be offered approved compounds or cannot be included in clinical trials due to inclusion and exclusion criteria receive best supportive care only and thereby lack chances to achieve a betterment of cell counts or a change of the natural course of the disease. Our department serves as a tertiary referral center for MDS patients since the early eighties. Since then we have developed the Düsseldorf MDS registry and set up or took part in numerous clinical trials for different MDS patient groups [1]. Meanwhile, the Düsseldorf MDS registry contains well-annotated data of 7500 patients with MDS diagnosed systematically at our cytology laboratory [3]. Relevant clinical data such as FAB and WHO types [4–6], cell counts, bone marrow findings, karyotypes [7], transfusion need and types of treatment are available.

From 1987 to 2017 we conducted or participated in 47 clinical trials for patients with different types of MDS [8–53]. The aims of the present study were to use these data to assess the average proportion of patients who fulfilled the inclusion criteria of these trials and to evaluate in a sample year (2016) the proportion of patients for whom a suitable clinical trial was available.

2. Materials and methods

Ethical approval was obtained by the local ethics board of the Heinrich-Heine-University (ID 3973). Procedures are in accordance with the current version of the Helsinki Declaration. Morphological diagnoses of the patients were systematically made in our laboratory according to the WHO 2008 classification [5,6]. Patients with a former FAB diagnosis of RAEB-T as well as patients with a mixed myelodysplastic/myeloproliferative phenotype (RARS-T, CMML 0, 1, 2) were also analyzed. We assessed clinical trials conducted at our department since 1987 and their main inclusion criteria (Table 1). We determined the proportion of patients hypothetically eligible for these clinical trials, assuming that the entire simulation cohort were alive and all studies were open for recruiting.

For this calculation we took into account the inclusion and exclusion criteria of all MDS trials performed in our institution since 1987. A prerequisite was the availability of the parameters that were crucial for eligibility, such as age, FAB/WHO type, IPSS at the time of diagnosis, cell counts, cytogenetic findings, information regarding previous treatment, ECOG performance status, as well as laboratory values reflecting liver and kidney function. All this information was available in 1809 registry patients, who subsequently served as our patient cohort for the simulation. In order to substantiate that we are dealing with a representative cohort, we compared these 1809 patients with the remaining patients of the registry and did not find any relevant differences with regard to WHO type distribution, survival and risk of AML evolution. Aspects not systematically assessed in the registry were individual patient preferences, problems with adherence, and some inclusion criteria unrelated to MDS, like willingness to perform double barrier contraception.

Categorical variables were analyzed by frequency tables, continuous variables were described via median (range). Time-to-event-curves were calculated according to the Kaplan-Meier method. Log-rank test was used for univariate comparisons. $\chi 2$-test was employed for univariate comparison cross tabulation. A p value $<.05$ was considered as statistically significant. Statistical analyses were performed using SPSS for Windows (Version 22, SPSS Inc. Chicago, IL).

3. Results

A total of 1809 patients with an IPSS assessed at the time of diagnosis were entered into the analyses. According to FAB classification 38.4 % were diagnosed as RA, 11.9 % as RARS, 27.3 % as RAEB, 10.9 % as RAEB-T and 11.2 % as CMML. Following the WHO 2008 classification, 5.1 % had a RCUD, 30.6 % a RCMD, 12.8 % a RAEB-1, 16.5 % a RAEB-2, 8 % a CMML-1, 2.9 % a CMML-2, and 8.8 % as AML (former RAEB-T). 11.7 % of all patients were diagnosed as MDS with isolated del(5q). 11 % were classified as therapy-associated MDS. Median age at the time of diagnosis was 68 years, 7 % were aged above 80 years. 40.1 % were females. 44 % were transfusion-dependent at the time of diagnosis. Distribution among IPSS risk groups was as follows: 24 % low risk, 39 % intermediate 1, 23 % intermediate II, and 14 % high risk. 23 % of the patients had participated in a clinical trial prior to our analysis, 38.5 % were untreated with the exception of transfusions.

In a first step, we assessed the eligibility of patients for every clinical trial and analyzed the proportion of patients in our simulation who were eligible, taking into account all inclusion and exclusion criteria (Table 2). The mean percentage of eligibility was 18 % (0.4–100 %). The proportion was up to 100 % in the very early years and subsequently dropped considerably over time (Fig. 1). The mean percentage of eligible patients was 69.1 % in the years before 2000 (4 trials), 27 % in the years 2000−2010 (12 trials), and 6.6 % in trials performed after 2010 (31 trials).

The lowest eligibility was 0.4 % in the trial "Lenalidomid maintenance after allogeneic HSCT" [32]. 60 % of the trials allowed inclusion of less than 10 % of the cohort, 32 % of the trials allowed participation of 10–49 %, and only 4 trials, all conducted before 2002, would have accepted more than 50 % of the cohort. IITs were suitable for 24.9 % of patients on average, trials sponsored by the pharmaceutical industry only for 16.5 % (15 trials only, the first started 2007). Eligibility of patients also differed between the types of clinical trials. 6.2 % of the patients were eligible for phase-1-trials (n = 5), 21.8 % for phase-2-trials (n = 28) and 9.7 % for phase-3-trials (n = 14).

We then analyzed which of the major criteria led to an exclusion of patients (Fig. 2). "Presence of comorbidities" (average exclusion rate 39 %), "prior therapies or drugs" (average exclusion rate 58 %) and "karyotype" (average exclusion rate 56 %) were the leading causes for exclusion.

We were also interested in how often certain exclusion criteria were employed in the trials under consideration (Fig. 3). Age, comorbidities and previously administered therapies were listed most frequently (in 29, 26 and 33 trials, respectively). Although karyotype was used less often as an inclusion/exclusion criterion (only 11 trials), it led to the exclusion of a large proportion of patients in our analyses.

Overall, the main impact on eligibility was attributable to IPSS risk group, FAB classification, the presence of del(5q), and the prerequisite of a previous stem cell transplantation. We performed analyses with regard to the proportion of eligible patients for each clinical trial, based on the above-mentioned prerequisites, which we named "major criteria" (Fig. 4 and Table 2).

Obviously, focusing on the major criteria leads to fewer exclusions and higher eligibility rates as compared to all inclusion and exclusion criteria (Fig. S1).

With regard to the type of trial, we assert that the average rate of inclusion in IIT-trials (24.9 %) is higher than in trials conducted by the pharmaceutical industry (16.5 %). This is due to the fact that industry-driven trials usually define more numerous and narrower inclusion and exclusion criteria.

We also observed that the average eligibility for trials conducted between 1987 and 2010 was 34.5 % and dropped to only 8% in the more recent trials run between 2010 and 2016 (Fig. 1).

According to our data, patient eligibility differed between early and later stage clinical trials. Among 47 clinical trials, 5 were phase 1, 28 phase 2, and 14 phase 3. The highest average proportion of eligible

Table 1
List of 47 clinical trials conducted for MDS patients at our site between 1987 and 2016. Major inclusion and exclusion criteria are listed for each trial.

Study number	Titel of study	Autor/ refe-rence number	Major in- and exclusion criteria	Type of trial
PMID: 3476364	Low dose cytosine arabinoside in patients with AML and MDS	1987 Heyll A, et al. [8]	- AML, AML after MDS - AML relapse, myelodysplasia - primary MDS	IIT
n.a.	Results of low-dose cytosine arabinoside and aggressive chemo-therapy in advanced MDS	1992 Aul C, et al. [9]	- FAB-types: RA, RARS, RAEB, RAEB-T, CMML -severe cytopenia: (platelets <50,000/µl, ANC < 1800/µl, Hb<10 g/dl) - splenomegaly or increasing medullary blasts	IIT
n.a.	Efficacy and toxicity of the oral iron chelator L1 (Deferiprone) in the treatment of secondary haemochromatosis	1993 Jaeger M, et al. [10].	- secondary iron overload - transfusion-dependent anemia	IIT
PMID 8219188	All-trans retinoic acid in patients with MDS: Results of a pilot study	1993Aul C, et al. [11]	- transfusion-dependent anemia - ANC < 500/µl, platelets <20,000/µl or increasing medullary or peripheral blasts - no infection, no abnormal transaminases, no renal insufficiency, no neurologic dysfunctions - age >15 and <60 - ECOG 0–2	IIT
PMID: 11588026	Intensive chemothera-py followed by alloge-neic or autologous stem cell transplanta-tion for patients with MDS and sAML	2001 de Witte T, et al. [12]	- FAB-types: RA; RARS; RAEB with <10 % med-ullary. blasts and multiple chromosomal aberra-tions, RAEB-T, CMML with ANC > 1600/µl or sAML - no prior induction chemotherapy - no cytarabine or "biological modifying therapy" - life expectancy >3 months	IIT
PMID: 11840256	Thalidomid for the treatment of patients with MDS	2002 Strupp C, et al. [13]	- IPSS low, intermediate-1, intermediate-2, high - FAB-types: RA;RARS;RAEB;RAEB-T; CMML - transfusion-dependent anemia or thrombocytopenia or ANC < 500/µl - age >15 < and <60	IIT
PMID:12200672	Chemotherapy only compared to chemo-therapy followed by transplantation in high risk MDS and sAML; two parallel studies adjusted for various prognostic factors	2002 Oosterveld M, et al. [14]	- FAB-types: untreated RAEB-T, RAEB with medullary blasts >10 % other MDS with multiple chromosomal aberrations and cytopenias (ANC < 500/µl or thrombocytes <20,000/µl) or CMML with medullary blasts >5% - secondary AML - ECOG 0–2, age >17	IIT
PMID: 14712285	A prospective, rando-mised, phase 2 study of horse antithymocyte globulin vs rabbit anti-thymocyte globulin as immune-modulating therapy in patients with low-risk MDS	2004 Stadler M, et al. [15]	- FAB-types: RA;RAEB; CMML - platelets <50,000/µL or ANC < 1,000/µl, Hb <10 g/dl - no donor or no planned allografting - no allergy against horse/rabbit ATG - no severe comorbidity - no prior inclusion to a clinical trial	IIT
PMID: 15785949	Treatment of MDS with isolated del(5q) including bands q31-q33 with a combination of all-trans-retinoic acid and tocopherol α	2005 Giagounidis A, et al. [16]	- ECOG 0–2, age >17 - IPSS low/intermediate-1 - FAB-types: RA,RARS,RAEB with < 10 % medullary blasts - isolated del(5q) - Hb<10 g/dl, transfusion-dependent anemia - ANC < 1000/µl, Platelets <50,000/µl	IIT
PMID:17577779	A pilot study of bendamustine in elderly patients with high-risk MDS and AML	2007 Strupp C, et al. [17]	- FAB-types: AML, RCMD, RAEB 2, RAEB-T or WHO: CMML 1,2 - IPSS intermediate-1, intermediate-2, high - transfusion-dependent anemia or thrombocytopenia - age >17 - ECOG 0–1	IIT
PMID: 17264294	A multicenter phase 2 study of the farnesyltransferase inhibitor tipifarnib in intermediate-to high-risk MDS	2007 Fenaux P, et al. [18]	- FAB-types: RAEB, RAEB-T, CMML with >10 % medullary blasts - IPSS intermediate-1, intermediate-2, high - splenomegaly and WBC > 10,000/µl - complex karyotype or chromosome 7 abnormalities - transfusion-dependent anemia, - WBC > 15,000/µl or platelets <50,000/µl - creatinine <1,5*ULN, bilirubin < 2*ULN - no t-MDS, no prior radiotherapy - age >60	Pharma
PMID:17559141	Intensive chemothera-py is not recommended for patients aged >60 years who have MDS or sAML with high-risk karyotypes	2007 Knipp S, et al. [19].	- FAB-types: RAEB; RAEB-T, RA or WHO: AML - no AML FAB M3, no solid tumor - no low Vitamin B12 or folic acid levels - no splenomegaly - no chronic inflammatory disease	IIT
PMID:18548095	Use of lonafarnib in MDS and CMML	2008 Feldmann, et al. [20]	- ECOG 0–2- FAB-types: RAEB, RAEB-T, CMML, sMDS - creatinine < 1,5*ULN - bilirubin < 2*ULN	Pharma
EUDRA-CT: 2010-022884-36	A randomized, double-blind, Placebo-controlled, multicenter study evaluating epoetin alfa versus placebo in	2009 Giagounidis A, et al. [21]	- age >17 - ECOG 0–2 - IPSS low, intermediate-1, no tMDS	Pharma

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Table 1 (*continued*)

Study number	Titel of study	Autor/ refe-rence number	Major in- and exclusion criteria	Type of trial
	anemic patients with IPSS low- or intermediate-1-risk myelodysplastic syndromes		- Hb <10 g/dl - thrombocytopenia - transfusion-dependent anemia - no low Vitamin B12, Folic acid, iron - no severe comorbidity, no active infection - no prior inclusion into clinical trials - no thromboembolisms - no prior allografting, no chelation - age >17 - ECOG 0–2	
NCT: 00071799	Efficacy of azacitidine compared with that of conventionl care regimes in the treatments of higher-risk MDS: a randomised, open-la-bel, phase 3 study	2009 Fenaux P, et al. [22].	- IPSS intermediate-2 or high, no tMDS - FAB-types: RAEB,RAEB-T,CMML with >10 % medullary blasts - no earlier treatment with Vidaza - no planned allografting	Pharma
NCT: 00002926	Value of allogenic versus autologous stem cell transplantation and chemotherapy in pati-ents with MDS or sAML. Final results of a prospective randomi-zed European Inter-group trial	2010 de Witte T, et al. [23]	- MDS with >10 % medullary blasts, other MDS-with complex karyotypes or cytopenia (ANC < 500/µl or platelets <20,000/µl), CMML with >5% medullary blasts - no earlier intensive chemotherapy or radiation - no earlier treatment with "biological response modifiers"	IIT
PMID: 20971823	Allogeneic stem cell transplantation for MDS with bone marrow fibrosis	2010 Kröger N, et al. [24]	- post allografting - no PMF, no overlap syndromes, no MPS - age >17 - ECOG 0–2, no infection	IIT
PMID: 21149672	Immunosuppressive therapy for patients with MDS: a prospec-tive randomized - phase 3 trial comparing antithymocyte globulin plus cyclosporine with best supportive care	2011 Passweg J, et al. [25]	- FAB-types: RA,RARS, RAEB - IPSS low, intermediate-1 - <10 % medullary blasts - transfusion-dependent anemia and/or Hb <8 g/dl, platelets < 20,000/µl, ANC < 500/µl - no tMDS - age >17	IIT
NCT:00179621	A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/inter-mediate-1-risk MDS with del5q	2011 Fenaux P, et al. [26]	- IPSS low, intermediate-1, no CMML - MDS with del(5q31) with or without additional aberrations - transfusion-dependent anemia - WBC < 12,000/µl - no earlier EPO, lenalidomide or chemo-therapy - creatinine <2*ULN, bilirubin <1,5*ULN - serum transaminases <3*ULN	Pharma
PMID: 26668126	Safety of Lenalidomide and Markers for Disease Progression in Patients With International Prognostic Scoring System (IPSS) Low- or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) With Isolated del5q (MDS-LE-MON-5)	2015 Schuler E, et al. [27]	- age >17 - del(5q) - medullary blasts <5% - IPSS low, intermediate-1 - transfusion-dependent anemia - no CMML with WBC > 12,000/µl - no ANC < 1000/µl, no platelets <50,000/µl - bilirubin <1,5*ULN - no low iron or Vitamin B12 levels	IIT
EudraCT:2008-001866-10				
PMID: 21483003	Low-dose decitabine versus best supportive care in elderly patients with intermediate to high risk MDS ineligible for intensive chemotherapy: final results of the randomized phase 3 study of the european organisation for research and treatment of cancer leukemia group and the german mds study group	2011 Lübbert M, et al. [28]	- no comorbidity, no infection, no bleeding - age >60 - ECOG 0–2 - pMDS, tMDS, CMML - IPSS intermediate-1, intermediate-2, high - medullary blasts 11–30% or <10% with poor risk karyotype - no comorbidity - not suitable for induction and allografting - no heart disease - no earlier chemotherapy or HMA	IIT
EudraCT:2010-018467-42	Comparison between 5-azacitidine treatment and 5-azacy-tidine followed by allogeneic stem cell transplantation in elderly patients with advanced MDS accor-ding to donor avail-ability: VIDAZALLO	2011 Kröger N, et al. [29]	- age 55–70, ECOG 0-2 - IPSS intermediate-2, high or intermediate-1 with poor risk karyotype - received no or no more than1 cycle Azacitidine - creatinine and bilirubin < 3*ULN - no heart disease - medullary blasts <30 % - life expectancy >6 months	IIT
PMID:21963618	Upfront allogeneic blood stem cell trans-plantation for MDS or s AML using a FLAMSA-based high-dose sequential conditioning regimen	2012 Saure C, et al. [30]	- no infections - no prior MDS treatment - age >17 - IPSS intermediate-2 or high risk - suitable for allografting and donor available	IIT
EudraCT: 2012-002471-34	A phase 3, multicenter, randomized, double-blind study to compare the efficacy and safety of oral azacitidine plus best		- age >17 - ECOG 0–2	Pharma

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Table 1 (*continued*)

Study number	Titel of study	Autor/ refe-rence number	Major in- and exclusion criteria	Type of trial
	supportive care versus placebo plus best supportive care in subjects with red blood cell transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS	2012 Garcia-Manero G, et al. [31]	- IPSS low, intermediate-1 - no t- MDS, no CMML, no CML, no MPD - transfusion-dependent anemia - platelets > 75,000/µl - no earlier treatment with Azacitidine, Lenalidomide, allogeneic or autologous stem cell transplantation - no comorbidity, no heart disease - no infections - creatinine <1,5*ULN, bilirubin <2*ULN - no low Vitamin B12/iron/folic acid levels	
PMID:22952334	Lenalidomide mainten-ance after allogenic HSCT seems to trigger acute graft versus host disease in patients with high-risk MDS or sAML and del(5q): results of the LENAMAINT trial	2012 Sockel K, et al. [32]	- IPSS high risk - complete remission after allografting - del(5q) abnormality	IIT
PMID: 22419577	Hematologic responses to deferasirox therapy in transfusion-dependent patients with MDS	2012 Gattermann N, et al. [33]	- MDS with iron overload due to transfusions with serum Ferritin >1000 ng/ml or liver iron concentration > 2 mg FE/g - life expectancy of at least 1 year - ECOG 0–2, age >17 - IPSS intermediate-2 or high risk or CMML (10–29% medullary blast) or AML (medullary blast 20–30%)	Pharma
EudraCT:2012-003436-22	A phase I study of romidepsin additional to 5-azacitidine in higher risk MDS after insufficient response to 5-azacitidine mono-therapy (ROMDS)	2013 Kündgen A, et al. (34)	- not suitable for allografting - treatment with 5- Azacitidine for at least 6 cycles - WBC < 30,000/µl - creatinine < 1,5*ULN, bilirubin <2*ULN, AST/ ALT < 2,5*ULN - no cardiac or pulmonary comorbidity, no infection	IIT
PMID: 24186004	Phase 2 Study of oral panobinostat (LBH589) with or without erythro-poietin in heavily trans-fusion-dependent IPSS low or int-1 MDS patients	2013 Platzbecker U, et al. [35]	- IPSS low, intermediate-1 - no response to or relapse after ESA - transfusion-dependent anemia - age >17	IIT
NCT: 00923234	Sequential combination of azacitine and lenalidomide in del (5q) higher-risk MDS sAML: a phase 1 study	2013 Platzbecker U, et al. [36]	- ECOG 0–3 - del(5q) - IPSS intermediate-2 or high risk MDS or AML - not suitable for allografting or no donor available - age >17	IIT
PMID: 23314834	Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell trans-plantation	2013 Schroeder T, et al. [37]	- ECOG 0-20–2 - hematological relapse of MDS or AML after allografting with medullary blast count >5% - no uncontrolled infections - bilirubin <1,5*ULN, creatinine < 2*ULN	IIT
PMID:23073603	Results from a 1-year, open-label, single arm, multicenter trial evaluating the efficacy and safety or oral Deferasirox in patients diagnosed with low and int-1 risk MDS and transfusion-dependent iron overload	2013 Nolte F, et al. [38]	- IPSS low, intermediate-1 risk - transfusion-dependent anemia with iron overload (Ferritin >1000ug/l)	IIT
PMID:25540937	Treatment of AML or MDS relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions-a retrospective multi-center analysis from the German cooperative transplant study group	2014 Schroeder T, et al. [39]	- relapse of MDS or AML after allografting	IIT
Eudra-CT: 2013-001290-24	An open label phase 1 dose escalation trail to investigate the maxim-um tolerated dose, sa-fety, pharmacokinetics and efficacy of intrave-nous Volasertib in com-bination with subcuta-neous azacitidine in patients with previous-ly untreated high-risk MDS (CMML) ineligible for high-risk therapy	2014 Platzbecker U, et al. [40]	- age >17 - ECOG 0–2 - IPSS high or intermediate-2 and 5–30% medullary blasts - no prior treatment of MDS or CMML - not suitable for allografting - bilirubin <1,5*ULN, creatinine <1,5*ULN - no comorbidity, no cardiac disease - no infection	Pharma
EudraCT:2013-001153-27	AZALENA: phase 3 tri-al to assess the efficacy and safety of lenalidomide in addition to 5-azacitidine and donor lymphocyte infusions (DLI) for the treatment of patients with MDS, CMML or AML who relapse after allogeneic transplantation	2014 Kobbe G, et al. [41]	- ECOG 0–2 - relapse of MDS or AML after allografting - no comorbidity, no infection - no previous treatment including chemotherapy, radiation - no prior inclusion into a clinical trial after relapse - AST/ALT < 3*ULN	IIT
EudraCT: 2014-000200-10	A randomized phase 3 study of decitabine with or without hydroxyurea in patients with advanced proliferative CMML	2015 Platzbecker U, et al. [42]	- ge >17 - ECOG 0–2 - CMML with <20 % medullary blasts - WBC > 13,000/l - either >5% medullary blasts and cytogenetic aberration or anemia, ANC > 1600 mg/dl, thrombocytopenia or splenomegaly or extramedullary involvement - no comorbidity - no pulmonary or cardiac disease - no earlier treatment besides ESA - bilirubin <1,5*ULN, AST/ALT <3*ULN, creatinine <2*ULN	IIT

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Study number	Titel of study	Autor/ refe-rence number	Major in- and exclusion criteria	Type of trial
PMID: 26400023	Decitabine versus best supportive care in older patients with refractory anemia with excess blasts in transformation (RAEB-T)- results of a subgroup analysis of the randomized phase 3 study 06011 of the EORTC Leukemia Co-operative Group and German MDS Study Group (GMDSSG)	2015 Becker H, et al. [43].	- not suitable for allografting - ge >60 - ECOG 0−2 - FAB RAEB, RAEB-T - IPSS intermediate 1, intermediate-2, high - medullary blasts 11−30% - poor risk cytogenetics - no previous intensive therapy or HMA	IIT
EudraCT: 2014-001479-30	Phase 1/2 study of sensitization of non-M3 AML blasts to alltrans retinoid acid (ATRA) by epigenetic treatment with tranylcypromine (TCP), an inhibitor of the histone lysine or the histone lysine demethylase 1 (LSD1) TRANSATRA	2015 Lübbert M, et al. [44]	- age >17 - ECOG 0−2 - AML, according WHO, or MDS/CMML with IPSS-R intermediate, high or very high - not eligible for standard treatment including allografting - patients with WBC < 30,000/µl - no APL - no comorbidity, no diabetes, no infection - no prior treatment within clinical trials - no allergy against study drug	IIT
PMID:24706489	Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/ int-1 risk MDS and thrombocytopenia	2015 Giagounidis A, et al. [45]	- IPSS low, intermediate-1 - Thrombocytopenia <20,000/µl or bleeding	Pharma
NCT: 02562443	Rigosertib versus best supportive care for patients with high-risk MDS after failure of hypomethylating drugs (ONTIME). A randomi-sed, controlled, phase 3 trial	2016 Garcia-Manero G, et al. [46]	- FAB: RA, RAEB, RAEB-T, CMML with failure after HMA - IPSS intermediate-2, high	IIT
EudraCT: 2015-002874-19	A study to evaluate Imetelstat (JNJ-63935937) in transfusion-dependent subjects with IPSS low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment	2015 Steensma DP, et al. [47]	- age >17 - ECOG 0−2 - IPSS low, intermediate-1 - relapse after or no response to ESA-treatment, Serum-EPO-Level >500 IU/l) - no infection - no comorbidity - transfusion-dependent anemia - ANC > 1500/µl, thrombocytes >75,000/µl - creatinine < 1,5*ULN, bilirubin <2*ULN - no previous chemotherapy	Pharma
NCT01749514	ACE-536 increases hemoglobin and reduces transfusion burden in patients with low or intermediate-1 risk MDS: Preliminary results from a phase 2 study (cohort 2A)	2015 Platzbecker U, et al. [48]	- age >17 - ECOG 0−2 - pMDS or CMML (WBC < 13,000/µl) - IPSS low, intermediate-1 - no infection - Hb <10 g/dl, transfusion-dependent anemia - no previous HMA, no „iron chelating therapy" - no previous inclusion to clinical trial - no cardiac disease - creatinine <1,5*ULN, normal levels of folic acid/Vitamin B12 - no prior ESA treatment/no EPO level <500 U/l	Pharma
NCT01749514	ACE-536 increases hemoglobin and reduces transfusion burden in patients with low or intermediate-1 risk MDS: Preliminary results from a phase 2 study (cohort 2B)	2015 Platzbecker U, et al. [48]	- age >17 - ECOG 0−2 - pMDS or CMML (WBC < 13,000/µl) - IPSS low, intermediate-1 - no infection - Hb <10 g/dl, transfusion-dependent anemia - no previous HMA, no „iron chelating therapy" - no previous inclusion to clinical trial - no cardiac disease - creatinine <1,5*ULN, normal levels of folic acid/Vitamin B12 - no prior ESA treatment/no EPO level <500 U/l	Pharma
PMID:26596971	Decitabine improves progression-free survival in older high-risk MDS patients with multiple autosomal monosomies: results of a subgroup analysis of the randomized phase 3 study 06011of the EORTC leukemia cooperative group and German MDS study group	2015 Lübbert M, et al. [49]	- age >60 - ECOG 0−2 - pMDS or tMDS or CMML - IPSS intermediate-1, intermediate-2, high - medullary blasts: 11−30% or <10% with poor risk cytogenetics - no cardiac disease - no prior induction chemotherapy or HMA	
EudraCT:2013-000918-37	A randomized, double-blind, placebo-controlled, phase III, multi-centre study of eltrombopag or placebo in combination with azacitidine in subjects with IPSS intermediate-1, -2 and high-risk MDS	2018 Dickinson M, et al. [50]	- age >17 - ECOG 0−2 - IPSS intermediate-1, intermediate-2, high - no infection - no CMML with WBC > 12,000/µl - thrombocytes <75.000/µl - bilirubin <1,5*ULN, creatinine <1,5*ULN - no cardiac disease	IIT

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Table 1 (*continued*)

Study number	Titel of study	Autor/ refe-rence number	Major in- and exclusion criteria	Type of trial
EudraCT:2010-022890-33	Eltrombopag for the treatment of thrombocytopenia due to low and intermediate risk MDS	2015 Oliva E.N, et al. [51]	- no previous chemotherapy or HMA - no previous treatment with Eltrombopag or Romiplostim - no prior allograting - no prior inclusion to clinical trial - no comorbidity - age >17 - thrombocytes <30.000/µl - IPSS low, intermediate-1 - relapsed after or unsuitable for treatment with HMA, Lenalidomide, induction chemotherapy or stem cell transplantation - no marrow fibrosis - no cardiac diesase -WBC <25,000/µl	IIT
PMID: 29777631	Effect of deferasirox + erythropoietin vs erythropoietin on erythroid response in Low/Int-1-risk MDS patients: Results of the phase II KALLISTO trial.	2016 Gattermann N, et al. [52]	- no prior inclusion in a clinical trial - no infection - time from MDS diagnosis >3 months and <3 years - IPSS low, intermediate-1 - no t-MDS - Hb 8–10 g/dl - EPO < 500 IU/l - ANC > 500/µl - thrombocytes >30,000/µl - creatinine <2 *ULN, bilirubin <1,5*ULN - no isolated del(5q) - no prior allografting or induction chemotherapy - no history of thromboembolic events - no relevant comorbidity - age >17 - ECOG 0–2 - presence of ring sideroblasts >15 % (RARS,RCMDRS) - IPSS low, intermediate-1, intermediate-2 - <5% marrow blasts - no MDS del(5q) - no tMDS	Pharma
EudraCt: 2015-003454-41	ACE536-MDS-001: Double blind randomized phase 3 trial to compare efficacy and safety of Luspatercept (ACE-536) versus Placebo for the treatment of anemia due to MDS with IPSS-R very low, low or intermediate risk in transfusion dependent patients with ring sideroblasts versus placebo (MEDALIST)	2016 Platzbecker U, et al. [53]	- intolerant/not suitable for treatment with ESA (>200mU EPO) - transfusion-dependent anemia - no prior treatment with IMIDS, HMA, immunosuppressants - no prior clinical trial - no deficiency of Vitamin B12, folic acid, or iron - no signs of hemorraghe - no cardiac disease - bilirubin <2*ULN - no relevant comorbidity - no history of thromboembolic events - no infection - thrombocytes >50,000/µl - ANC > 500/µl	Pharma

patients was found in phase 2 trials (21.8 %), followed by phase 3 trials (9.7 %) and phase 1 trials (6.3 %).

To see things from a different angle, we assessed the percentage of patients eligible for one or more of the 9 ongoing trials at our department in 2016 (marked in bold in Table 2). 462 patients (25.5 %) could have been offered at least one clinical trial, 134 (7.4 %) were eligible for two different trials, 25 patients (1.4 %) may have chosen from three different trials, and only one person was eligible for four trials (Fig. S2). Conversely, 1187 (65.6 %) patients of our cohort had no chance to participate in any of these clinical trials. This was based solely on inclusion and exclusion criteria, regardless of the patients' wish or other factors that may influence trial participation.

Interestingly, the chance to be eligible for a clinical trial increased with more unfavourable IPSS risk profile, 19 % of patients with IPSS low, 37.8 % with IPSS intermediate-1, 35.7 % with IPSS intermediate-2 and 44.4 % of high risk patients could be offered at least one clinical trial (Fig. S3).

Only 12.6 % of patients with treatment-related MDS were eligible for a clinical trial because this type of MDS was an exclusion criterion in most of the studies. In contrast, 37.2 % of patients with primary MDS had the chance to participate in a trial. The difference was statistically significant ($p < 0.0005$). Similarly, among 210 patients with CMML, 38.6 % were eligible for at least one of the clinical trials.

4. Discussion

Based on a simulation model we could show a) that on average, only 18 % of patients from a well-documented MDS patient population are hypothetically eligible for a clinical trial, b) that despite conducting 9 clinical trials in the year 2016 at our center, only 34 % of the patients could be offered participation in at least one of these trials and c) that the percentage of eligible patients is lower in more recently conducted trials and also in trials sponsored by the pharmaceutical industry as compared to IITs. Narrow inclusion and exclusion criteria, which are in conflict with the clinical heterogeneity of MDS, are the main reason for the paucity of recruitment opportunities. Also, patients with CMML or treatment-related MDS were usually not eligible for trial participation. The strictness of criteria increased over time, partly due to clinical trials focusing on certain genetically/molecularly defined subtypes, and was more common in pharmaceutically driven trials than in IITs which leads

Table 2
Eligible patients per study, considering all inclusion and exclusion criteria versus major criteria only (Studies ongoing in 2016 marked in bold).

ref	Study title	Number (%) of patients eligible, considering all inclusion criteria	Number (%) of patients eligible, considering only major inclusion criteria
8	low dose cytosine arabinoside	1809 (100 %)	1809 (100 %)
9	low dose cytosine arabinoside/ chemotherapy	1390 (77 %)	1522 (84.1 %)
10	Deferiprone	309 (17.1 %)	309 (17.1 %)
11	ATRA	968 (53.5 %)	1202 (76.4 %)
12	Chemotherapy followed by allografting	242 (13.1 %)	242 (14.1 %)
13	Thalidomide	1517 (84 %)	1521 (84 %)
14	Chemotherapy +/- allogeneic PBSCT	207 (11.4 %)	671 (37.1 %)
15	Horse ATG/Rabbit ATG	150 (8.2 %)	768 (80.2 %)
16	ATRA and tocopherol-alpha	148 (8%)	177 (9.7 %)
17	Bendamustine	825 (45.6 %)	1346 (74.4 %)
18	Tipifarnib	330 (18.2 %)	1346 (74.4 %)
19	Intensive chemotherapy	693 (38.3 %)	671 (43 %)
20	Lonafarnib	667 (36.8 %)	671 (43 %)
21	Epoetin alfa versus placebo	78 (5%)	438 (24.2 %)
22	Efficacy of azacitidine	280 (15.4 %)	671 (43 %)
23	Allogeneic versus autologous SCT	821 (45.3 %)	671 (43 %)
24	Allogeneic SCT for MDS with marrow fibrosis	190 (10.5 %)	250 (10.5 %)
25	Antithymocyte globulin plus cyclosporine	343 (18.9 %)	663 (36.6 %)
26	Lenalidomide versus placebo	55 (3%)	120 (6.6 %)
27	Lemon-5	36 (1.9 %)	106 (5.8 %)
28	Low-dose decitabine	125 (6.9 %)	1346 (74.4 %)
29	Vidazaallo	121 (67 %)	671 (43.5 %)
30	FLAMSA	162 (8.9 %)	671 (43.5 %)
31	**Oral azacitidine**	45 (2.4 %)	1138 (62.9 %)
32	Lenamaint	7 (0.4 %)	31 (1.7 %)
33	Deferasirox	249 (13.8 %)	311 (17.1 %)
34	Romidepsin plus 5-Aza	24 (1.3 %)	101 (5.6 %)
35	Panobinostat	153 (8.4 %)	1138 (62.9 %)
36	Azacitidine and lenalidomide	122 (6.7 %)	122 (6.7 %)
37	**Azacitidine and donor lymphocyte infusions**	121 (6.7 %)	250 (13.8 %)
38	Deferasirox	206 (11.3 %)	206 (11.3 %)
39	Azacitidine and donor lymphocyte infusions after allogeneic stem cell transplantation	80 (4.4 %)	80 (4.4 %)
30	Volasertib	159 (8.7 %)	671 (43 %)
41	**AZALENA**	32 (1.8 %)	80 (4.4 %)
42	**Decitabine with/without hydroxyurea**	32 (1.7 %)	87 (4.5 %)
43	Decitabine versus best supportive care	36 (1.9 %)	1346 (74.4 %)
44	**TRANSATRA**	224 (124%)	1346 (74.4 %)
45	Romiplostim	193 (10.6 %)	1138 (62.9 %)
46	Rigosertib	126 (6.9 %)	129 (7.1 %)
47	**Imetelstat**	81 (4.4 %)	470 (25.9 %)
48	**ACE 536-03 cohort 2a**	79 (4.3 %)	132 (7.2 %)
48	**ACE 536-03 cohort 2b**	150 (8.3 %)	470 (25.9 %)
49	Decitabine	145 (8%)	1346 (74.4 %)
50	Eltrombopag or placebo	173 (9.5)	1346 (74.4 %)
51	**Eltrombopag**	43 (2.4 %)	180 (10 %)
52	Deferasirox + Epo (Kallisto)	104 (5.7 %)	403 (22.3 %)
53	ACE 536-001	41 (2.2 %)	114 (6.3 %)

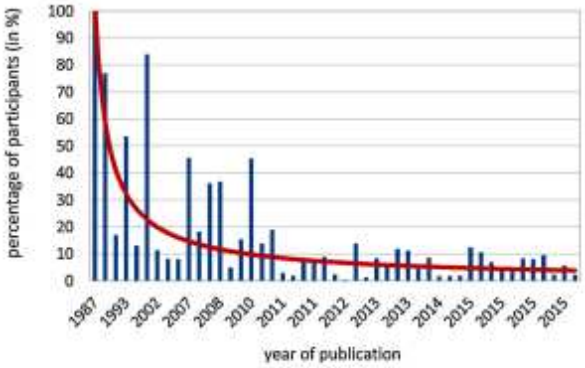

Fig. 1. Average eligibility of MDS patients for clinical trials per year between 1987 and 2015, taking into account all inclusion and exclusion criteria.

to a lower eligibility rate. We considered that many clinical trials, especially more recently performed, had a rather narrow definition of the target population, due to a specific biological activity of the investigational medicinal product or due to certain genetic or clinical criteria. For example, such trials may exclude a large proportion of patients by focusing on subtype- or therapy-specific aspects such as karyotype (del5q) or a certain disease status like relapse after allogeneic stem cell transplantation. Another major barrier is pre-treatment with erythropoiesis-stimulating agents, lenalidomide, hypomethylating agents, or other drugs. On the other hand, patients may be excluded from clinical trials if they have not proven resistant to the above-mentioned medications.

Due to methodological reasons we were not able to assess other parameters that may deter from trial participation, such as patient preference or logistical problems. Therefore, the proportion of study participants among MDS patients in an every-day clinical setting is expected to be even lower. As the analyses are based on clinical trials offered at an institution with special expertise in MDS, the access to trials of new therapies is probably even worse in other centres and heavily relies on referral of MDS patients to centres of excellence. A potential limitation of our analysis might be that data on aspects such as comorbidities and prior treatment are not available in the overall group of 7500 patients in contrast to our analysis cohort of 1809 patients. Nevertheless, the selected cohort is representative to the overall cohort with regards to the distribution of MDS risk groups and overall survival/ risk for progression into sAML. Advanced age is another confounding factor. Median age at the time of MDS diagnosis is about 71 years [3]. Only 10 % are younger than 50 years [1]. Geriatric patients tend to be more reluctant or have logistical barriers to participate in a clinical trial, partly because of the more frequent travel required. Some patients do not like to participate in a randomized phase 3-trial without opportunity for cross-over, fearing that their chance to potentially benefit from a promising compound is limited. Other patients do not consent to repeat bone marrow punctures, including trephine biopsies, or other procedures that might be performed more frequently in the context of a clinical trial. Non-disease-specific exclusion criteria such as kidney and liver dysfunction, psychiatric comorbidities etc., did not explain the unsatisfactory patient recruitment in our study. It is mainly the restrictions due to disease-specific criteria that cause problems regarding eligibility. Some clinical trials conducted by the pharmaceutical industry have extremely narrow inclusion criteria resulting in a pronouncedly low number of patients eligible. As a consequence, the results of such trials pertain to a rather small proportion of the general MDS patient population and are often not confirmed in a real-world setting [54,55]. Finally, we observed a seemingly paradoxical correlation between eligibility for study participation and life expectancy. Patients who were eligible to participate in a clinical trial had a shorter survival time on average. This observation is probably due to selection bias, as higher-risk patients with a more unfavourable prognosis have a strong

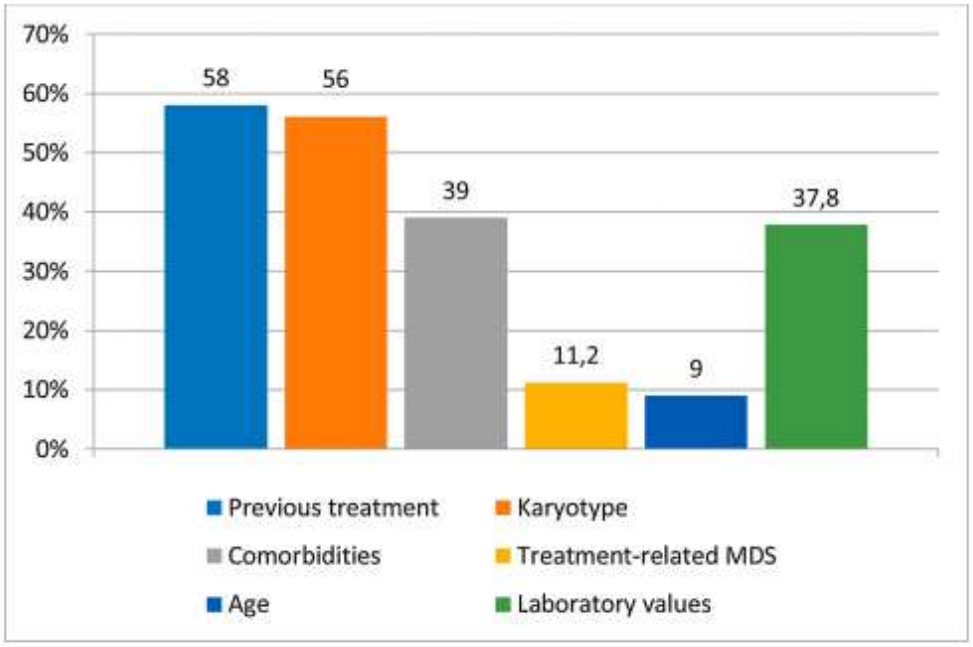

Fig. 2. Frequency of each major criterion leading to exclusion in our simulation cohort.

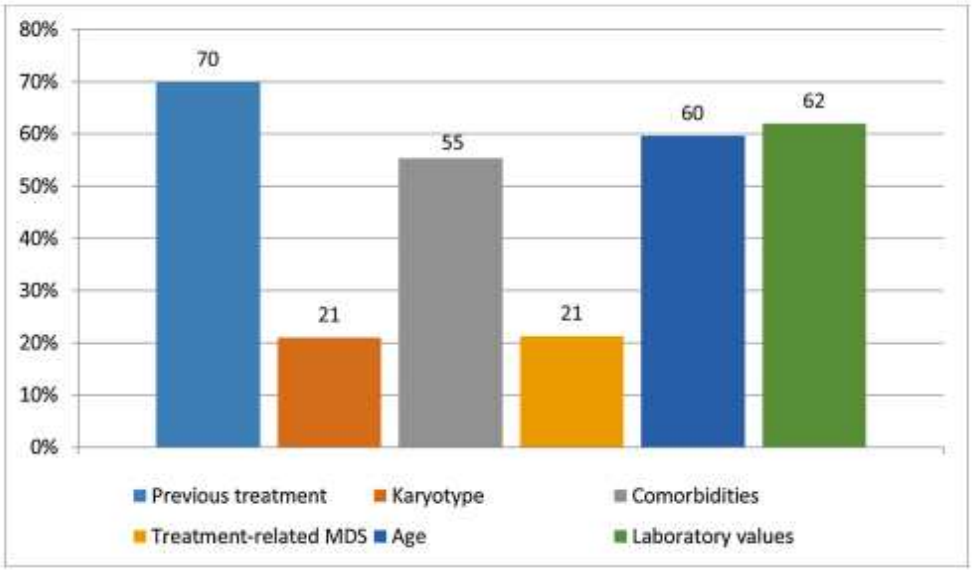

Fig. 3. Frequency of major exclusion criteria employed in the clinical trials under consideration.

need for therapeutic intervention and are more likely to be entered into clinical trials.

We are aware of the importance of a homogenous trial cohort for statistical evaluation, and we do not intend to advocate diffuse inclusion criteria. However, if study populations are generated too far from real-life by inclusion and exclusion criteria, patient recruitment becomes very difficult and trials may even be terminated early. A review article by Zeidan et al. [56] and commentaries published in Cancer [57] and in Leukemia [58] address the problem of low patient accrual in MDS trials and the differences between results from clinical trials and "real-life" data from registries. Potential solutions are discussed, namely revised inclusion and exclusion criteria, improvements in trial logistics, and greater flexibility in applying entry criteria.

The Düsseldorf MDS Registry is a valuable tool for planning clinical trials, allowing investigators to simulate the impact of more stringent or more relaxed inclusion criteria, thus helping to avoid the definition of unrealistic study populations.

Since there is a strong need for novel therapeutic options, promising compounds should be tested and made available to as many MDS patients as possible. To achieve proper risk stratification, validated prognostic scoring systems that better describe the course of the disease of specific MDS types such as the IPSS-R [59], the WPSS for MDS del(5q) [60], and the CPSS and CPSSmol [61,62] for patients with CMML, should be harnessed for clinical trials. We strongly recommend to consult with a clinical registry and simulate various inclusion/exclusion criteria before initiating a clinical trial for patients with MDS.

Data sharing statement

Original data sharing not possible due to SOP of MDS Registry. However, pseudonymized data can be sent to other researchers on demand.

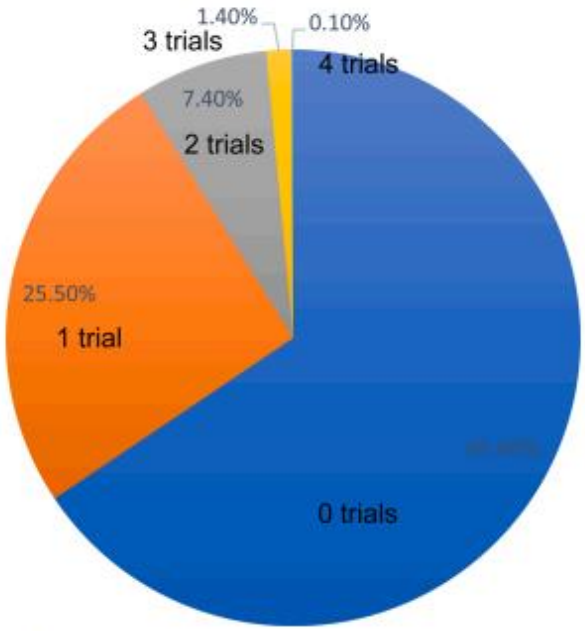

Fig. 4. Proportion of patients eligible for up to 9 MDS trials recruiting at our center in 2016.

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Declaration of Competing Interest

Kathrin Nachtkamp received speakers honoraria from Jazz und bsh medical, and travel support from Celgene. Thomas Schroeder received lecture fees and honoraria for consultancy from Celgene, JAZZ Pharmaceuticals, Takeda, Pfizer, Novartis and Janssen, research funding from Celgene and travel support from Celgene and Janssen. Esther Schuler received travel grants from Abbvie, Alexion, Celgene and Novartis and honoraria from Novartis. Jennifer Kaivers received travel support from Jazz und Novartis. Aristoteles Giagounidis participated in advisory boards from Amgen and Celgene as well as in a data monitoring committee from Novartis. Christina Rauternberg received travel support from Celgene und Jazz and lecture fees from Celgene. Norbert Gattermann received lecture honoraria from Novartis and participated in an advisory board from Novartis and received research support from Takeda. Ulrich Germing received speakers honoraria from Novartis, Celgene, Jazz, Janssen and Hexal and participated in an advisory board from Celgene. Josefine Stark, Andrea Kündgen, Corinna Strupp, Judith Strapatsas, Carlo Aul, Volker Runde, Rainer Haas and Guido Kobbe have no conflicts of interests to declare.

Acknowledgements

Kathrin Nachtkamp and Ulrich Germing designed the study, performed statistical analyses and wrote the manuscript.

Josefine Stark collected data and performed statistical analyses.

Andrea Kündgen, Thomas Schroeder, Corinna Strupp, Judith Strapatsas, Esther Schuler, Jennifer Kaivers, Axel Heyll, Aristoteles Giagounidis, Christina Rautenberg, Carlo Aul, Volker Runde, Rainer Haas, Guido Kobbe and Norbert Gattermann collected and entered data into the MDS registry and lead or performed clinical trials.

All approved the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2021.106611.

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