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RESEARCH

Outcomes in patients with acute myeloid leukemia older than 70 years within the last 30 years, a single center experience

Felicitas Schulz[1] · Claudia Roggenbuck[1] · Andrea Kündgen[1] · Annika Kasprzak[1] · Kathrin Nachtkamp[1] · Paul Jäger[1] · Sascha Dietrich[1] · Guido Kobbe[1] · Ulrich Germing[1] · Frank Neumann[1]

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Abstract

As median age of patients with acute myeloid leukemia is 72 years, older patients continue to be a vulnerable cohort representing significant challenges in clinical practice. Patient-specific comorbidities as well as leukemia-specific unfavorable molecular- and cytogenetics confer even poorer outcomes. Treatment of AML therefore needs to be less toxic to prevent harm while lowering or eradicating leukemic burden to prolong survival. In this retrospective analysis we included 365 older AML patients from the Düsseldorf registry who were diagnosed and treated in our department of hematology over a period of 31 years. Most patients were treated with HMA (37.3%) followed by 35.3% of patients who received either low dose chemotherapy or BSC. 9% of patients were treated with induction chemotherapy while 8.5% of patients received a combination of HMA with venetoclax. 4.1% of patients underwent allografting. At the time of last follow up, 35 patients (9.6%) were still alive. Of those patients who were treated with induction chemotherapy or HMA+venetoclax, 18.2% and 29.0% were still alive, whereas 60% of the patients who underwent allogeneic stem cell transplantation were still alive ($p<0.001$). Median overall survival of the entire patient population was 6 months. Longest survival was observed in patients who underwent aHSCT with an unreached median overall survival followed by patients who were treated with induction chemotherapy (21 months) or HMA plus venetoclax (11 months). The implementation of HMA+venetoclax and increasing numbers of aHSCT improved prognosis and survival even in older AML patients.

Keywords Acute myeloid leukemia · Prognosis · Treatment strategies

Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease of older patients with a median age at initial diagnosis of 72 years [1]. The classification of different subtypes according to the World Health Organization (WHO) and International Consensus Classification (ICC) of 2022 is based on cytomorphological, cytogenetical and molecular characteristics. While the 5th edition of the WHO classification still defines AML presenting with a minimum of 20% myeloid blasts in the bone marrow, the ICC enables diagnosing AML with at least 10% myeloid marrow blasts [2, 3]. Compared to the WHO classification of 2016, AML with myelodysplasia-related changes (AML-MRC), the most common subtype in older patients, is now called AML myelodysplasia-related (AML-MR) in WHO 2022 and is split up into AML with myelodysplasia-related gene mutations (AML-MR-M), AML with myelodysplasia-related cytogenetic abnormalities (AML-MR-C) and AML with mutated TP53 [2–4] in ICC 2022.

Although today there are more therapeutic options to treat AML, treatment-related mortality as well as therapy resistance confer a poor prognosis in elderly patients (≥70 years) [5, 6]. The proportion of patients with favorable genetic profiles as CBF translocations or isolated NPM1 mutations decreases with increasing age, whereas the number of patients with unfavorable karyotypes and mutations, such as for example TP53, increases [7–9].

Based on the patients' age and their concomitant comorbidities, a relevant number of patients is not suitable for intensive treatment such as induction therapy or allogeneic

✉ Felicitas Schulz
FelicitasIsabel.Schulz@med.uni-duesseldorf.de

[1] Department of Hematology, Oncology and Clinical Immunology, Heinrich-Heine University, Moorenstr. 5, Duesseldorf 40225, Germany

hematopoietic stem cell transplantation (aHSCT) while this remains the only curative option for patients suffering from secondary or therapy-related AML [5].

Both the National Comprehensive Cancer Network (NCCN) as well as the European LeukemiaNet (ELN) refrain from defining explicit criteria to decide whether an older patient is eligible for intensive treatment or not [7, 10]. In a considerable proportion of patients, best supportive care often remains the only option.

Several analyses within the last years showed that standard induction therapy in patients older than 75 years of age led to inferior survival and higher early death rates while patients with an ECOG ≥ 3 even had a significantly increased risk of death compared to younger patients [5–7]. However, over the last decades, several therapeutic strategies with different mechanisms of action have emerged. These comprise therapies with hypomethylating agents (HMA) with or without the bcl2-inhibitor venetoclax [11, 12], the addition of gemtuzumab ozogamicin to induction therapy [13, 14], gilteritinib and midostaurin for patients with mutated FLT3 [15, 16], and IDH inhibitors for patients with mutations in IDH1 or IDH2 [17, 18].

In our present analyses, we focus on data from 365 AML patients with a median age of 75 years and a minimum age of 70 years treated at the university hospital in Düsseldorf over a period of more than three decades to describe the impact of different therapies and changes in standard of care.

Table 1 Patient characteristics at the time of AML diagnosis

		n (%)	median (range)
Year of diagnosis	<2000	14 (3.8)	
	2000–2017	249 (68.2)	
	>2017	102 (28.0)	
Gender	Female	39.5	
	Male	60.5	
Age			75 (70–93)
Medullary blast count (%)			35 (20–99)
Blast count in peripheral blood (%)			28 (0–100)
Hemoglobin g/dl			9.1 (2.1–14.9)
WBC x 1000/µl			5.8 (0.4–365)
ANC x 1000/µl			1.32 (0–113.4)
Platelets x 1000/µl			59 (1–650)
LDH U/l			350 (94–5212)
Fever at diagnosis		34 (9.3)	
Infection at diagnosis		83 (22.7)	
Bleeding at diagnosis		21 (5.8)	
Extramedullary manifestation		14 (3.8)	
ECOG	0	35 (9.6)	
	1	84 (23.0)	
	2	68 (18.6)	
	3	33 (9.0)	
	4	8 (2.2)	
	unknown	137 (37.5)	

Methods

In this retrospective analysis we included 365 older AML patients from the Düsseldorf registry who were diagnosed and treated in our department of hematology over a period of 31 years. Patients were allocated to three different groups depending on time of diagnosis. The periods chosen were before the year 2000, between 2000 and 2017 and later than 2017 because of the rollout of HMAs in 2000 and venetoclax in 2018. Patient characteristics and treatment history were evaluated and survival times according to the various treatment modalities such as non-intensive cytotoxic chemotherapy, induction chemotherapy, allogeneic blood stem cell transplantation (aHSCT), hypomethylating agents (HMA) with or without venetoclax and best supportive care (BSC) including red blood cell and platelet transfusions as well as growth factors were calculated. Patients were classified according to the most intensive treatment they received during the course of the disease. Besides survival, the causes of death, ECOG and Karnofsky index, the ELN risk categories [19] as well as selected molecular genetics were evaluated. Descriptive statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 28 (SPSS, Chicago, IL, USA). Clinical and hematological data at the time of diagnosis were compared using the χ^2 and Wilcoxon rank sum test. A two-sided p-value of less than 0.05 was considered as statistically significant. The probability of survival was estimated using Kaplan–Meier method [20].

Results

Patient characteristics at the time of AML diagnosis are shown in Table 1. Median age at diagnosis was 75 years (range 70–93) with 60.5% of patients being male. 68.2% of patients were diagnosed between 2000 and 2017. ECOG performance status at the time of diagnosis was 0 in 9.6% of patients, 1 in 23.0%, 2 in 18.6%, 3 in 9.0% and 4 in 2.2% of patients and remained unknown in 137 patients due to missing data. The majority of patients (57%) were classified as AML-MR while 11.2% of patients suffered from a myeloid neoplasm post cytotoxic therapy as shown in Table 2. Patients were allocated to the different risk groups of ELN 2022 if possible, meaning that they were only classified in case of complete molecular data or enough data to allocate them to the adverse risk group (e.g. complex karyotype or TP53 mutation). The remaining patients were allocated to

Table 2 AML subtypes according to WHO 2022

WHO Type	*n* (%)
AML with recurrent cytogenetics	**242 (66.3)**
AML MR	208 (57.0)
AML with NPM1	30 (8.2)
AML with CEBPA	3 (0.8)
AML with MECOM-r	1 (0.3)
AML defined by differentiation	**77 (21.1)**
AML with minimal differentiation	5 (1.4)
AML without maturation	24 (6.6)
AML with maturation	21 (5.8)
Acute myelomonocytic leukemia	10 (2.7)
Acute monoblastic and monocytic leukemia	16 (4.4)
Pure erythroid leukemia	1 (0.3)
Myeloid neoplasm post cytotoxic therapy	**41 (11.2)**
Unknown	**5 (1.4)**

Table 3 Molecular genetics at time of diagnosis

Type of mutation	*n* (%)
NPM1	30 (8.2)
FLT3	23 (6.3)
ITD	16 (4.4)
TKD	7 (1.9)
IDH	22 (6.0)
IDH1	8 (2.2)
IDH2	14 (3.8)
ASXL1	18 (4.9)
RUNX1	16 (4.4)
CEBPA	10 (2.7)
TP53	9 (2.5)

Table 4 Patients' risk categories according to ELN 2022

Risk category	*n* (%)
Favorable	22 (6.0)
Intermediate	19 (5.2)
Adverse	141 (38.6)
Undefined	183 (50.1)

the 'undefined' cohort. A complete molecular panel was only available in 13.3% of patients while for example NPM1 was analyzed in 35% of patients. 6.0% of patients were categorized as favorable according to ELN2022, 5.2% were allocated to the intermediate risk category and 38.6% of patients belonged to the adverse risk group while 50.1% had missing genetic data and could not be classified explicitly. Further details according to molecular genetics as well as cytogenetics at time of diagnosis and the resulting ELN 2022 risk categories can be found in Tables 3 and 4.

Most patients were treated with HMA (37.3%) followed by 35.3% of patients who received either low dose chemotherapy or BSC. 9% of patients were treated with induction chemotherapy while 8.5% of patients received a combination of HMA with venetoclax. 5.8% of patients did not receive any treatment and 4.1% of patients underwent aHSCT as shown in Table 5.

Patients who did not receive any therapy as well as those who were treated with low dose chemotherapy alone had a median survival time of 1 month while those ones receiving best supportive care survived 2 months. The use of HMA increased the survival time up to 7 months ($p<0.05$). A survival time of 11 and 18 months could be observed in patients treated with HMA in combination with venetoclax or induction chemotherapy. Patients who underwent aHSCT had the best prognosis with a median survival time of 36 months as shown in Fig. 1. To further investigate patient's outcomes, we additionally looked at patients being safely categorized according to ELN 2022 alone and analyzed those 182 patients separately. Patients who received induction chemotherapy survived longer (21 vs. 18 months) while the median overall survival of patients who underwent allogeneic stem cell transplantation was not reached. Detailed information is shown in Table 6. Overall survival of patients according to time of first diagnosis got better with future time of diagnosis and is shown in Fig. 2. Multivariate analysis including patients' age, gender, ECOG, ELN 2022, time of first diagnosis and type of treatment showed that only the

Table 5 Major characteristics of the different treatment groups

	All patients ($n=365$)	No treatment ($n=21$)	BSC ($n=65$)	Cytoreduction ($n=64$)	HMA ($n=136$)	HMA+BCL2 inhibition ($n=31$)	Induction ($n=33$)	Allografting ($n=15$)	*p*-value
Age, median	75	76	78	76	74	76	72	72	
Male	221 (60.5%)	9 (42.9%)	40 (61.5%)	36 (56.3%)	84 (61.8%)	18 (58.1%)	20 (60.6%)	14 (93.3%)	
Year of diagnosis < 2000	15 (4.1%)	6 (28.6%)	7 (10.8%)	2 (3.1%)	0	0	0	0	0.001
Year of diagnosis 2000–2017	248 (67.9%)	14 (66.7%)	44 (67.7%)	54 (84.4%)	103 (75.7%)	0	29 (87.9%)	4 (26.7%)	0.001
Year of diagnosis > 2017	102 (27.9%)	1 (4.8%)	14 (21.5%)	8 (12.5%)	33 (24.3%)	31 (100%)	4 (12.1%)	11 (73.3%)	0.001
Median survival in months (range)	6	1 (0.4–2.2)	2 (0.6–3.4)	1 (0.2–1.8)	7 (5.5–8.5)	11 (1.8–20.2)	18 (14.8–21.2)	36 (21.9–84.3)	0.001

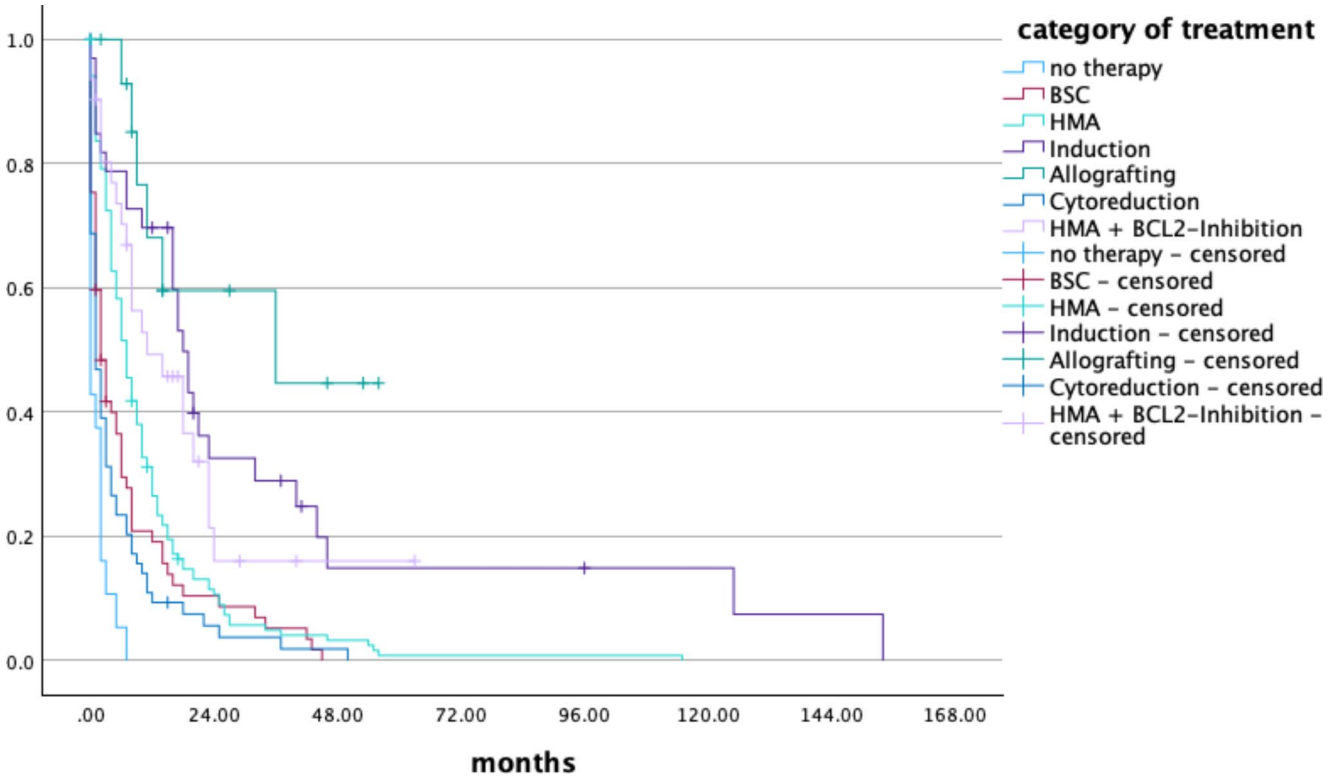

Fig. 1 Survival time according to most intensive treatment category

Table 6 Major characteristics of the different treatment groups, only patients with exact ELN2022 risk score ($n=182$)

	All patients ($n=182$)	No treatment ($n=5$)	BSC ($n=20$)	Cytoreduction ($n=24$)	HMA ($n=76$)	HMA+BCL2 inhibition ($n=30$)	Induction ($n=14$)	Allografting ($n=13$)	*p*-value
Age, median	74	73	77	77	74	76	72	72	
Male	118 (64.8%)	4 (80%)	14 (70.0%)	15 (62.5%)	47 (61.8%)	17 (56.7%)	9 (64.3%)	12 (92.3%)	
Year of diagnosis < 2000	1 (0.5%)	0	1 (5.0%)	0	0	0	0	0	0.001
Year of diagnosis 2000–2017	98 (53.8%)	5 (100%)	11 (55.0%)	20 (83.3%)	50 (65.8%)	0	10 (71.4%)	2 (15.4%)	0.001
Year of diagnosis > 2017	83 (45.6%)	0	8 (40.0%)	4 (16.7%)	26 (34.2%)	30 (100%)	4 (28.6%)	11 (84.6%)	0.001
Median survival in months (range)	6	1 (0.1–1.2)	1 (0–2.6)	2 (0.7–3.4)	6 (3.7–8.3)	11 (5.1–16.9)	21 (16.5–25.5)	Not reached	0.001

intensity of treatment had indepedent impact on survival, whereas the categorization according to ELN 2022 as well as the other variables did not. Further information regarding 95% CI and p-value are shown in Table 7.

Discussion

Acute myeloid leukemia is a disease most frequently diagnosed in older, comorbid patients who are often not eligible for intensive treatment due to pre-existing conditions as well as disease-related problems mostly linked to associated cytopenia. Furthermore, the underlying disease biology and differences in treatment tolerance still lead to poor outcomes. Relying on chronological age alone as a surrogate for patients being eligible for intensive treatment remains a limitation and perpetuates the balancing act between under- and over-treatment resulting in the fact that these patients still comprise a challenge in clinical daily routine.

Until today, there is no consensus regarding optimal therapy and standard of care for older adults with AML [21, 22], which is why we analyzed 365 AML patients with a median age of 75 years treated at our department of hematology over a period of more than three decades. Looking at

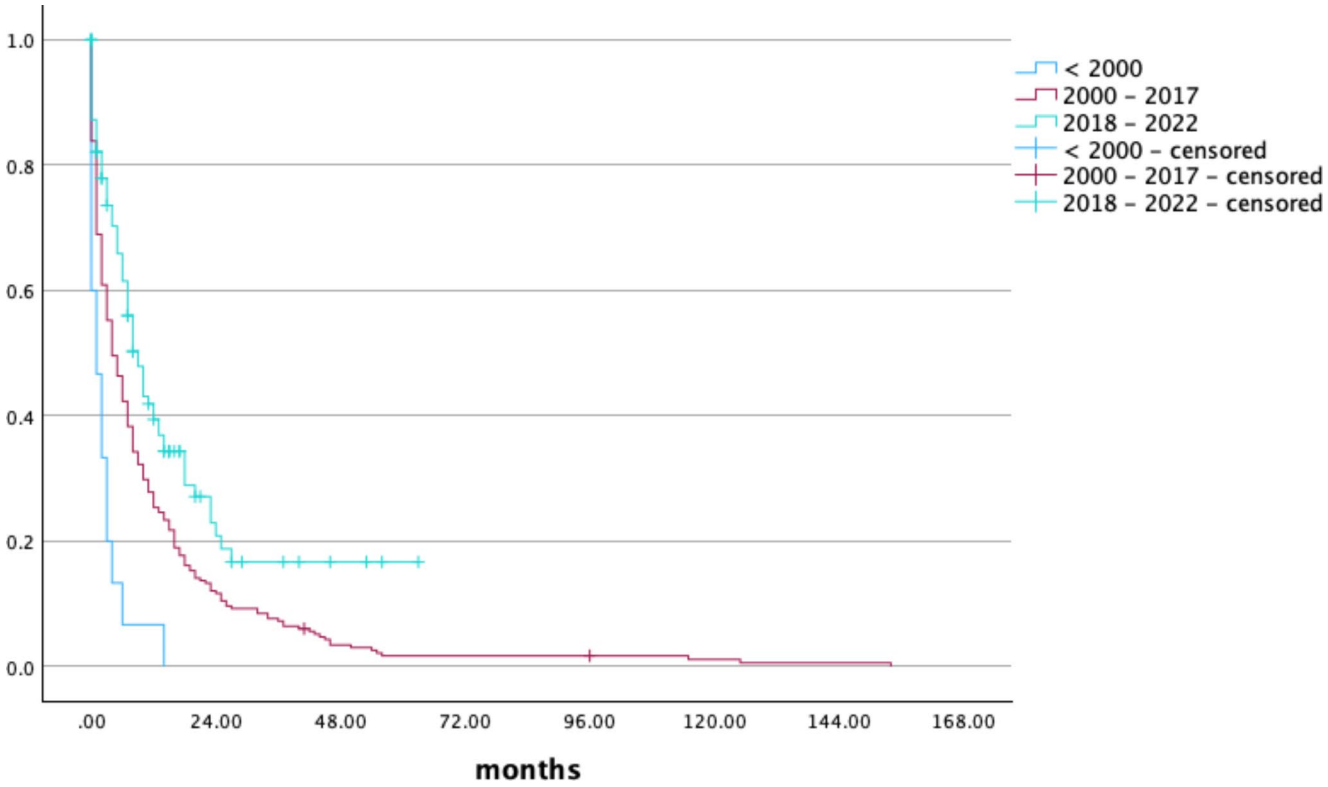

Fig. 2 Survival time according to time of diagnosis

Table 7 Significant results of multivariate analysis

Type of treatment	χ^2	*p*-value	Relative risk	95% CI
• Allografting	48,602	<0.001		
• Induction	0.689	0.407	1.663	0.5–5.528
• HMA + Venetoclax	4.321	0.038	3.109	1.067–9.058
• HMA	11.875	<0.001	5.984	2.163–16.555
• No treatment, BSC, cytoreduction	20.807	<0.001	11.11	3.948–31.265

our cohort, with a minimum age of 70 and the highest age of 93 years, patients were quite old compared to the literature where being categorized as an 'old patient' predominantly begins with the age of 60 years [5]. Compared to a large analysis within the United States where between 2000 and 2010 only 40% of patients being newly diagnosed with AML in an age > 60 years received AML-directed therapy [23], the number of patients within our cohort who received no treatment or best supportive care was quite low with only 23.4% between 2000 and 2017. After 2017, 78% of patients were treated with at least an hypomethylating agent being in line with the trend of recent studies towards more frequent use of leukemia-directed therapy in adults aged 65–80 years in the US [24, 25]. With AML-MR being the most frequent and myeloid neoplasm post cytotoxic therapy being the second AML subtype of our cohort, the composition was representative [26]. Since analyses of molecular genetics via next generation sequencing have been further developed and improved over the last 20 years [27], referring data was missing and in our cohort, with NPM1 being the most detected mutation and TP53 mutation only occurring in 2.5% of patients, not representative. Hereby, allocating patients to the different risk categories of ELN 2022, was only possible in 49.9% of cases. Regarding the most intensive treatment option patients did receive, treatment with hypomethylating agents like azacytidine or decitabine was the most frequent option in 37.3% of patients followed by cytoreduction and best supportive care each in a frequency of almost 18%. The median overall survival of 7 months in patients treated with hypomethylating agents was in line with data found in the literature ranging from 7 to 9 months in older AML patients treated with either azacytidine or decitabine [28, 29]. The small number of patients treated with a combination of azacytidine + venetoclax was the result of the approval for treatment with venetoclax in 2021 and its rollout in 2018 and fitted the fact that only patients with date of diagnosis in 2018 or later received this type of therapy. The median survival time of 11 months was shorter than described by DiNardo et al. who observed a median overall survival of 17.5 months in elderly patients [30]. Longer duration of median overall survival with 18 months was

seen in our patients undergoing intensive induction chemotherapy which was quite long compared to results of previous studies with a median overall survival < 1 year regarding the well-known 7 + 3 induction regimen as well as CPX-351 [5, 6, 31]. Regarding relapse rates, early mortality or complications like infections or febrile neutropenia, the combination of hypomethylating agents and venetoclax compared to induction therapy turned out to be equivalent or even better [32, 33] being in line with the development within our cohort to treat only a few justified exceptional cases with induction therapy or hypomethylating agents alone instead of a combination of HMA + venetoclax after 2018. Longest median overall survival of 36 months (and even an unreached median overall survival when only looking at the smaller group of 182 patients with a safely known ELN category) could be observed in patients who underwent allografting with only the smallest amount of 4% receiving an allograft but observing increasing numbers with only 4 patients undergoing aHSCT between 2000 und 2017 and 11 patients after 2017. This was again in line with data of the US where the number of aHSCT in older patients has increased visibly in the past decades, rising from less than 0.1% of transplants in 2000 to almost 4% by 2013 [34] and further increasing every year. Expanded knowledge and handling of transplant complications, increasing accessibility to unrelated donors, increased utilization of haploidentical donors and development of reduced-intensity conditioning strategies helped to improve transplant outcome and survival over time while low-intensive induction regimens such as HMA/venetoclax now serve as bridging therapy for remission induction prior to aHSCT making allografting a realistic option even for older patients with AML or other hematologic malignancies. Due to the concept of upfront allogeneic stem cell transplantation in patients not having a high leukemic burden, transplantation rates in our cohort have become quite high with 10% of patients being diagnosed after 2017. Other therapeutic options we were not able to discuss due to missing data were IDH-inhibitors, FLT3-inhibitors, Menin-Inhibitors as well as triplet combinations. In patients with *IDH1* mutation, ivosidenib in combination with HMA improved median overall survival as well as event free survival and response rates compared to monotherapy with HMA [35] while IDH-mutated AML patients who were considered too frail for HMA-based treatment may be offered monotherapy with IDH1/IDH2 inhibitors [17, 36]. The role of FLT3-inhibitors in older patients remains limited as it was mainly combined to intensive induction chemotherapy, but gilteritinib has been approved in the relapsed/refractory setting as monotherapy with a median overall survival of almost ten months [37]. The role of Menin inhibitors in previously untreated, older AML-patients with NPM1 mutations and KMT2A rearrangement is still under investigation in current clinical trials [38] and same applies to triplet combinations like IDH- or FLT3-inhibitors with HMA and venetoclax [39, 40].

Our analyses of 365 older AML patients diagnosed at our department of hematology over a quarter of a century has limitations. Looking at the distribution of patients within our cohort, a relevant number of 68.2% of patients were diagnosed between 2000 and 2017 with only 3.8% of patients being diagnosed before the year 2000 leading to a time bias as well as there is a time-lead bias regarding patients who received an aHSCT due to the fact that patients had to live long enough to experience allogeneic transplantation. Since genetic analyses have evolved over the last 20 years and molecular testing has become more frequent, there is a huge lack of data making important gain of information like ELN classification of the whole cohort impossible. As our analyses are retrospective and documentation of patients has not always been as extensive and disposable as today, we were not able to give evidence about interesting end points like event-free survival, remission or relapse rates as well as treatment-related mortality.

Conclusion

Older patients suffering from acute myeloid leukemia and hematologic malignancies in general continue to be a vulnerable patient cohort representing significant challenges in clinical daily practice. Patient-specific factors like comorbidities as well as leukemia-specific factors such as underlying unfavorable molecular- and cytogenetics presuppose even poorer outcomes than in younger cohorts. Treatment of AML therefore needs less toxic and more targeted options to prevent harm maintaining quality of life while lowering or eradicating leukemic burden to prolong survival.

As the combination of HMA and venetoclax has enhanced treatment of AML and other therapeutic options in terms of targeted therapies are evolving, the paradigm of conventional 7 + 3 induction is no longer a favored option in vulnerable patient cohorts. With more targeted and simultaneously less toxic therapies, the aim is to widen the landscape of treatment possibilities for elderly patients with AML while prolonging survival and reducing treatment-related mortality.

The combination of upfront allogeneic stem cell transplantation in patients not having a high leukemic burden with less toxic options of conditioning regimens and further experience in transplant complications made allografting a realistic option even for older AML patients.

In conclusion, therapy for older patients with AML has evolved while more therapeutic options are in the pipeline

reinforcing even more that care of older and unfit adults needs to essentially stay personalized.

Author contributions F.S., C.R. and U.G. wrote the main manuscript text, prepared figures and tables and did statistical analyses. A.Kuendgen, A. Kasprzak, K.N., P.J., G.K., S.D. and F.N. edited the manuscript. All authors reviewed the manuscript and agreed to the published version.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Heinrich-Heine University in Duesseldorf.

Informed consent Informed consent was obtained from all subjects in the study.

Competing interests F.N.: Stock in Gilead and 270Bio, equity in ORNA, MPM entrepreneur partner. G.K.: Advisory Role, Speaker Honoraria and/or travel support: MSD, Pfizer, Amgen, Novartis, Gilead, BMS-Celgene, Abbvie, Medac, Biotest, Takeda, Eurocept. Financing of scientific research: BMS-Celgene, Amgen, Abbvie, Eurocept, Medac. U.G.: Institutional research support: BMS, Abbvie, Jazz. Speaker honoraria: BMS, Jansen.

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