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ARTICLE

Real-world outcomes of unselected elderly acute myeloid leukemia patients referred to a leukemia/hematopoietic cell transplant program

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Abstract

Due to perceived intolerance, many elderly AML patients do not receive therapy, and few are considered for hematopoietic cell transplantation (HCT). To better understand "real-world" outcomes, 323 consecutive AML patients ≥ 60 years referred from 2009 to 2017 were evaluated (median age 70 [60–88] years); favorable (fav) in 48 (15%), intermediate (int) in 112 (35%) and poor risk in 161 (50%). Remission induction therapy, either intensive chemotherapy (IC, $n = 205$) or hypomethylating agents (HMA, $n = 57$), was given to all but 61 (19%) patients. With median f/u of 34 months, 2-year overall survival (OS) for the whole cohort was 31%; 40 and 33% for IC- and HMA-treated vs. 0% for untreated patients. Early mortality was 14%. Remission (CR/CRi) was achieved in 60% of patients, with approximately half of these surviving 2 years. In transplant-eligible patients (60–75-year-old, int/poor risk, achieving remission), 54 (46%) of 118 received HCT. Transplanted patients had improved 2- and 3-year post-remission survival of 59% and 40% compared to 26% and 18% in similar patients not receiving HCT (HR = 0.59, 95% CI 0.37–0.93, $p = 0.023$). These results suggest that survival of elderly AML patients may be improved through a coordinated approach of remission induction therapy for most patients followed by HCT when feasible.

Introduction

Although acute myeloid leukemia (AML) accounts for only about 1% of all cancers, it is the most common acute leukemia in adults. In the United States, it is estimated that 19,520 new cases of AML will be diagnosed in 2018 and 10,670 AML-related deaths will be recorded [1]. AML is generally a disease of older adults and is uncommon before the age of 45. The median age at diagnosis is 68 years, with patients diagnosed most frequently between ages 65 and 74 years.

Current treatment guidelines recommend intensive chemotherapy (IC) induction for most younger patients with AML, which should include an anthracycline and cytarabine, with treatment aimed at achieving a complete remission (CR). This is typically followed by curative-intent post-remission therapy which can vary from chemotherapy alone for favorable risk AML to allogeneic hematopoietic cell transplant (HCT) for poor-risk patients. Such an approach can lead to long-term disease control in approximately 40–50% of younger adult AML patients [2].

Older AML patients, ≥60 years of age, have significantly worse outcomes and the optimal approach to treatment for these patients remains less clear. Older AML patients have higher risk disease characteristics including less favorable cytogenetics and molecular findings, as well as a higher incidence of drug resistance [3]. Advanced age can also be accompanied by comorbidities and frailty which may have an important impact on tolerance to intensive therapies. However, studies show that age is more likely to be a surrogate for these other risk factors [4], and therefore age by itself probably is not a good variable to determine treatment or predict outcome.

Due to a perceived intolerance, many elderly AML patients do not receive therapy, and few are considered for curative intent HCT. This occurs despite the fact that multiple studies

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have now confirmed the efficacy of treatment vs. palliative approaches in improving outcomes for elderly AML patients [5–7]. A recent study documenting treatment patterns in the US utilizing the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database demonstrated that 48% of AML patients 66−80 years of age in the US receive no treatment for their disease [6]. Even more striking is the infrequent use of HCT which is utilized in only 6% of AML patients between 66 and 75 years of age [6].

Many experts now agree that outside of a clinical trial, physicians should (1) aim to deliver conventional IC in most "fit" elderly AML patients regardless of age, which should be followed by HCT in patients with intermediate or poor-risk disease when feasible, (2) avoid supportive care alone as a therapeutic approach as much as possible, and (3) administer at least low intensity chemotherapy, such as a hypomethylating agent (HMA) to patients not fit for IC [8, 9]. These principles form the basis of our treatment approach for patients referred to our combined Leukemia/HCT Program. In order to better understand treatment patterns and potential outcomes of a contemporary cohort of elderly AML patients, we analyzed 323 consecutive AML patients (≥60 years) referred to our program from 2009 to 2017.

Patients and methods

Patient characteristics

Institutional Review Board (IRB) approval was granted for this retrospective review of 323 consecutive newly diagnosed AML patients ≥60 years of age who were referred to the leukemia program at Northside Hospital between January 2009 and December 2017 for evaluation and management. All initial leukemia referrals seen in either inpatient or outpatient consultation during the above time frame were reviewed for eligibility. To be included in this analysis, patients had to be ≥60 years of age at the time of diagnosis, have a diagnosis of AML by the 2016 revised World Health Organization (WHO) criteria [10] and have received no prior therapy for AML. Patients receiving prior therapy for myelodysplastic syndrome (MDS) or other myeloid malignancy prior to AML diagnosis were not excluded. Patients with a diagnosis of acute promyelocytic leukemia (APL) were excluded from the analysis.

Treatment approach

Our treatment algorithm is to offer IC to all elderly AML patients that are deemed "fit" enough to tolerate such therapy. The decision to offer IC is solely at the discretion of the treating physician. No formal geriatric assessment is performed, and no fitness and/or comorbidity criteria are used for this decision. For patients deemed "unfit" for IC, most patients were encouraged to receive an HMA, either decitabine or azacitidine. A supportive care alone approach was generally discouraged but considered based on patient wishes and perceived feasibility of treatment.

As a rule, HCT was considered optimal consolidation therapy for all transplant-eligible patients age 60–75 years with intermediate- or poor-risk AML, who achieved a complete remission with or without complete blood count recovery (CR or CRi). Therefore, donor searching was initiated at the time of treatment initiation in all potentially transplant-eligible patients. Potential donor options included matched sibling, 8/8 matched unrelated, haploidentical and cord blood donors. The decision to eventually pursue HCT was based on donor availability, fitness, comorbidity burden, psychosocial issues (including sufficient caregiver support) and patient wishes.

Data analysis and endpoints

Baseline characteristics were prospectively recorded in our institutional database, and events (induction, consolidation and HCT type, response assessment, disease relapse, death, and cause of death) were entered into the database prospectively. These data were retrospectively extracted from the database at the time of analysis.

The major goal of the study was to analyze the real-world treatment patterns and survival of an unselected group of elderly AML patients ≥60 years of age referred to our program for evaluation and treatment, as well as to identify baseline characteristics predictive of survival outcomes. A secondary goal was to perform a preplanned subset analysis of AML patients between 60 and 75 years of age at remission (transplant-eligible) to identify post-remission survival outcomes and rates of HCT utilization in intermediate/poor-risk patients.

Statistical methods

Continuous variables were summarized as median and range. Pearson chi-square test and Wilcoxon rank sum test were respectively used to associate categorical and continuous characteristics with induction type or HCT status. Probability of overall survival (OS) was estimated using the Kaplan −Meier method. Survival outcomes were assessed between different groups using the log-rank test. A Cox proportional hazards model was built to examine the effects of baseline variables on hazard functions for OS since diagnosis. The following variables were considered in building Cox model: age at diagnosis (Dx) (60–66, 67–72, 73–88), WBC at Dx (<2.5, 2.5–25.8, ≥25.8), gender, race, AML subtype, NCCN risk, induction type (IC, HMA, none/other) and year of Dx (2009–2011, 2012–2014, 2015–2017).

In order to evaluate the effect of HCT on OS, a different Cox model was built for post-remission survival. HCT was retained as a time-dependent covariate in the model. Age at remission, gender, race, AML subtype, NCCN risk, induction type and year of remission were considered in building this Cox model. The forward stepwise selection algorithm was used for building both Cox models. The variables were selected by the 0.05 significance threshold. Receipt of HCT was identified as the only covariate significantly associated with post-remission survival. For selected variables, the proportional hazard assumption was tested by creating and including the time-dependent variable, $Z \times \log(t)$. Statistical analysis was performed by using the SAS software (version 9.4, the SAS institute, Cary, NC).

Results

Characteristics of the study cohort

A total of 323 consecutive elderly AML patients with a median age of 70 years (range 60, 88) were referred to our program between January 2009 and December 2017 for evaluation and management. Patient characteristics are listed in Table 1. At diagnosis, median (range) WBC was 7.4 (0.3, 251.4). AML was de novo in 68%, therapy-related in 10% and secondary (arising from antecedent hematologic disorder) in 22% (prior MDS—19%, prior MPN—3%). NCCN risk category [11] was favorable, intermediate, poor or unknown in 15%, 34%, 50% and 1% respectively.

Treatment patterns

Overall, 262 (81%) patients received treatment with a goal of remission induction; 205 (63%) received IC while 57 (18%) received HMA. Palliative-directed treatment was offered to 61 (19%) patients with supportive care ± palliative chemotherapy. Specific IC regimens included FLAG with (79) or without (39) idarubicin, idarubicin plus cytarabine "7 + 3" (58), CPX-351 (12) and other (11). Specific HMA regimens included decitabine (5-day) (13), decitabine (10-day) (12) or azacitidine (14). A treatment flowchart by age tertile is presented in Fig. 1. Among age tertiles (60–66, 67–72, 73–88 years), there were significant differences in treatment type: IC (86% vs. 72% vs. 31%), HMA (8% vs. 10% vs. 35%) and palliative treatment (6% vs. 18% vs. 33%), respectively ($p < 0.001$).

Patient characteristics according to treatment type are listed in Table 1. Compared to patients receiving IC, patients receiving HMA were older (median 76 vs. 67 years, $p < 0.001$) with lower presenting WBC (median 2.4 vs. 9.3, $p < 0.001$). There were no significant differences in AML subtype or NCCN risk category between IC- and HMA-treated patients. In the subset of patients age 60–75 years (potentially eligible for HCT), 76% of patients received IC while 10% received HMA. In these patients, the major IC regimens used were FLAG-Ida in 30%, 7 + 3 in 21%, FLAG in 14% and CPX-351 in 7%.

Response to induction therapy and early death

Overall, 130 (50%) of 262 treated patients achieved CR/CRi to the first induction attempt (either IC or HMA). Of patients not achieving remission, 29 additional patients achieved remission with further reinduction attempts so that 159 (61%) of 262 treated patients eventually achieved CR/CRi. Success at achieving CR/CRi varied significantly by age. Among age tertiles (60–66 years, 67–72 years and 73–88 years), CR/CRi to first induction was achieved in 60% vs. 57% vs. 26% of treated patients, respectively ($p < 0.001$); overall CR/CRi was seen in 72% vs. 68% vs. 36%, respectively ($p < 0.001$). In patients with fav risk AML, overall CR/CRi was 81%, compared with 66% and 48% in patients with int- and poor-risk disease, respectively. CR/CRi was achieved significantly more frequently in patients receiving IC vs. HMA treatment (CR/CRi to first induction, 59% vs. 16%; overall CR/CRi, 70% vs. 26%; $p < 0.001$).

Early death (ED), defined as death occurring <60 days after AML diagnosis, occurred in 37 (14%) of 262 treated patients; 9 (15%) of 58 receiving HMA and 28 (14%) of 204 patients receiving IC. For HMA-treated patients, ED occurred in 8/38 (21%) of patients aged 73–88 years vs. 2/20 (10%) for younger patients. For IC-treated patients, ED occurred in 9/93 (10%) of patients aged 60–66 years vs. 13/77 (17%) and 6/34 (18%) in the upper two age tertiles, respectively.

HCT utilization

In order to assess the likelihood that appropriate patients reach the planned goal of HCT consolidation, we analyzed the target population of int/poor-risk AML patients, age 60–75 years, who achieve CR/CRi following induction. HCT was performed in 54 (46%) of the 118 patients, which constituted 26% of total population of 60–75-year-old patients with intermediate/poor-risk AML. HCT was also performed for primary refractory disease in one patient and for recurrent AML in eight patients (four with int/poor risk and four with favorable risk disease).

For patients consolidated with HCT in first remission, median (range) days from remission to HCT was 93 (16, 217) days. HCT type for the 54 patients transplanted in first remission was autologous in 5 patients and allogeneic in 49 patients. Donor type was HLA-matched related, HLA-matched unrelated and haploidentical in 20, 19 and 10 patients, respectively. For the additional nine patients

Table 1 Patient characteristics according to treatment type ($n = 323$)

	Whole cohort ($n = 323$)		IC ($n = 205$)		HMA ($n = 57$)		Palliative ($n = 61$)		p value
Age									
Median	70		67		76		75		<0.001
Range	60–88		60–80		63–88		60–88		
Sex									
Female	137	42%	87	42%	21	37%	29	48%	0.556
Male	186	58%	118	58%	36	63%	32	52%	
Race/ethnicity									
W	278	86%	175	85%	50	88%	53	87%	0.925
B	27	8%	18	9%	5	9%	4	6%	
A	10	3%	7	3%	2	3%	1	2%	
H	8	3%	5	2%	0	0%	3	5%	
WBC									
Median	7.4		9.3		2.4		13		<0.001
Range	0.3–251.4		0.3–251.4		0.4–142		0.4–207		
Subtype									
De novo	218	68%	144	70%	37	65%	37	61%	0.592
Therapy-related	33	10%	21	10%	5	9%	7	11%	
Secondary	72	22%	40	20%	15	26%	17	28%	
NCCN risk									
Favorable	48	15%	36	18%	6	10%	6	10%	0.051
Intermediate	112	34%	71	35%	22	39%	19	31%	
Poor	161	50%	98	48%	29	51%	34	56%	
Unknown	2	1%	0	0%	0	0%	2	3%	
Induction type									
IC	205	63%							
HMA	57	18%							
None/palliative	61	19%							
IC subtype									
FLAG	39	12%							
FLAG-Ida	79	24%							
7 + 3	58	18%							
CPX-351	18	6%							
Other	11	3%							
HMA subtype									
Decitabine	41	13%							
Azacitadine	16	5%							

A Asian-Pacific Islander, *B* Black, *H* hispanic/latino, *HMA* hypomethylating agent, *IC* intensive chemotherapy, *W* White, non-hispanic, *WBC* white blood cell count at diagnosis

transplanted with relapsed or refractory disease, donor type was HLA-matched related, HLA-matched unrelated and haploidentical in 1, 5 and 3 patients, respectively.

Survival

With a median follow-up of 34.2 months (range 6, 107), the probability of OS at 1-, 2- and 3-year post diagnosis was 47%, 31% and 22%, respectively, in the whole cohort of 323 patients. In the youngest age tertile (60–66 years), predicted OS at 1-, 2- and 3-year post diagnosis was 53%, 35% and 25%, respectively, compared with 53%, 38%, and 29% and 34%, 19%, and 10% in patients age 67–72 and 73–88 years, respectively. There were no significant differences in survival between patients age 60–66 years compared with 67–72 years, whereas patients >72 years had inferior prognosis (Fig. 2a). In patients with NCCN favorable risk AML, predicted OS at 1-, 2- and 3-year post diagnosis was 66%, 58% and 46%, respectively, compared with 54%, 35%, and 22% and 36%, 20%, and 14% in

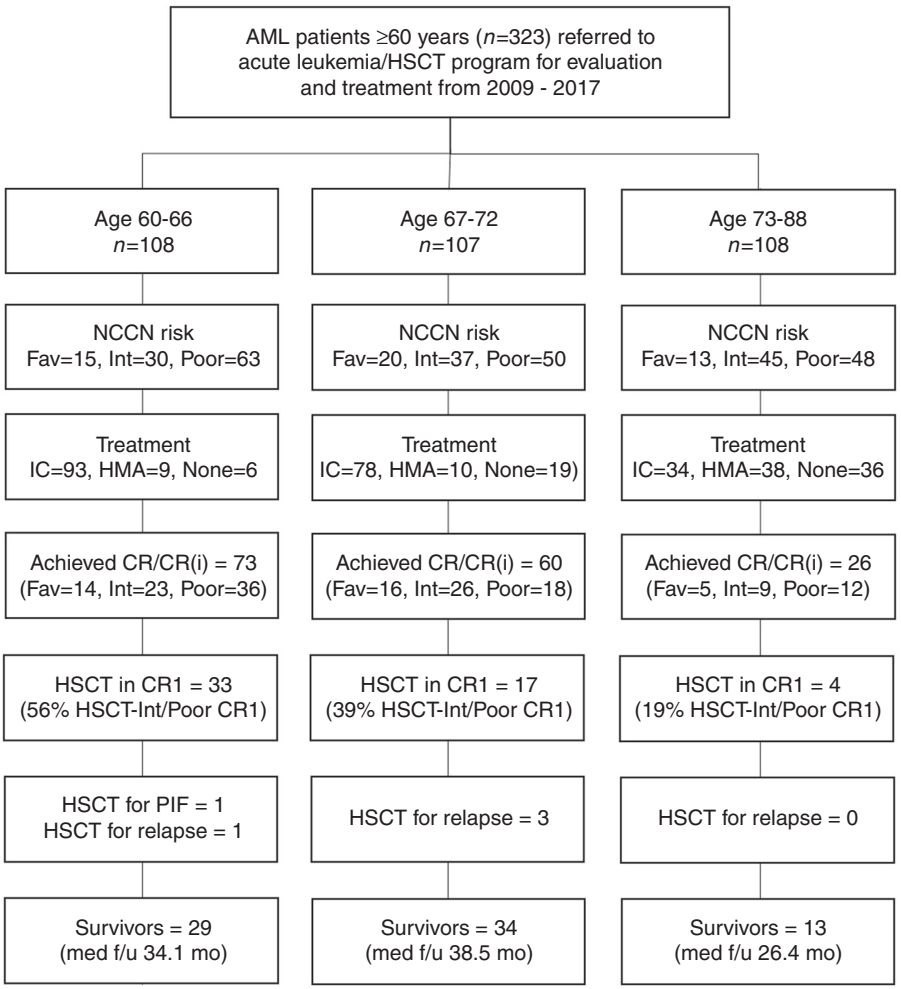

Fig. 1 Treatment flowchart by age tertile

patients with intermediate and poor-risk disease, respectively (Fig. 2b).

Low WBC at diagnosis (<2500 per microliter) was associated with statistically significant improvement in OS (Fig. 2c) compared with higher presenting WBC (2-yr OS of 38% vs. 26% and 28% for WBC 2500–25,800 and >25,800). Secondary AML, arising from an antecedent MDS or MPN, was associated with lower OS (Fig. 2d) compared with de novo or therapy-related AML (2-yr OS of 19% vs. 35% and 30% respectively). In multivariate analysis, characteristics associated with superior OS included low WBC at diagnosis (<2500 per microliter), NCCN risk category (favorable) and receipt of induction (IC or HMA vs. none/other) (Table 2).

OS was not statistically different for patients receiving either IC or HMA for induction therapy (Fig. 3a), but significantly better than patients receiving palliative care alone (2-yr OS was 40% and 33% vs. 0%, respectively). In patients receiving induction therapy (either IC or HMA), OS was correlated with the achievement of remission. Patients achieving CR/CRi to induction therapy ($n = 159$) had a better predicted 2-yr OS than the 103 patients that never achieved remission (52% vs. 16%, $p < 0.001$). Although HMA-treated patients achieved remission less frequently than those receiving IC (26% vs. 70%), OS was similar in remission patients regardless of induction type (1-, 2- and 3-year OS was 100%, 60% and 23% vs. 69%, 52%, and 37% respectively in HMA- vs. IC-treated remission patients). However, in patients not achieving CR/CRi, HMA-treated patients had a significantly better OS than IC-treated patients (Fig. 3b, long rank $p = 0.03$). In both IC- and HMA-treated patients, there was no statistically significant differences in survival between patients achieving CR/CRi with the first induction attempt vs. second or later induction attempt (data not shown).

To determine the effect of HCT consolidation on survival, we considered post-remission survival in a subset of transplant-eligible patients, defined as those age 60–75 years with intermediate/poor-risk AML, who achieved CR/CRi with induction therapy. Receipt of HCT was evaluated as a time-dependent covariate in the Cox model for post-remission survival. Receipt of HCT had a significant protective effect against mortality events after remission (HR = 0.59, 95% CI 0.37–0.93, $p = 0.023$). Baseline

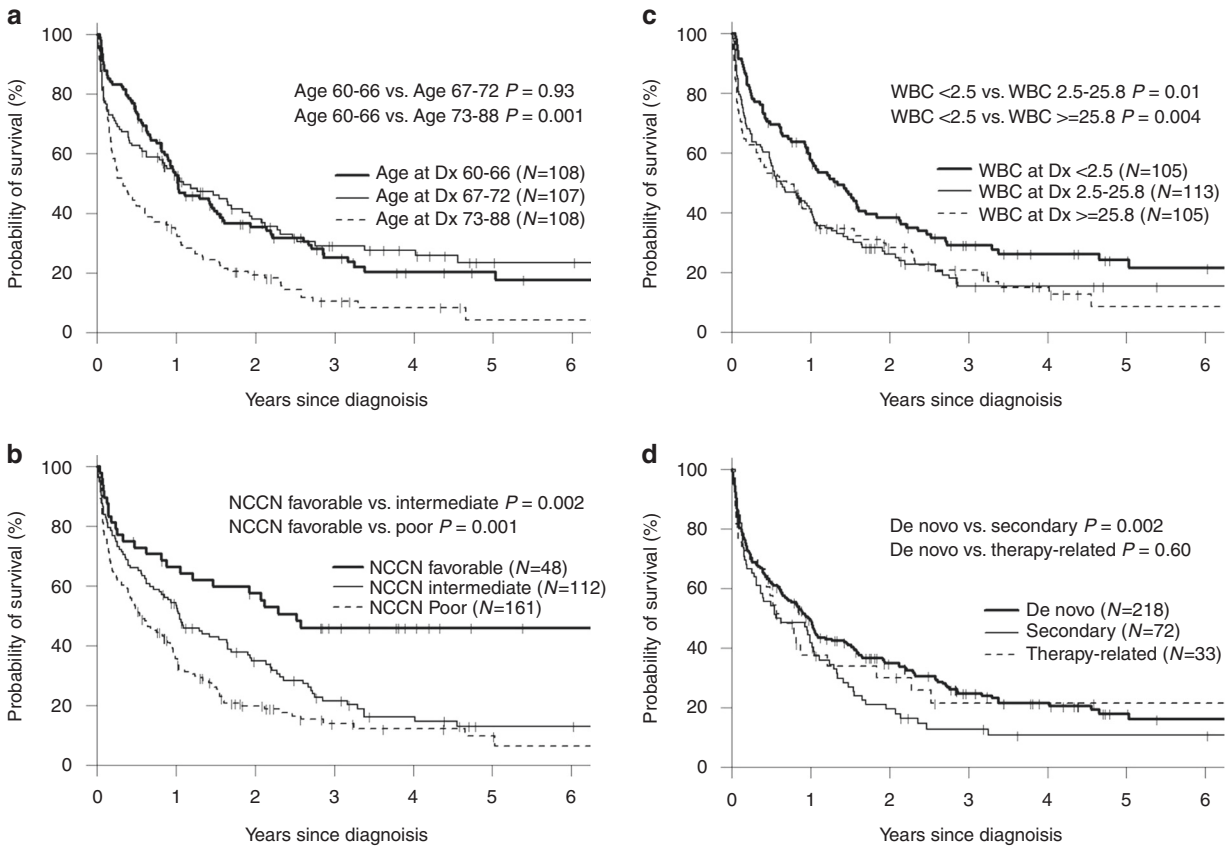

Fig. 2 Overall survival of elderly AML patients according to **a** age tertile, **b** NCCN disease risk category, **c** WBC count at diagnosis and **d** AML subtype

Table 2 Multivariate Cox model of baseline characteristics associated with overall survival

Factor	Effect	HR	95% CI	*p* value
WBC at Dx	[2.5, 25.8) vs. <2.5	1.92	1.40 – 2.63	<0.001
	≥25.8 vs. <2.5	1.93	1.39 – 2.68	<0.001
NCCN risk	Intermediate vs. favorable	2.02	1.29 – 3.16	0.002
	Poor vs. favorable	2.71	1.74 – 4.21	<0.001
Type of induction	HMA vs. IC	1.20	0.84 – 1.69	0.315
	None/other vs. IC	7.65	5.38 – 10.88	<0.001

The following baseline variables were considered in building Cox model: age at Dx (60–66, 67–72, 73–88), WBC at Dx (<2.5, 2.5–25.8, ≥25.8), gender, race, AML subtype, NCCN risk, induction type (IC, HMA, none/other), year of Dx (2009–2011, 2012–2014, 2015–2017)

characteristics were similar between those patients receiving or not receiving HCT including NCCN risk category, AML subtype, presenting WBC or type of induction (Table 3), although transplanted patients were slightly younger (median age 65 vs. 67 years, $p = 0.027$). OS was significantly improved by the receipt of HCT in first remission (Fig. 4). Post-remission survival at 1, 2 and 3 years in patients receiving HCT in first remission was 73%, 59% and 40% respectively, compared with 47%, 26% and 18% for patients not transplanted in first remission. The primary causes of death for patients receiving HCT included relapse/progression (60%), organ failure (17%), infection (12%) and graft-versus-host disease (9%).

Discussion

In this report, we describe the long-term outcome results of 323 consecutive AML patients ≥60 years referred to our leukemia program for evaluation and management. Data gathered in this study represent "real-world" outcomes that can be achieved when treating elderly AML patients with the intent of remission induction followed by HCT consolidation when feasible. In this unselected cohort of referred patients, approximately 60% of patients ultimately achieved CR/CR(i) with treatment with approximately half of remission patients surviving 2 years. The safety of this approach was evidenced by an acceptably low 60-day mortality rate of 14%. Patients with favorable NCCN risk

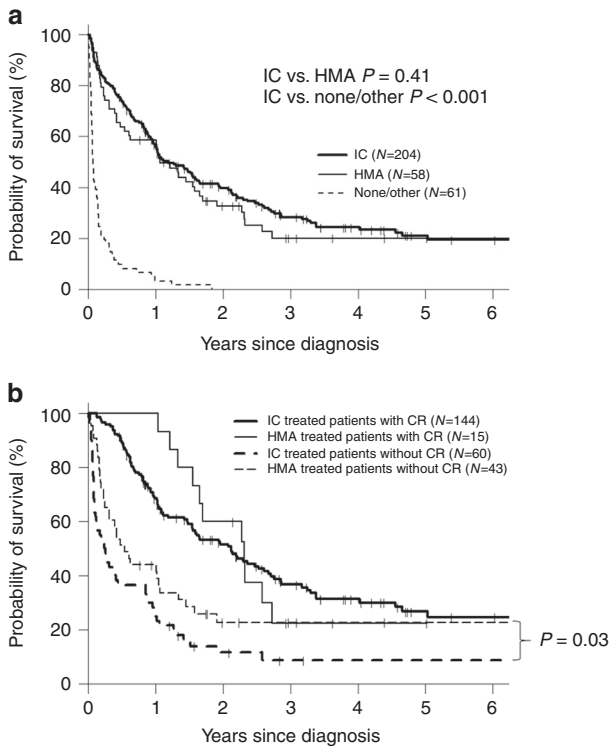

Fig. 3 Overall survival of elderly AML patients according to **a** receipt of induction therapy and **b** type of induction therapy and remission status

AML, although constituting only 15% of cases, had a particularly good outcome with 81% of patients achieving CR/CRi and a 2-year OS of 58%, compared to 35% and 20% in patients with int- and poor-risk AML, respectively.

This study also confirms the very poor prognosis of elderly AML patients who do not receive antileukemic treatment but only palliative care. In this single institution study, induction therapy with either IC or HMA resulted in a survival advantage, with patients who ultimately achieved remission having the greatest benefit. Interestingly, OS was not significantly different between IC- and HMA-treated patients despite a higher proportion of patients achieving remission in the former group (70% vs. 26%). This was due to a significant improvement in OS for HMA-treated patients not achieving remission compared with non-remission IC-treated patients, which led to comparable overall survival outcomes. However, it is important to emphasize that there were significant baseline differences in patients receiving HMA therapy, including older age and more indolent disease (lower WBC at Dx), which make direct treatment comparisons problematic.

When our analysis was restricted to the 255 patients age 60–75 years (potentially transplant-eligible by age), 86% of patients received induction therapy (76% IC, 10% HMA) and treated patients had a 2- and 3-year predicted OS was 42% and 30%, respectively. For the subset of 60–75-year-old patients with intermediate/poor-risk AML who achieved CR/CRi ($n = 118$), the population for which HCT consolidation is the preferred treatment approach, 54 (46%) patients eventually received HCT. Transplanted patients had a significantly improved 2- and 3-year predicted OS of 59% and 40% compared to 26% and 18% in similar patients not receiving HCT, which remained significant in a time-dependent Cox multivariate analysis.

Despite the fact that a sizeable number of elderly AML patients achieve durable progression-free survival with induction therapy with or without HCT, there remains a common misperception that intensive treatment results in poor response rates and unacceptable toxicity. As a result, a large number of elderly AML patients are not even offered curative intent therapy. Between 2000 and 2009, a linked SEER-Medicare database analysis demonstrated that 48% of 5067 patients between 66 and 80 years of age with newly diagnosed AML received no treatment other than supportive care (no treatment offered to 33%, 45% and 59% for ages 66–70, 71–75 and 76–80, respectively) [6]. Similarly, according to recent estimates, only about 6% of AML patients older than 60 in the United States undergo HCT [12].

Despite the real-world reluctance of physicians to offer therapy to elderly AML patients, the published data argues that most elderly AML patients should be offered remission induction therapy. National registry data from Sweden has shown that (1) early death rates are always lower in patients receiving intensive therapy compared with those receiving palliation only, (2) long-term survivors can be found among elderly patients given intensive treatment despite poor initial performance status and (3) survival of elderly AML patients is improved in the geographic areas where most elderly AML patients are given standard intensive therapy [13]. Other studies have also demonstrated improved outcomes for elderly AML patients receiving intensive therapy compared to supportive care approaches alone [7, 14]. Chronological age alone appears to be a particularly unreliable way to assess which patients will tolerate intensive chemotherapy [15, 16]. Therefore, it seems prudent to apply the same therapeutic principles that we apply in younger adults, namely that intensive chemotherapy induction remains the first choice whenever feasible and realistic on clinical grounds.

For patients who are not candidates for intensive treatment, every effort should be made to give lower intensity therapy such as HMAs. Although these agents result in a lower incidence of complete remission, they have a significant role in decreasing disease progression and improving patient quality of life [17, 18] and has shown a survival benefit in at least one randomized trial [19]. Even more impressive is recently published data on the combination of azacitidine or decitabine with venetoclax which has produced a promising CR/CRi rate of 67% and a

Table 3 Characteristics by BMT status in transplant-eligible patients, 60–75 years of age with intermediate-to-poor-risk AML achieving remission

	All patients		HCT in first remission		No HCT in first remission		*P* value
N	118		54		64		
Age							
Median	66		65		67		0.027
Range	60, 75		60, 75		60, 75		
Sex							
Male	69	58%	32	59%	37	58%	0.874
WBC							
Median	5.4		3.7		8.1		0.655
Range	0.5, 222		0.5, 216		0.7, 222		
Subtype							
De novo	83	70%	37	69%	46	72%	0.886
Therapy-related	26	22%	13	24%	13	20%	
Secondary	9	8%	4	7%	5	8%	
NCCN risk							
Intermediate	55	47%	27	50%	28	44%	0.498
Poor	63	53%	27	50%	36	56%	
Induction type							
IC	109	92%	51	94%	58	91%	0.436
HMA	9	8%	3	6%	6	9%	
Achieved CR/Cri							
to first induction	94	80%	43	80%	51	80%	0.994
to other induction	24	20%	11	20%	13	20%	
Time from CR to HCT							
Median days			93		836[a]		
Range			16, 217		657, 2213		
HCT type							
MRD			20	37%			
MUD			19	35%	2[a]		
HID			10	19%	2[a]		
Auto			5	9%			
# of survivors	35		21		14		
Survivor follow-up (mo)							
from Dx, M(range)	26	(6, 107)	26	(6, 92)	21	(7, 107)	0.827
from CR, M(range)	21	(5, 106)	25	(5, 91)	20	(5, 106)	0.699

A Asian-Pacific Islander, *Auto* autologous, *B* Black, *CR/CR(i)* complete remission with or without complete blood count recovery, *Dx* diagnosis, *H* hispanic/latino, *HID* haploidentical donor, *HCT* hematopoietic cell transplantation, *HMA* hypomethylating agent, *IC* intensive chemotherapy, *M* median, *mo* months, *MRD* matched related donor, *MUD* matched unrelated donor, *W* White, non-hispanic, *WBC* white blood cell count at diagnosis

[a]HCT performed for recurrent AML in second remission

median OS of 17.5 months in a large multicenter phase Ib clinical trial in patients 65 years of age or older with treatment-naive AML who were ineligible for intensive chemotherapy [20]. In contrast, patients treated with palliative approaches (supportive care with or without palliative chemotherapy) have a median OS of less than 6 months [21], and therefore such an approach should likely be avoided in the vast majority of elderly AML patients.

In elderly AML patients that achieve remission following induction therapy, fit patients up to 75 years of age should be evaluated for HCT consolidation. Although still a tremendously underutilized treatment modality [12], the use of HCT in older AML patients has increased significantly over the past 20 years likely due to the development of reduced-intensity conditioning (RIC) regimens and the use of alternative donors (haploidentical and cord blood) [22]. In 2015,

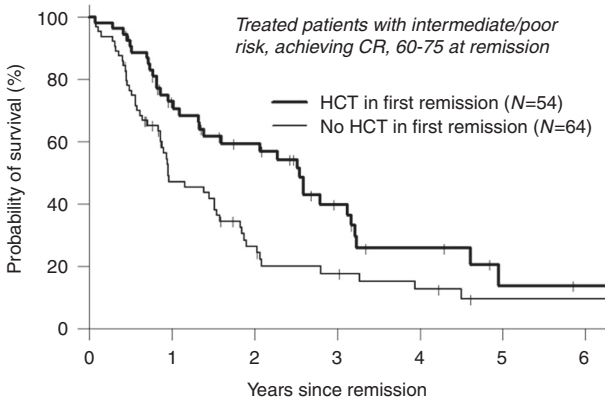

Fig. 4 Overall survival of elderly AML patients, 60–75 years, with intermediate/poor-risk disease in CR/CRi according to receipt of HCT

25% of all allogeneic HCT recipients were 60 years or older, increased from 5% in 2000 [22]. Patient age alone up to 75 years does not appear to impact survival after RIC HCT according to the Acute Leukemia Working Committee for the CIBMTR that reported a 2-year posttransplant OS of 35% [23]. Second, multiple retrospective analyses have demonstrated an advantage for HCT compared with conventional chemotherapy approaches in older AML patients [24–26]. Finally, a recent meta-analysis analyzing 14 studies with a sample size of 749 transplanted elderly AML patients demonstrated 3-year relapse-free survival and cumulative incidence of relapse of 35% and 39%, respectively [27]. Although these studies are all retrospective and subject to important patient selection bias, our data combined with the prior published literature suggest that a sizeable number of older AML patients can achieve durable remissions following HCT and argue against using age alone up to 75 years as a factor in patient selection. However, it is important to balance any discussion of survival benefit of HCT consolidation with important morbidity and quality-of-life implications associated with graft-versus-host disease [28–30].

This published experience of 323 consecutive elderly AML patients, referred for evaluation and treatment, suggest that survival may be improved through a coordinated approach of remission induction therapy followed by HCT when feasible. Due to a commitment to the goal of achieving remission, 81% of patients received induction treatment with nonresponding patients offered reinduction chemotherapy if feasible. With this approach, 60% of treated elderly AML patients ultimately achieved remission, with approximately half of these surviving 2 years. Furthermore, the integrated nature of our leukemia/HCT program, as well as the use of alternative donors, allowed for a 46% rate of HCT utilization in our study for transplant-eligible patients achieving remission to induction therapy. Such a rate compares favorably to the 14% rate of HCT seen in similar patients in a previously published prospective feasibility analysis [31]. Similar to other published studies, transplanted elderly AML patients in our study enjoyed a favorable 2- and 3-year post-remission survival probability of 59% and 40%, respectively. Patients with favorable cytogenetic or molecular risk also achieved good outcomes without HCT with a 3-year survival probability of 46%. In contrast, patients with poor-risk AML remain a challenge with only 48% of these patients ultimately achieving remission and a 3-yr OS of only 14%. New treatment strategies are clearly needed to improve outcomes in this patient population.

There are however some important limitations of this study. In addition to the standard concerns of bias and confounding that are inherent in retrospective studies, it is also important to account for potential referral bias, whereby frailer or higher disease risk patients might never be referred for evaluation. Additionally, there were important differences in the racial/ethnic composition of the elderly AML patients referred to our program which could affect the generalizability of the results, namely the higher number of non-Hispanic white patients in our study population (86%) compared with younger AML referrals (<60 years of age) to our program during a similar time period (64%), the latter of which more correctly reflects the racial distribution of AML in our state. The lower minority representation of elderly AML referrals should be an important area of future study. Furthermore, the determination of treatment (IC, HMA, palliative care) was not standardized in our study, further introducing potential bias. It is also important to realize that no formal geriatric testing was performed, and no assessments of frailty or comorbidity burden were utilized for treatment assignment. However, regardless of these concerns, our survival data are robust and add to a growing body of literature suggesting that a significant proportion of elderly AML patients benefit from a curative intent treatment approach. Referral to a comprehensive leukemia/HCT specialty center is therefore appropriate for most elderly AML patients up to 80 years of age.

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Compliance with ethical standards

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

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