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Comparisons of commonly used front-line regimens on survival outcomes in patients aged 70 years and older with acute myeloid leukemia

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ABSTRACT

In older patients with acute myeloid leukemia, the more frequent presence of biologically inherent therapy-resistant disease and increased comorbidities translate to poor overall survival and therapeutic challenges. Optimal front-line therapies for older patients with acute myeloid leukemia remain controversial. We retrospectively evaluated survival outcomes in 980 elderly (≥70 years) acute myeloid leukemia patients from a single institution between 1995 and 2016. Four treatment categories were compared: high-intensity (daunorubicin/cytarabine or equivalent), hypomethylating agent, low-intensity (low-dose cytarabine or similar without hypomethylating agents), and supportive care therapy (including hydroxyurea). At a median follow up of 20.5 months, the median overall survival for the entire cohort was 7.1 months. Multivariate analysis identified secondary acute myeloid leukemia, poor-risk cytogenetics, performance status, front-line therapy, age, white blood cell count, platelet count, and hemoglobin level at diagnosis as having an impact on survival. High-intensity therapy was used in 360 patients (36.7%), hypomethylating agent in 255 (26.0%), low-intensity therapy in 91 (9.3%), and supportive care in 274 (28.0%). Pairwise comparisons between hypomethylating agent therapy and the three other treatment groups demonstrated statistically significant superior median overall survival with hypomethylating agent [14.4 months) *vs.* high-intensity therapy 10.8 months, hazard ratio 1.35, 95% confidence interval (CI): 1.10-1.65; P=0.004], low-intensity therapy (5.9 months, hazard ratio 2.01, 95%CI: 1.53-2.62; P<0.0001), and supportive care (2.1 months, hazard ratio 2.94, 95%CI: 2.39-3.61; P<0.0001). Our results indicate a significant survival benefit with hypomethylating agents compared to high-intensity, low-intensity, or supportive care. Additionally, high-intensity chemotherapy resulted in superior overall outcomes compared to low-intensity therapy and supportive care. Results from this study highlight the need for novel therapeutic approaches besides utilization of intensive chemotherapy in this specific aged population.

Introduction

The incidence of acute myeloid leukemia (AML) increases with age, with a median age of ≥65 years at time of diagnosis.[1-3] Between 1975 and 2001, the 5-year survival of younger AML patients has more than doubled, yet the survival of patients over the age of 65 continues to remain dismal. These differences can primarily be attributed to the clinical and functional heterogeneity of disease in elderly patients. Compared with their younger counterparts, older patients have AML

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that is more frequently associated with chemotherapeutic resistance, unfavorable cytogenetics, increased frequency of somatic mutations, and preceded by myelodysplastic syndromes, making therapeutic decisions difficult.[4,5] Many patients have their treatment chosen more on the basis of chronological age rather than the inherent disease biology (i.e. karyotype, molecular heterogeneity, antecedent hematologic disorders, and leukocyte count at diagnosis) and overall fitness of patients.[6]

Like many other malignancies, optimizing medical care of patients with AML is dependent on clinical trials. Unfortunately, older patients, particularly those who are ≥70 years of age, are under-represented in randomized controlled trials. The lack of clear clinical data in this subset of patients often leads to uncertainty regarding optimal treatment strategies.

Over the past decade, new treatment strategies have emerged targeting the biological challenges in AML; however, there has been a lack of significant progress in optimizing strategies in the older AML population. Numerous studies have assessed risk stratification of this subgroup of patients with a goal toward building a comprehensive approach; however, a model to help guide treatment has yet to be validated.[2,7-10] The lack of a validated decision model has led to individualized and variable care of older AML patients. In an attempt to create a comprehensive decision analysis model, we present the results of a very large, single institution retrospective study of 980 patients aged ≥70 years. The aim of our study was to compare survival outcomes of older AML patients treated with various induction regimens. Such a study offers the advantage of combining cytogenetics, comorbidities, and functional status information and importantly accounts for therapeutic decisions in older patients with AML.[11-14]

Methods

Data collection

We retrospectively analyzed patients ≥70 years of age who presented to Moffitt Cancer Center between 1995 and 2016 for evaluation of newly diagnosed and previously untreated AML. The study was approved by the University of South Florida institutional review board. Inclusion criteria for the study were age 70 years or older and diagnosis of AML that was untreated prior to patient presentation at our institution. Patients with antecedent hematologic malignancies were included regardless of treatment. Compiled data were supplemented by direct review of medical records as necessary. A dual data entry technique was used to ensure data accuracy and quality. Baseline patient characteristics collected included vital status, age at diagnosis, sex, race/ethnicity, comorbidities for calculation of Charlson comorbidity index (CCI), Eastern Cooperative Oncology Group (ECOG) performance status, and antecedent hematologic disease and its treatment. Collected disease-specific characteristics included baseline cytogenetics, type of AML (*de novo* or secondary AML), complete blood count with peripheral blood blast percentage at time of diagnosis, choice of therapy, responses to treatment including complete remission (CR), complete remission with incomplete count recovery (CRi), relapsed disease, partial remission, and whether allogeneic hematopoietic stem cell transplant was performed. We defined secondary AML as an AML arising from an antecedent hematologic disorder or therapy-related AML.

Treatment groups

Patients were categorized into four different treatment groups: high-intensity therapy [defined as cytarabine and daunorubicin/idarubicin (7+3) or "7+3" equivalent], low-intensity therapy (defined as low-dose cytarabine or similar but not including hypomethylating agents), hypomethylating agent (HMA) therapy, and supportive care (including hydroxyurea). "7+3" equivalent regimens included high-dose cytarabine-based regimens, specifically CLAG+/-M (cladribine, cytarabine, granulocyte colony stimulating factor (G-CSF), with or without Mitoxantrone), MEC (Mitoxantrone, etoposide, cytarabine), and HIDAC (high-dose cytarabine) regimens. A categorical distinction between low-intensity therapy and HMA therapy was made on the basis of recent randomized reports suggesting the modest superiority of HMA *versus* conventional care regimens (including low-dose cytarabine), in addition to practice pattern differences worldwide that utilized either HMA or low-dose cytarabine as standard front-line therapy for older adults with newly diagnosed AML. Patients enrolled in clinical trials were assigned to one of the four treatments groups depending on the intensity of treatment received as part of the clinical trial.[15,16]

Definition of clinical end points

Response to therapy was defined as those who achieved CR or CRi as per the 2003 International Working Group response criteria for AML.[17] Overall survival was defined as time from date of diagnosis of AML to date of death if known or censored at the time of last follow up. Relapse-free survival was calculated as time from achievement of CR or CRi to date of relapse as defined by International Working Group 2003 criteria.

Statistical analysis

Survival function was estimated by the Kaplan-Meier method and compared across groups using the log-rank test. Cox proportional hazards regression model was used to determine the association between the variables and overall survival. Variables with $P<0.25$ in the univariate model were included in the initial multivariate analysis. The backward elimination method was used to select the variables for the ultimate multivariate model. Variables with $P>0.05$ were excluded. Pairwise comparisons of survival between different treatment groups were performed using the stratified log-rank test and propensity score matching to adjust for potential treatment indication bias between groups. Within pairwise comparison groups, the stratified Cox proportional hazards regression model was used to assess correlations between clinical variables and overall survival. Patients who had no information on response were considered as non-responders per the intention-to-treat approach. For treatment-related mortality (TRM) at day 30, patients who were censored before 30 days (n=5) were not eligible and were excluded from the analysis. Raw *P*-values were computed by the χ^2 test, and the Bonferroni method was used to adjust for multiplicity. A two-sided $P<0.05$ was considered significant. Statistical analysis was performed using SAS version 14.3 (Cary, NC, USA).

Results

In the total cohort of 980 patients, 360 (36.7%) received high-intensity therapy, 255 (26.0%) received HMA therapy, 91 (9.3%) received low-intensity therapy, and 274 (28.0%) received supportive care; their baseline characteristics are represented in Table 1. Median age of patients when first diagnosed with AML was 75.6 years (range, 70-95.7 years). Among patients with antecedent hematologic

Table 1. Demographics and clinicopathological characteristics.

Clinical Parameter	All Patients	Front-line Therapy Group				P
		HMA (n=255)	HI Therapy (n=360)	LI Therapy (n=91)	Supportive Care (n=274)	
Median age (range), years	75.6 (70-95.7)	76.5 (70.1-95.2)	73.9 (70-89.8)	77.9 (70.5-90.4)	77 (70-95.7)	<0.0001
Sex						0.18
Male	650 (66.3%)	162 (63.5%)	247 (68.6%)	67 (73.6%)	174 (63.5%)	
Female	330 (33.7%)	93 (36.5%)	113 (31.4%)	24 (26.4%)	100 (36.5%)	
Race/ethnicity						0.63
Other	75 (7.7%)	22 (8.6%)	28 (7.8%)	4 (4.4%)	21 (7.7%)	
White	905 (92.3%)	233 (91.4%)	332 (92.2%)	87 (95.6%)	253 (92.3%)	
Type of AML						<0.0001
De novo	422 (43.1%)	123 (48.2%)	193 (53.6%)	22 (24.2%)	84 (30.7%)	
Secondary	558 (56.9%)	132 (51.8%)	167 (46.4%)	69 (75.8%)	190 (69.3%)	
Prior hematologic disease**	507 (51.7%)	110 (43.1%)	153 (42.5%)	66 (72.5%)	178 (65%)	<0.0001
HMA for prior hematology malignancy	264 (52.1%)	31 (28.2%)	82 (53.6%)	46 (69.7%)	105 (59%)	<0.0001
ECOG PS						<0.0001
0-1	777 (79.3%)	212 (83.1%)	303 (84.2%)	78 (85.7%)	184 (67.2%)	
2-4	186 (19%)	42 (16.5%)	46 (12.8%)	11 (12.1%)	87 (31.8%)	
Median WBC, $\times 10^9$/L	3.3 (0.2-230.7)	2.5 (0.2-147.8)	5.3 (0.2-230.7)	3 (0.6-215.3)	3.4 (0.6-215.7)	<0.0001
Median platelet, $\times 10^9$/L	51 (1-996)	69 (1-743)	50.5 (2-996)	50 (1-274)	39 (4-485)	<0.0001
Median hemoglobin, g/dL	9.4 (4.8-15.2)	9.5 (5-15.2)	9.3 (4.8-14.5)	9.6 (6.9-13.9)	9.3 (4.8-14.7)	0.073
Median PB blasts, %	14 (1-99)	10 (1-93)	21 (1-98)	8 (1-99)	13 (1-96)	<0.0001
Median BM blasts, %	35 (2-98)	30 (4-94)	45.5 (2-98)	33.5 (9-91)	30 (16-94)	<0.0001
Karyotype (n=874)						<0.0001
Adverse	304 (31%)	85 (33.3%)	80 (22.2%)	36 (39.6%)	103 (37.6%)	
Diploid/intermediate	554 (56.5%)	147 (57.6%)	234 (65%)	47 (51.6%)	126 (46%)	
Favorable	16 (1.6%)	3 (1.2%)	11 (3.1%)	0 (0%)	2 (0.7%)	
FLT3-ITD mutation (n=328 tested)	36 (11%)	10 (8.7%)	23 (16.9%)	0 (0%)	3 (5.4%)	0.019
NPM1 mutation (n=320 tested)	39 (12.2%)	10 (8.8%)	23 (18%)	2 (9.1%)	4 (7.1%)	0.080

*P-value was computed by χ^2 test or Kruskall-Wallis test. **Myelodysplastic syndrome accounted for >97% of all prior hematologic malignancies; others included myelofibrosis, polycythemia vera, and essential thrombocytosis. AML: acute myeloid leukemia; BM: bone marrow; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HI: high intensity; HMA: hypomethylating agent; LI: low intensity; PB: peripheral blood; WBC: white blood cell.

disorders (51.7%), myelodysplastic syndrome accounted for 93.9% of the population and over one-third (36.5%) of such patients had received HMA. In the HMA-treated AML cohort (n=255), 31 patients (12.1%) had previously received HMA therapy for an antecedent hematologic disorder. Cytogenetically, 56.5% of the patients had intermediate-risk or normal diploid karyotype whereas 31% had poor-risk karyotype as defined by National Comprehensive Cancer Network.[18]

Clinical variables that affected survival

We performed a univariate analysis on the entire cohort to identify clinical variables that may have affected survival. We found that secondary AML, poor-risk cytogenetics, increasing age at diagnosis, CCI score ≥ 3, ECOG performance status ≥ 2, increasing white blood cell (WBC) count at diagnosis, lower hemoglobin level at diagnosis, and lower platelets at the time of diagnosis, and choice of front-line therapy negatively affected overall survival (Table 2). However, our multivariate analysis showed that only increasing age [hazard ratio (HR)=1.14, 95% confidence interval (CI): 1.05-1.23; *P*=0.002], increasing WBC (HR 1.19, 95%CI: 1.13-1.25; *P*<0.0001), secondary AML (HR=1.44, 95%CI: 1.23-1.68; *P*<0.0001), poor-risk cytogenetics (HR = 1.92, 95%CI: 1.64-2.25; *P*<0.0001), higher ECOG performance status (HR = 1.80, 95%CI: 1.48-2.18; *P*<0.0001), and choice of front-line therapy affected overall survival (Table 3). Interestingly, CCI did not affect overall survival in the multivariate analysis.

Choice of front-line treatment and its effect on survival outcomes

The median overall survival for the entire cohort of 980 patients was 7.1 months, with a median follow up of 20.5 months. Per Kaplan-Meier survival analysis and log-rank test for significance (Figure 1), median overall survival was significantly greater for patients treated with HMA compared with those who received high-intensity therapy (14.4 *vs.* 10.8 months; HR=1.35, 95%CI: 1.10-1.65; *P*=0.004). Moreover, patients in the HMA treatment group also had better overall survival than patients in the low-intensity therapy (14.4 *vs.* 5.9 months, HR = 2.01, 95%CI: 1.53-2.62; *P*<0.0001) or supportive care groups (14.4 *vs.* 2.1 months, HR = 2.94, 95%CI: 2.39-3.61; *P*<0.0001). The estimated survival probability at one year with HMA treatment was significantly greater at 55.4% *versus* 42.7% with high-intensity therapy, 25.3% with low-intensity therapy, and 14.2% with supportive care (*P*<0.0001).

Table 2. Univariate analyses, with dichotomization of Eastern Cooperative Oncology Group Performance Status (0-1 *vs.* ≥2).

Clinical Parameter	*P*	Hazard Ratio	95% Confidence Interval	
			Lower	Upper
Sex				
Male	Reference			
Female	0.28	1.08	0.94	1.24
Race/ethnicity				
White	Reference			
Other	0.97	1.00	0.78	1.27
Type of AML				
De novo	Reference			
Secondary	<0.0001	1.56	1.36	1.78
Prior hematologic disease				
No	Reference			
Yes	<0.0001	1.52	1.33	1.74
Karyotype				
Favorable or intermediate	Reference			
Adverse	<0.0001	1.82	1.57	2.11
ECOG PS				
0-1	Reference			
2-4	<0.0001	2.10	1.77	2.48
Clinical trial as front-line therapy				
No	Reference			
Yes	0.97	1.00	0.83	1.20
Front-line therapy				
HMA	Reference			
HI therapy	0.002	1.32	1.11	1.57
LI therapy	<0.0001	1.92	1.50	2.46
Supportive care	<0.0001	3.38	2.80	4.07
CCI				
0-2	Reference			
≥ 3	0.011	1.28	1.06	1.55
Age at diagnosis (per 5-year increase)	<0.0001	1.16	1.09	1.25
BM blast at diagnosis (per 10% increase)	0.42	1.01	0.98	1.05
WBC, per 1 log increase	<0.0001	1.12	1.07	1.17
Platelets, per 1 log increase	<0.0001	0.72	0.68	0.78
Hemoglobin, per 1 log increase	<0.0001	0.88	0.84	0.91

AML: acute myeloid leukemia; BM: bone marrow; CCI: Charlson comorbidity Index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HI: high intensity; HMA: hypomethylating agent; LI: low intensity; PB: peripheral blood; WBC: white blood cell.

High-intensity therapy resulted in superior median overall survival compared with supportive care (10.8 *vs.* 2.1 months; *P*<0.0001) and low-intensity therapy (10.4 *vs.* 5.9 months; *P*=0.001), and low-intensity therapy was superior to supportive care (5.9 *vs.* 2.1 months; *P*<0.0001).

Because 185 patients (36.5%) had prior hematologic disease and thus received prior HMA, we created a univariate and multivariate model after excluding this subgroup, yielding a cohort of 795 HMA-naïve patients and assessed the impact of front-line treatment modality (Table 3). Variables that emerged as prognostically significant were identical to the variables from the multivariate model for the entire cohort. Within this HMA-naïve group, Kaplan-Meier analysis for overall survival was again noted to be superior in patients treated with HMA *versus* the other therapy groups, including the high-intensity (*P*=0.008), low-intensity (*P*<0.0001), and supportive care treatment groups (*P*<0.0001) (*data not shown*).

A pairwise comparison using propensity score matching to minimize the selection bias for front-line treatment was used to create a multivariate model to validate the prognostic impact of the different variables. The multivariate model confirmed our previous findings regarding the effects of HMA *versus* high-intensity treatment (HR=0.78, 95%CI: 0.63-0.97; *P*=0.027) and HMA *versus* low-intensity treatment (HR=0.56, 95%CI: 0.42-0.74; *P*<0.0001) on mortality. In patients with non-adverse risk karyotype (intermediate-risk and favorable-risk), superiority of HMA treatment was also demonstrated compared to intensive chemotherapy (HR=0.71, 95%CI: 0.55-0.92; *P*=0.008). Low-intensity treatment was also inferior to high-intensity treatment (HR=1.32, 95%CI: 1.01-1.72; *P*=0.040) (*data not shown*).

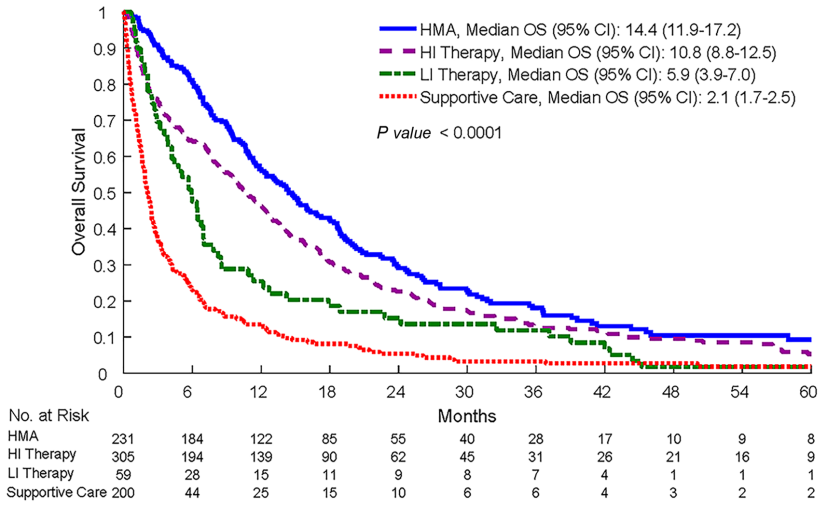

Figure 1. Overall survival (OS) among various front-line therapies for acute myeloid leukemia (AML) in patients ≥ 70 years old. CI: confidence interval; HI: high intensity; HMA: hypomethylating agent; LI: low intensity.

Survival outcomes based on time periods

To account for changes that have occurred over the years in AML treatments and supportive care management, the entire cohort was divided and grouped according to the year of treatment initiation: Group A (treatment before 2005, n=140) and Group B (treatment after 2005, n=840). A trend towards improved median overall survival (mOS) was noted among the 2 groups but did not reach statistical significance (Group A *vs.* B, mOS 5.7 months *vs.* 7.3 months; P=0.051). Baseline characteristics of Group B is provided in *Online Supplementary Table S1*. When assessing for the survival outcomes of HMA-naïve patients from Group B, the difference in mOS due to chosen front-line therapy persisted (P<0.0001) (*Online Supplementary Figure S1*).

Survival outcomes in patients with previous hypomethylating agent exposure

We also assessed the efficacy of front-line treatments in the small subset of evaluable patients who had previously received HMA for non-AML diagnoses (n=185), focusing on identifying whether a benefit was seen in this subgroup *versus* high-intensity treatment. Of these 185 patients, 24 patients (13.0%) received HMA subsequently for AML diagnosis, 55 (29.7%) received high-intensity therapy, 32 (17.3%) received low-intensity therapy, and 74 (40%) received supportive care only. We noted similarly poor median overall survival among the HMA group (7.8 months), the high-intensity therapy group (5.9 months), and the low-intensity group (5.9 months). However, all three treatment groups had better overall survival than the supportive care group (2.9 months) (P<0.0001) (*data not shown*). Moreover, multivariate analysis of the group also demonstrated the inferiority of supportive *versus* HMA and high-intensity and low-intensity therapy (Table 3). This improved survival *versus* supportive care suggested that this subgroup may benefit from some other type of therapy rather than supportive care only.

Responses and early mortality rates

The rate of composite CR (CR and CRi) and 30-day TRM (defined as death within 30 days of treatment initiation) were compared among the HMA, high-intensity, and low-intensity treatment groups (Figure 2). The rate of composite CR was significantly higher in the cohort treated with high-intensity chemotherapy than in the HMA (43.1% *vs.* 22.7%; adjusted P<0.001) and low-intensity therapy groups (43.1% *vs.* 7.7%; adjusted P<0.001). Early TRM was significantly lower with HMA treatment at 1.2%, compared with 7.5% with high-intensity chemotherapy (adjusted P<0.01). Among the patients who achieved CR/CRi, we calculated a median relapse-free survival of 10.5 months with HMA *versus* 9.1 months with high-intensity treatment (P=0.09) and 4.4 months with low-intensity treatment, which was significantly inferior to both HMA (P=0.009) or high-intensity treatment (P=0.036). However, it should be noted that the low-intensity subgroup had an extremely small sample size (n=5).

Discussion

Treatment of elderly patients with AML is a therapeutic challenge for clinicians as the choice of optimal front-line regimens continues to remain controversial. Here we present the results of the largest single institution report of outcomes amongst AML patients ≥70 years old. Using pairwise comparisons with propensity score matching, our results indicated a survival benefit with front-line HMA compared with high-intensity, low-intensity, or supportive care therapies. These results confirm and expand on previous reports that elderly patients with AML can benefit from treatment over supportive care.[2,10,19,20]

Clinical trials with the HMA azacitidine or decitabine have previously demonstrated their ability to induce remission and prolong survival in elderly AML patients.[16,19,21-23] After adjusting for potential treatment bias between the treatment groups with propensity score matching, we observed a statistically significant overall survival benefit with HMA *versus* our other treatment groups, with patients treated with HMA having median overall survival of 14.4 months. Our results were comparable to the 12.1 months previously observed by Dombret *et al.*[15]

Not unexpectedly, high-intensity chemotherapy was

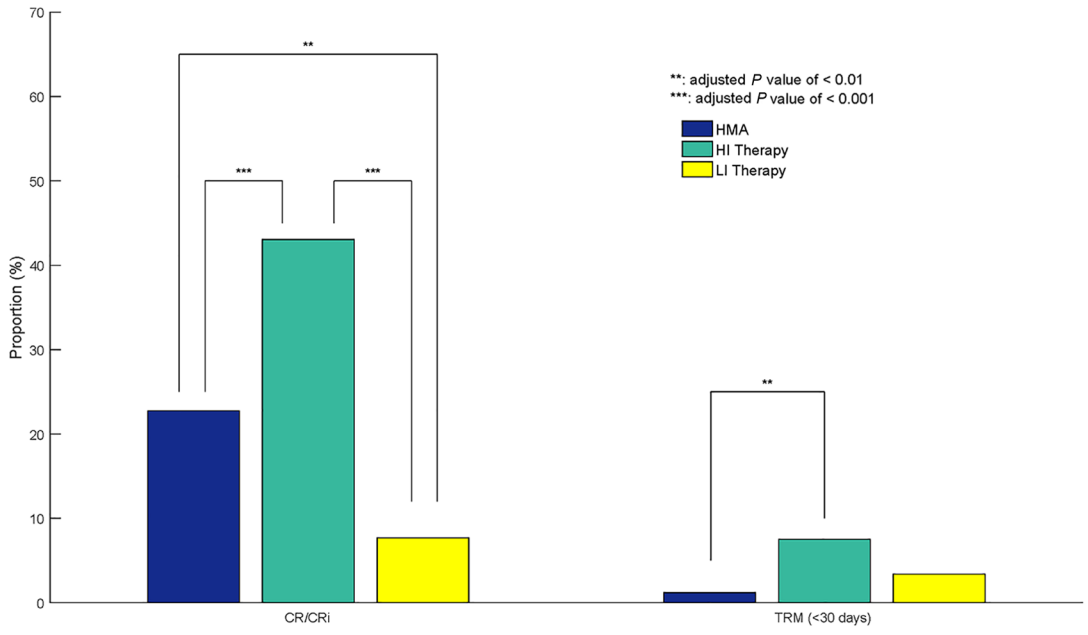

Figure 2. Treatment responses based on various treatment modalities. CR/Cri: complete response or complete response with incomplete count recovery; HI: high intensity; HMA: hypomethylating agent; LI: low intensity; TRM: treatment-related mortality.

also shown to be superior to supportive care with respect to overall survival. Interestingly, among the high-intensity and low-intensity treatment cohorts, overall survival significantly favored high-intensity treatment. Superior outcomes with high-intensity chemotherapy *versus* lower intensity chemotherapy and supportive care have been previously reported in older AML patients.[1,3,24,25] Together with our results, it is apparent that providing any treatment is superior to no treatment (supportive care) and these data may provide support to select intensive chemotherapy over lower intensity treatment in eligible patients. However, given the heterogeneity of the disease, risk stratification based on biological features of disease, functional status, comorbidity assessment, and cytogenetics rather than age alone should help guide treatment decisions.[2,6,10,26,27]

Although the superiority of high-intensity treatment over supportive care or low-intensity treatment was evident, high-intensity treatment failed to show survival superiority *versus* HMA in both our univariate and multivariate analyses. We found that high-intensity therapy conferred at least 35% higher risk of mortality than treatment with HMA. To eliminate the selection bias in our retrospective non-randomized study and to be able to accurately estimate the effects of treatment by reducing the bias due to confounding variables (such as baseline CCI among other co-variates), we implemented the propensity score matching method. Even with this method, the overall survival benefit was upheld with HMA treatment compared with high-intensity treatment (*Online Supplementary Table S2*). Our findings contrast somewhat from data previously reported by Quintas-Cardama *et al.* that indicated therapeutic equivalence between HMA and high-intensity therapy, including within the intermediate-risk cytogenetic group.[28] However, our data focused on a somewhat older population and used propensity score matching to minimize selection bias for front-line treatment options.

The higher rate of TRM that we observed with high-intensity treatment compared with HMA treatment (7.2% *vs.* 1.5%) may be implicated as a potential cause for the overall inferior survival, although it cannot be the sole reason for overall inferiority. Distinct disease biology of AML in older patients (compared with younger patients with AML) is certainly a contributing factor for suboptimal treatment responses. Secondary AML originating from a prior myelodysplastic syndrome is common in the elderly and portends a poor prognosis. In our patient cohort, a significant proportion (56.9%) had secondary AML, primarily stemming from myelodysplastic syndromes. For this subgroup of patients, induction with intensive chemotherapy is frequently utilized, but the duration of response and long-term outcomes continue to remain poor.[29]

Treatment with a prior HMA has been previously shown to be an independent negative predictive factor for responses and overall survival in patients with secondary AML.[30] In our analysis of this high-risk subgroup with prior HMA exposure, treatment with a high-intensity regimen did not produce significantly superior overall outcomes (HR=1.25, 95%CI: 0.68-2.27; *P*=0.47) compared with HMA. Moreover, low-intensity treatment also failed to produce improved outcomes compared with HMA treatment (HR=1.42, 95%CI: 0.76-2.66; *P*=0.28). Interestingly, the supportive care cohort had far inferior outcomes than patients in the HMA group (HR=2.29, 95%CI: 1.30-4.02; *P*=0.004). These results further reinforce the notion that some therapy may be superior to supportive care only, including that a clinical trial should be strongly considered whenever possible for this group.

A small minority (12.1%) of the patients in the HMA cohort had been previously treated with HMA. Typical approaches for such patients at our institution include

Table 3. Multivariate analysis and comparisons of entire cohort *versus* patients without prior exposure to hypomethylating agent prior to diagnosis of acute myeloid leukemia and *versus* patients who received hypomethylating agent prior to the diagnosis of acute myeloid leukemia.

Clinical Parameter	All Patients (n=980)				Without Prior Exposure to HMA (n=795)				With Prior Exposure to HMA (n=185)			
	P	Hazard Ratio	95%CI Lower	95%CI Upper	*P*	Hazard Ratio	95%CI Lower	95%CI Upper	*P*	Hazard Ratio	95%CI Lower	95%CI Upper
Type of AML												
De novo	Reference				Reference				Excluded			
Secondary	<0.0001	1.44	1.23	1.69	0.001	1.34	1.13	1.59				
Karyotype												
Favorable or intermediate	Reference				Reference				Reference			
Adverse	<0.0001	1.92	1.64	2.25	<0.0001	2.02	1.69	2.41	0.001	1.87	1.29	2.72
ECOG PS												
0-1	Reference				Reference				Excluded			
2-4	<0.0001	1.80	1.48	2.18	<0.0001	1.82	1.47	2.26				
Front-line therapy												
HMA	Reference				Reference				Reference			
HI therapy	0.004	1.35	1.10	1.65	0.024	1.29	1.03	1.61	0.47	1.25	0.68	2.27
LI therapy	<0.0001	2.01	1.53	2.62	<0.0001	2.12	1.54	2.91	0.28	1.42	0.76	2.66
Supportive care	<0.0001	2.94	2.39	3.61	<0.0001	3.02	2.40	3.81	0.004	2.29	1.30	4.02
Age at diagnosis (per 5-year increase)	0.002	1.14	1.05	1.23	0.036	1.10	1.01	1.21	0.001	1.38	1.14	1.67
WBC, per 1 log increase	<0.0001	1.19	1.13	1.25	<0.0001	1.18	1.11	1.25	<0.0001	1.34	1.16	1.54
Platelets, per 1 log increase	<0.0001	0.81	0.75	0.87	<0.0001	0.80	0.73	0.88	0.002	0.80	0.69	0.92
Hemoglobin, per 1 log increase	<0.0001	0.91	0.86	0.95	0.0003	0.91	0.86	0.96	0.035	0.87	0.77	0.99

AML: acute myeloid leukemia; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HI: high intensity; HMA: hypomethylating agent; LI: low intensity; WBC: white blood cell.

clinical trials (if available), intensive chemotherapy, lower-intensity approaches, or best supportive care. If HMA therapy is continued, we may utilize a different dosing schedule (10-day decitabine or 7-day azacitidine if treated with a 5-day schedule) or switch to the alternative HMA agent. Although limited, our data suggest that patients treated previously with HMA do not benefit from any specific standard-of-care approach, indicating the importance of clinical trials for this subpopulation.

Since the Food and Drug Administration approval of CPX-351 for secondary AML (AML with myelodysplasia-related changes and therapy-related AML) that established a new standard of care for this distinct high-risk AML subgroup, the treatment landscape for AML has become increasingly complex.[31] CPX-351 is considered an intensive chemotherapy and is demonstrated to have similar early TRM as "7+3". However, CPX-351 has not been compared head-to-head with HMA-based therapies and were not included in our study. But such a comparison is warranted to determine the optimal treatment choice for older AML patients aged ≥70 years.

While the results of our study are potentially practice-changing, there are several limitations. Although this is the largest single-institution series of AML patients ≥70 years of age, a referral bias affecting baseline disease characteristics is expected. In our cohort, 50% of the patients had prior hematologic malignancy and >90% of these patients had diagnosis of MDS. In addition, treatment outcomes of patients seen at a tertiary care center may not reflect outcomes of the general community, thereby limiting its general applicability. For instance, per the SEER registry studies, only 10-20% of elderly patients are treated with HMA or intensive chemotherapy, compared with 58% of the patients in our cohort.[11,13] The non-randomized retrospective nature of this study also does not allow for definitive conclusions to be made as there might be some inadvertent, inherent biases introduced that we did not consider, although we attempted to account for such bias *via* utilization of propensity score matching.

Although most patients in our cohort had cytogenetic results, the lack of molecular data in our analysis is another study limitation. Prior studies have shown that with advanced age there is an increase in the incidence of unfavorable cytogenetics, aberrant karyotypes, and molecular abnormalities.[32-36] Testing newly diagnosed AML patients irrespective of their age for key molecular markers (including FLT3, NPM1, and KIT) should be universally done given their prognostic and therapeutic implications. Unfortunately, molecular testing and routine testing of all elderly patients with AML have only become a standard practice during the past ten years. The lack of available testing likely explains the lack of available molecular data in our database, which incorporates patients dating back to 1995.

Accurate assessment of baseline performance status and comorbidity measurements in elderly patients with AML can provide useful prognostic information and help guide treatment decisions. Functionality and comorbidity are independent prognostic variables and should be measured independently in elderly patients.[37] A retrospective study by Etienne *et al.* reported that patients with a CCI score >1 had significantly lower rates of obtaining a CR than those having CCI scores <1.38 Analyses of the SEER data have also shown that survival of those with CCI of 0-1 improved with therapy, whereas those with CCI >2 experienced early death and had minimal improvements in

overall survival.[11] It should be noted that, despite these survival differences, the SEER registries lacked functional and cytogenetic data, thus limiting applicability of these results. In our analysis, 79.3% of patients had an ECOG performance status of 0 or 1, and only 13.4% of patients had a high CCI of ≥3. The fact that most of our patients had good performance status or low CCI could account for the increased tolerability to induction chemotherapy, therefore conferring an additional survival advantage to treatment compared with supportive care or low-intensity treatment. On the other hand, Juliusson *et al*. demonstrated in a leukemia registry that even older patients with poor performance status seemed to benefit from chemotherapy compared with best supportive care.[20]

Although the need for quality of life (QOL) assessments before and after treatment are well recognized in AML, and may represent an important outcome measure, currently, clinical trials mainly focus on quantitative assessments of life rather than qualitative. Geriatric assessments in combination with conventional clinical and disease-specific factors can accurately predict vulnerability to treatment toxicity; however, such assessment models specific to AML are lacking.[39] Oliva *et al*. reported a study on elderly AML patients in which QOL physical functioning was of prognostic relevance; however, these results did not correlate with physician-assessed ECOG performance status.[40] As shown previously, even hematologic improvements from reduction in transfusions can lead to improved QOL.[41,42] Although QOL is an important measure of treatment outcomes, our study did not capture such information, posing a limitation regarding the effects of treatment options on QOL. Therefore, prospective studies regarding whether HMA treatment *versus* intensive chemotherapy can improve QOL are warranted to assess this vital component of AML care.

In conclusion, as shown in our analysis of a large patient cohort, patients over the age of 70 years with AML had a significant survival benefit with HMA or high-intensity therapy compared with supportive care or low-intensity therapy. Moreover, patients who were treated with HMA showed a striking survival advantage over those who received traditional high-intensity therapy. Because of the present lack of a clear decision model to allow for comparing treatments more objectively, elderly patients with AML may receive suboptimal treatment. The results presented here contribute to an ongoing effort to design a comprehensive decision analysis model comparing treatment effectiveness to baseline characteristics in elderly patients with AML.

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