Leukemia Research 78 (2019) 45–51

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

A retrospective study evaluating treatment patterns and survival outcomes in elderly patients with acute myeloid leukemia treated in the United States with either 7 + 3 or a hypomethylating agent

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ARTICLE INFO

Keywords:
Acute myeloid leukemia
Elderly
Hypomethylating agents
7 + 3
Survival
Treatment patterns

ABSTRACT

Intensive treatment for newly diagnosed acute myelogenous leukemia (ND-AML) patients are reserved for "fit" patients. While guidelines recommend evaluation of age, performance status and comorbidities, there is no consensus on the definition of "fitness" or optimal therapy for elderly AML patients. This retrospective study evaluated characteristics and survival outcomes of 274 patients (age ≥60 years) with ND-AML treated with 7 + 3 (cytarabine + an anthracycline) vs. hypomethylating agents (HMAs). Most patients received 7 + 3 (60.2%) vs. HMAs (39.8%) in first-line therapy (1 L T); more HMA patients were ≥75 years old and had more comorbidities. Median progression-free survival (PFS) following 1 L T was longer for patients who received 7 + 3 vs. HMAs (6.7 months [95% confidence interval (CI)]: 4.9, 11.1) vs. 4.1 months (95% CI: 2.8, 4.9, respectively). Median overall survival (OS) following 1 L T was also longer for patients who received 7 + 3 vs. HMAs (14.7 months [95% CI: 11.0, not estimated] vs. 4.3 months [95% CI: 3.2, 5.8], respectively). An age-adjusted Charlson Comorbidity Index score of ≥4 vs. < 4 negatively affected PFS and OS irrespective of treatment. Overall, choosing an HMA over 7 + 3 in elderly patients with ND-AML may be influenced by age and comorbidities; patients receiving 7 + 3 had longer survival than those on an HMA.

1. Introduction

Acute myeloid leukemia (AML) is a cluster of clonal hematological neoplasms characterized by proliferation of immature myeloid cells in the bone marrow resulting in cytopenias. AML primarily affects older adults, with a median age at diagnosis of 69 years [1,2]. Treatment for newly diagnosed patients with (ND)-AML can be classified as "more" or "less" intensive, with more intensive induction therapies such as cytarabine plus an anthracycline (i.e., 7 + 3) utilized as the backbone of therapy for patients "fit" enough to tolerate this regimen. While 7 + 3 has been the backbone of treatment for several decades, with a complete response rate of 60%–80% in younger adults, its efficacy is reduced in elderly patients, with complete responses reported in 40%–60% of those ≥60 years of age [3].

The choice of therapy for patients with ND-AML is complicated due to the lack of applicability of results from randomized studies, as inclusion criteria are often not representative of the entire patient population with AML. For example, the vast majority of significantly older patients (age > 75 years) and/or those with severe comorbidities are not included in these trials [2]. Further, whereas prognostic indices may predict response to therapy and early treatment-related mortality with intensive, induction chemotherapy, no consensus exists regarding optimal therapy specifically for elderly patients with AML [3–6].

The National Comprehensive Cancer Network (NCCN®) Guidelines® recommend that age, patient performance status, adverse features (e.g., de novo AML without favorable cytogenetics or molecular markers; therapy-related AML; or AML with an antecedent hematologic disorder), and comorbid conditions should be considered when determining treatment options for patients [6]. However, less intensive therapies, such as the hypomethylating agents (HMAs) azacitidine or decitabine, are increasingly used among elderly patients, perhaps reflecting concerns about the ability of elderly patients to tolerate intensive therapy [7].

In this study, we evaluated patient characteristics, real-world

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[1] A wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

https://doi.org/10.1016/j.leukres.2019.01.008
Received 23 November 2018; Received in revised form 18 January 2019; Accepted 21 January 2019
Available online 24 January 2019

treatment patterns, and survival outcomes of elderly (age ≥60 years) patients with ND-AML treated in routine clinical practice with 7 + 3 vs. less intensive therapy with HMAs (i.e., azacitidine and decitabine).

2. Materials and methods

2.1. Study design

This was a retrospective cohort study using the Humedica Electronic Medical Record Database. The Humedica Electronic Medical Record Database represents a large group of integrated delivery networks (IDNs) within the United States. Each IDN in Humedica is a comprehensive healthcare delivery system that offers patients a multitude of services across the clinical care spectrum, including acute inpatient and outpatient care. These organizations provide care for patients from all 50 states and account for over 140,000 providers, 6500 clinics, and 600 hospitals.

Patients with AML diagnosed between 1/1/2008 to 7/31/2015 were identified from the database; the date of AML diagnosis was the index date, and the 12 months prior to the index date was the baseline period. Patients were followed for ≥60 days from the index date (except patients who died < 60 days from index date) until death, loss to follow up, or end of study (9/30/2015).

2.2. Study population

Patients were ≥60 years of age with ND-AML. AML diagnosis was based on ≥1 inpatient or ≥2 outpatient records with an AML International Classification of Diseases, Ninth Revision/Tenth Revision (ICD-9/ICD-10) diagnosis code (ICD-9 code: 205.0; ICD-10 codes: C92.0, C92.5, C92.6, C92.9, C92.A). Eligible patients had to have continuous care for 12 months in the baseline period and ≥60 days in the follow-up period, treatment within the IDN, and evidence of first-line therapy (1 L T) with either the 7 + 3 regimen (cytarabine plus either daunorubicin or idarubicin) or an HMA as monotherapy (either azacitidine or decitabine) in the follow-up period. Patients were excluded for evidence of any chemotherapy or stem cell transplantation (SCT), other primary cancer, metastatic disease, myelodysplastic syndromes, or myelofibrosis in the baseline period.

2.3. Baseline and clinical characteristics

Baseline demographics were recorded on the index date and included age, gender, and race. Clinical characteristics, which included Charlson Comorbidity Index (CCI) and the presence of each comorbidity that comprise the CCI score, were captured via ICD-9/ICD-10 codes in the baseline period. In addition, an age-adjusted CCI score was calculated, and patients were categorized into 2 age-adjusted CCI cohorts (age-adjusted CCI ≤ 3 or ≥4) [8]. Further, the presence of any renal insufficiency (RI), cardiovascular disease (CVD), and the number of discrete diagnosis codes for comorbid conditions were obtained during the baseline period. A frailty index was also generated using the JEN Frailty Index (JFI) algorithm. The JFI is a risk-scoring tool that uses 13 condition categories, encompassing nearly 1800 diagnoses, found to be significantly related to concurrent or future need for long-term care services [9]. The 13 categories include minor ambulatory limitations, severe ambulatory limitations, cognitive developmental disability, chronic mental illness, dementia, sensory disorders, self-care impairment, syncope, cancer, chronic medical disease, pneumonia, renal disorders, and systemic disorders (e.g., septicemia). Laboratory values for hemoglobin, bone marrow blast count, platelets, and neutrophils recorded during the baseline period and/or within 30 days in the follow-up period were captured; the laboratory value closest to the index date was used as the baseline value. Use of AML supportive care, defined as erythrocyte/platelet transfusions; thrombopoietic-, erythropoietic-, and granulocyte-stimulating factors, and hydroxyurea were also identified during the baseline period.

2.4. Study outcomes

Patients in this analysis received 1 L T, with either the 7 + 3 regimen or an HMA as monotherapy initiated on or after the index date. Agents started within the initial 28 days from the start of the line of therapy were captured as part of the regimen. Early switches (i.e., within 28 days of first induction for a failed induction therapy) were considered part of the 1 L T. Second-line therapy (2 L T) was defined as the addition/substitution of any AML-related treatment (defined as azacitidine, cladribine, clofarabine, cytarabine, daunorubicin, decitabine, etoposide, fludarabine, gemtuzumab, idarubicin, mitoxantrone, and sorafenib) > 28 days after 1 L T or a gap of ≥60 days. Treatments in the 2 L T were categorized as follows: 7 + 3, HMA therapy, idarubicin or daunorubicin monotherapy, cytarabine monotherapy, and other. Evidence of SCT was collected via a natural language processing system in the medical record, and the date of the first SCT record was used as the SCT date. SCT was considered part of the line of therapy in which it occurred. AML supportive care received during the follow-up period also was identified. Time to treatment initiation was defined as the time from the index date to the first evidence of chemotherapy in the follow-up period, and duration of therapy was defined as the time from initiation of 1 L T to the last day of therapy, plus a 28-day run-out period.

Progression-free survival (PFS) and overall survival (OS) were evaluated from the initiation of 1 L T. PFS was defined as time to initiation of 2 L T or death by any cause, whereas OS was defined as time to death by any cause.

2.5. Statistical analysis

Descriptive analyses were conducted for demographics, baseline clinical characteristics, treatment patterns, and survival outcomes. Descriptive statistics were used for categorical measures of counts and percentages, whereas continuous measures were presented as the mean, standard deviation (SD), median, and interquartile range (IQR). For the survival outcomes, median PFS and OS, and 2-year OS and PFS rates were evaluated using Kaplan-Meier analyses. PFS and OS were compared among patients treated with 7 + 3 vs. HMAs, and by treatment groups and age-adjusted CCI using a log-rank test. Analyses were conducted using SAS® version 9.2 (SAS Institute; Cary, NC, US).

3. Results

A total of 10,431 patients with AML were identified. Of these, 274 were aged ≥60 years and received 1 L T with either 7 + 3 or an HMA (Fig. 1). Among patients treated with either 7 + 3 or an HMA, the mean age was 71.5 years (SD: 7.1), 55.8% were male, and 93.4% were white. The proportion of patients with a CCI score of ≥2 was 20.4%, and 40.5% had an age-adjusted CCI score of ≥4. The most common CCI comorbidities were diabetes (17.9%), chronic pulmonary disease (16.8%), cerebrovascular disease (8.0%), peripheral vascular disease (7.7%), and congestive heart failure (6.9%). The mean JFI score was 2.6 (SD: 2.4); 51.1% had low-risk frailty, 39.1% had medium-risk frailty, and 9.8% had high-risk frailty.

The majority of elderly patients received 7 + 3 (n = 165, 60.2%) vs. HMAs (n = 109, 39.8%). The median time to 1 L T (in months) was longer for patients treated with an HMA compared with those treated with 7 + 3 (0.3 [9 days] [IQR: 0.1, 0.2] vs. 0.1 [3 days] [IQR: 0.1, 0.7]; $P < 0.0001$) (Table 1). The median duration of 1 L T did not differ significantly between the 2 treatment groups and was 2.0 months (IQR: 1.2, 4.0) for all elderly patients. Of the patients who received 7 + 3 (n = 165), idarubicin was the predominant anthracycline used over daunorubicin (n = 108, 65.5% vs. n = 57, 34.5%). Of the patients who received an HMA (n = 109), azacitidine predominated over decitabine

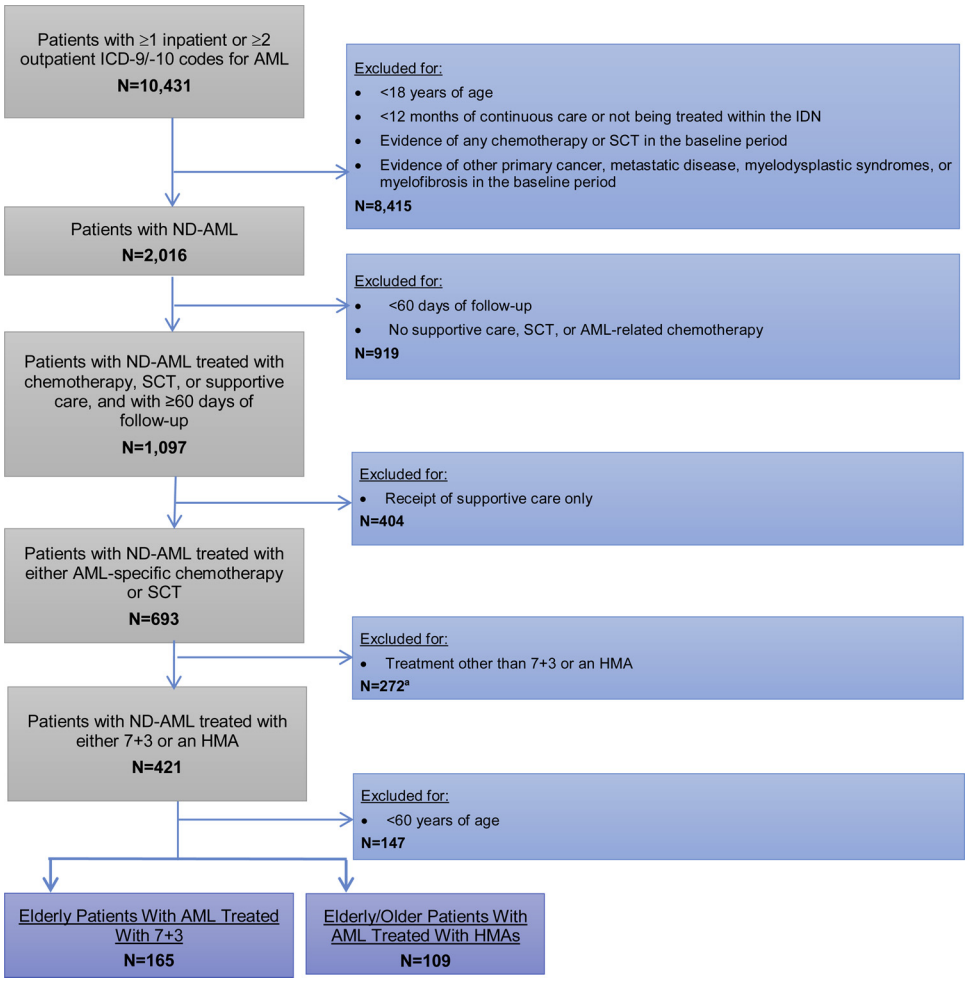

Fig. 1. Patient Attrition [a] Includes 92 patients with evidence of SCT only; 61 patients treated with anthracycline monotherapy; 33 patients treated with cytarabine monotherapy, and 86 patients treated with "other" cytotoxic combination or monotherapy (with 23 of these patients receiving a combination of cytarabine with etoposide and/or mitoxantrone; 20 receiving 7 + 3 plus cladribine, clofarabine, or fludarabine; and 8 patients receiving sorafenib monotherapy). Key: 7 + 3 – cytarabine plus either idarubicin or daunorubicin; AML – acute myeloid leukemia; HMA – hypomethylating agent (i.e., azacitidine or decitabine monotherapy); ICD – International Classification of Diseases; IDN – integrated delivery network; ND – newly diagnosed; SCT – stem-cell transplant.

(n = 66, 60.6% vs. n = 43, 39.4%).

A higher proportion of patients who received an HMA were aged ≥75 years compared with those who received 7 + 3 (67.0% vs. 15.8%; $P < 0.0001$) (Table 1). In addition, patients receiving HMAs also had a higher mean number of unique comorbid conditions at baseline (17.9 [SD: 15.9] vs. 14.1 [SD: 15.1]; $P = 0.0471$), and a higher proportion of those on HMAs had comorbid CVD with RI (13.8% vs. 4.9%; $P = 0.0092$). In concordance with this finding and with the older age among those treated with HMAs, a significantly higher proportion of patients in the HMA group had an age-adjusted CCI score of ≥4 (64.2% vs. 24.9%; $P < 0.0001$) vs. those in the 7+3 group. Also, patients treated with HMAs had higher a mean JFI score compared with patients treated with 7+3 (3.2 [SD: 2.2] vs. 2.3 [SD: 1.9]; $P = 0.0002$) (Table 1).

Following 1 L T, 52 (19.0%) elderly AML patients received 2 L T; a higher proportion of those who received 7 + 3 in 1 L T proceeded to 2 L T than those who received an HMA (n = 43 [26.1%] vs. n = 9 [8.3%]). Of the 43 patients who received 1 L T with 7 + 3, 20 (46.5%) switched to an HMA, 3 (7.0%) received 7 + 3 again, 2 (4.7%) received cytarabine alone, and 18 (41.9%) received other regimens in 2 L T (Fig. 2). For the 9 patients who received an HMA as 1 L T, 3 (33.3%) received an HMA again, 2 (22.2%) received 7 + 3, 1 (11.1%) received cytarabine alone, and 3 (33.3%) received other regimens.

At a median follow-up time of 6.8 months (IQR: 2.6, 14.6), a significantly higher proportion of elderly patients who were given 7 + 3 in 1 L T were progression-free at both 1 and 2 years from 1 L T initiation compared with those who received HMAs (41.6% and 30.4% vs. 21.3% and 9.9%, respectively; $P < 0.0001$ for both) (Fig. 3A). The median PFS was 6.7 months (95% CI: 4.9, 11.1) for those who received 7 + 3 vs. 4.1 months (95% CI: 2.8, 4.9) for those who received an HMA (Fig. 3A).

Further, 1- and 2-year OS rates after initiation of 1 L T were significantly higher for elderly patients who received 7 + 3 in 1 L T (55.9% and 42.8%, respectively, and 23.8% and 11.3%, respectively; $P < 0.0001$ for both) vs. those who received an HMA (Fig. 3B). The median OS for elderly patients receiving 7 + 3 vs. those receiving an HMA was 14.7 months (95% CI: 11.0, not estimated) vs. 4.3 months (95% CI: 3.2, 5.8) (Fig. 3B).

In subgroup analyses of 274 elderly AML patients by treatment group and age-adjusted CCI score, 40.5% (n = 111) that had an age-adjusted CCI score of ≥4, with a notably larger proportion receiving HMAs vs. the 7 + 3 regimen (n = 70 [64.2%] vs. n = 41 [24.9%]). Within each treatment group, an age-adjusted CCI score of ≥4 was associated with worse 1- and 2-year PFS and OS rates, as well as a lower median PFS and OS compared with those with an age-adjusted CCI of < 3 (Table 2). Additionally, 1- and 2-year PFS and OS differed across the treatment groups, with patients who received HMAs in either age-adjusted CCI cohort (i.e., age-adjusted CCI ≤ 3 vs. ≥ 4) reporting worse outcomes than those patients within each age-adjusted CCI cohort who received 7 + 3 (Table 2; Fig. 4).

4. Discussion

This study evaluated real-world treatment patterns and survival outcomes of elderly patients with AML who received intensive therapy with 7 + 3 and less intensive therapy with HMAs as 1 L T. The majority of elderly patients with AML in our analysis received 7 + 3 as 1 L T. While no consensus currently exists on what criteria should be considered or the weight given to certain patient characteristics when considering "fitness" for intensive therapy, our study reveals that an age

Table 1
Baseline Characteristics by Treatment.

Type of Therapy		Overall		7 + 3[a]		HMAs		*P*-value (7 + 3 vs. HMAs)
Overall, N		N = 274		n = 165		n = 109		
Time from diagnosis to initiation of 1 L T, median in months (IQR)[b]		0.2	0.1, 0.3	0.1	0.1, 0.2	0.3	0.1, 0.7	< **0.0001**
Duration of 1 L T, median in months (IQR)		2.0	1.2, 4.0	1.7	1.2, 3.7	2.2	1.2, 4.0	0.1753
Follow-up time, median in months (IQR)		6.8	2.6, 14.6	8.7	3.2, 17.3	5.0	2.5, 10.0	**0.0046**
Baseline Characteristics[c]								
Age, years, n (%)	≥75 years	99	(36.1)	26	(15.8)	73	(67.0)	< **0.0001**
Bone marrow blast count, n (%)	Unknown	193	(70.4)	114	(69.1)	79	(72.5)	0.1564
	≤30%	38	(13.9)	27	(16.4)	11	(10.1)	
	> 30%	43	(15.7)	24	(14.6)	19	(17.4)	
Hemoglobin[d] n (%)	Unknown	37	(13.5)	19	(11.5)	18	(16.5)	0.6094
	≤10.3 gm/dL	178	(65.0)	108	(65.5)	70	(64.2)	
	> 10.3 gm/dL	59	(21.5)	38	(23.0)	21	(19.3)	
Platelets[d] n (%)	Unknown	11	(4.0)	4	(2.4)	7	(6.4)	0.1797
	≤28 K/L	66	(24.1)	45	(27.3)	21	(19.3)	
	> 28 K/L	197	(71.9)	116	(70.3)	81	(74.3)	
Fibrinogen[d] n (%)	Unknown	148	(54.0)	70	(42.4)	78	(71.6)	**0.0458**
	≤150 mg/dL	4	(1.5)	1	(0.6)	3	(2.8)	
	> 150 mg/dL	122	(44.5)	94	(57.0)	28	(25.7)	
LDH[d] n (%)	Unknown	62	(22.6)	27	(16.4)	35	(32.1)	0.959
	≤700 IU/L	183	(66.8)	119	(72.1)	64	(58.7)	
	> 700 IU/L	29	(10.6)	19	(11.5)	10	(9.2)	
CCI score[e] mean (SD)		0.8	(1.3)	0.6	(1.1)	1.1	(1.5)	**0.0011**
CCI ≥2, n (%)		56	(20.4)	25	(15.2)	31	(28.4)	**0.0076**
Age-adjusted CCI score,[e,f] mean (SD)		3.6	(1.6)	3.0	(1.2)	4.4	(1.8)	< **0.0001**
Age-adjusted CCI ≤ 3[g]		163	(59.5)	124	(75.2)	39	(35.8)	
Age-adjusted CCI ≥ 4		111	(40.5)	41	(24.9)	70	(64.2)	
JFI, mean (SD)		2.6	(2.1)	2.3	1.9	3.2	2.2	**0.0002**
0–2 (Low risk)		140	(51.1)	96	(58.2)	44	(40.4)	**0.0109**
3–5 (Medium risk)		107	(39.1)	57	(34.6)	50	(45.9)	
6–13 (High risk)		27	(9.8)	12	(7.3)	15	(13.8)	
CVD without RI[e] n (%)		30	(11.0)	19	(11.5)	11	(10.1)	0.7119
RI without CVD[e] n (%)		31	(11.3)	16	(9.7)	15	(13.8)	0.2985
CVD and RI[e] n (%)		23	(8.4)	8	(4.9)	15	(13.8)	**0.0092**
Number of CCI comorbidities at baseline[e] mean (SD)		15.6	(15.5)	14.1	(15.1)	17.9	(15.9)	**0.0471**

Note: Due to rounding, numbers may not add up to 100.
Key: 1 L T – first-line therapy; 2 L T – second-line therapy; AML – acute myeloid leukemia; CCI – Charlson Comorbidity Index; CVD – cardiovascular disease; HMA – hypomethylating agent (i.e., azacitidine or decitabine monotherapy); IQR – interquartile range; JFI – JEN Frailty Index; LDH – lactate dehydrogenase; RI – renal insufficiency; SD – standard deviation.
[a] Includes patients who received cytarabine plus either daunorubicin or idarubicin.
[b] IQR presents the 25th and 75th percentiles, and measures the variability of the data around the median.
[c] Baseline levels were relative to the 12 months prior to the index AML diagnosis date and up to 30 days after the index AML diagnosis date, with the exception of hemoglobin, which was only prior to the index diagnosis date; the value closest to the index diagnosis date was used.
[d] Parameters and thresholds were derived from the AML risk score, which is derived from an algorithm that predicts complete remission and risk for early death, specifically in untreated patients aged ≥60 years who are eligible for intensive treatment [4].
[e] Baseline comorbidities were relative to the 12 months prior to the index AML diagnosis date.
[f] Age-adjusted CCI score [8].
[g] Due to the inclusion criteria of patients aged of ≥60 years in our analysis, no patients had an age-adjusted CCI score of.0–1.

≥75 years, the number of comorbid conditions, an age-adjusted CCI score of ≥4, and presence of RI and CVD may influence treatment toward less intensive therapy with HMAs. This finding is consistent with the fact that the majority of experience with the more intensive 7 + 3 regimen is in younger patients and that older patients tend to have more comorbidities and are at greater risk for treatment-related mortality with the more intensive regimens [1]. Further, this is concordant with other recent studies of patients with AML who received routine care, which showed that less intensive therapies were utilized in older patients, and that age > 70 years and impaired performance status are the strongest predictors of receipt of intensive therapy [10,11]. Since AML is primarily a disease of the elderly, there is a need for more objective assessments of "fitness" and measurement of treatment-related mortality and morbidity to help inform treatment choices among this patient population [12].

Patients treated with the more intensive 7 + 3 regimen had better survival outcomes, with both 1- and 2-year PFS and OS rates being significantly higher than in patients who received HMA treatment. Further, although patients in the HMA group were older, had more comorbidities, and a higher JFI score than patients who received 7 + 3, when stratified by age-adjusted CCI score (age-adjusted CCI ≤ 3 and CCI ≥ 4), patients who received 7 + 3 still had higher median OS vs. those who received HMAs in both age-adjusted CCI categories. Medeiros et al reported similar results in a Medicare-eligible population, although patients in the study were aged ≥65 years and those with prior MDS were included [13]. In this study, median OS assessed from the time of diagnosis was 18.9 months for patients who received intensive therapy and 6.6 months for patients who received HMAs [13]. In addition, OS rate at 2 years for these two treatment groups were similar to that reported in our study [13].

Another retrospective study conducted in a single center in The Netherlands, compared intensive chemotherapy with azacitidine and best supportive care among patients with AML who are at least 60 years old and reported different results. This study reported no significant difference in the rate of OS at 2 years between patients receiving azacitidine and patients receiving intensive chemotherapy (35% versus 35%, respectively, $P = 0.92$); the results remained consistent after controlling for differences between the groups. The differences with our

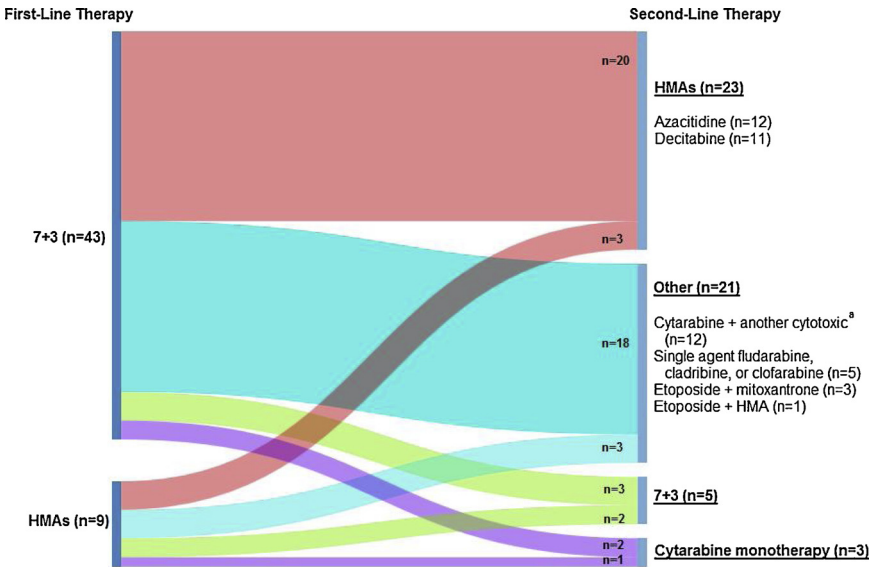

Fig. 2. Switch Patterns From 1 L T to 2 L T. [a] Another cytotoxic includes cladribine, an anthracycline or mitoxantrone + etoposide, etoposide, or fludarabine. Key: 1 L T – first-line therapy; 2 L T – second-line therapy; 7 + 3 – cytarabine plus either daunorubicin or idarubicin; HMA – hypomethylating agent (i.e., azacitidine or decitabine monotherapy).

results could be a result of the differences in the HMA treatment groups; our study included patients who received decitabine in the HMA treatment group. Additionally, these results represents the experience of a single center, and there are likely differences in practice patterns between these countries [14]. A retrospective analysis of clofarabine vs. the more intensive FLAG regimen (fludarabine, cytarabine, and filgrastim support) in patients age ≥60 years revealed that for all patients, the OS and event-free survival was 4.2 and 3.7 months, respectively [15]. After matching based on patient age, CCI, albumin, AML classification (de novo or secondary), and risk classification based on cytogenetics and molecular abnormalities, patients receiving the more intensive FLAG regimen had a non-significant but increased median OS and event-free survival compared with those on the less intensive clofarabine therapy [14]. However, this was primarily driven by an increased 30-day mortality in the clofarabine arm (21.9% vs. 3.1%), perhaps indicating the limitations of the clofarabine regimen in terms of efficacy and/or toxicity—or, alternatively, that other differences in the patient population may have contributed to poor clinical outcomes and require elucidation to more appropriately select therapy for this elderly population [15].

Overall, these results highlight the importance of developing new data and tools to appropriately select therapy, as well as new treatment options for elderly patients with AML, particularly those who are deemed unfit for intensive therapy with 7 + 3. In our study, 40.5% of our population had an age-adjusted CCI score of ≥4, which was shown to negatively affect survival irrespective of the treatment chosen. Given the poorer outcomes in this patient population, future therapies that focus on improving both survival and tolerability are essential.

Finally, very few patients (19.0%) went on to receive 2 L T, and there are currently no approved, effective 2 L T options for patients with AML after progression on 1 L T. This, coupled with the relatively short

Table 2
Age-adjusted CCI and 1-Year, 2-Year, and Median PFS and OS by Regimen Type, HMAs vs. 7 + 3.

Parameters		Age-adjusted CCI ≤ 3 N = 163		Age-adjusted CCI ≥ 4 N = 111	
Regimen Type		7 + 3 = 124	HMAs n = 39	7 + 3 N = 41	HMAs n = 70
PFS	1-Year PFS[a]	43.2%	30.6%	36.9%	15.9%
	2-Year PFS[a]	31.0%	15.7%	28.7%	5.3%
	Median (95% CI), in months	8.0 (4.9, 14.1)	5.7 (2.6, 9.7)	6.7 (1.8, 12.3)	4.1 (2.5, 4.6)
OS	1-Year OS[a]	62.1%	38.1%	36.1%	14.9%
	2-Year OS[a]	46.2%	21.8%	32.1%	4.7%
	Median (95% CI), in months	17.5 (12.7, NE)	9.0 (3.7, 14.3)	9.5 (4.3, 13.2)	4.1 (2.5, 4.8)

Key: CCI – Charlson Comorbidity Index; 7 + 3 – cytarabine plus either daunorubicin or idarubicin; CI – confidence interval; HMA – hypomethylating agent (i.e., azacitidine or decitabine monotherapy); NE – not estimable; OS – overall survival; PFS – progression-free survival.
[a] $P < 0.0001$ by log-rank test.

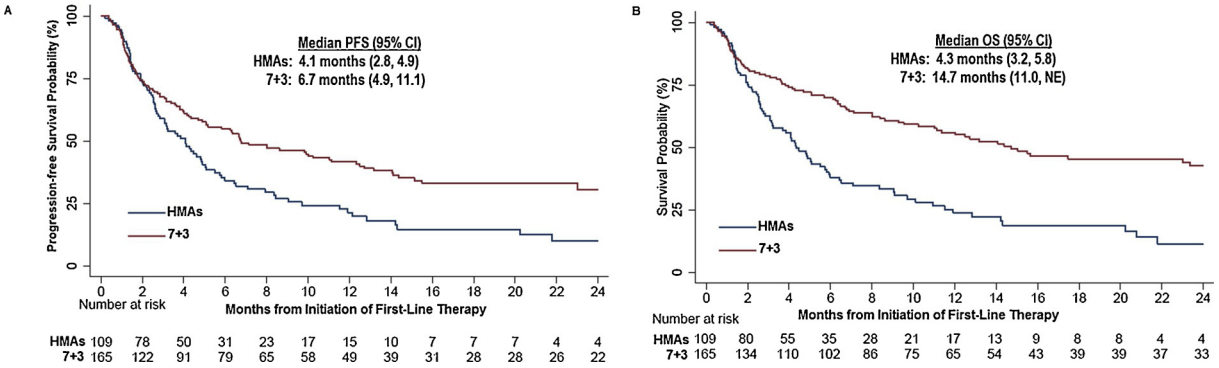

Fig. 3. PFS (A) and OS (B) in Older Patients With AML by Regimen Type, HMAs vs. 7 + 3 Key: 1 L T – first-line therapy; 2 L T – second-line therapy; 7 + 3 – cytarabine plus either daunorubicin or idarubicin; AML – acute myeloid leukemia; CI – confidence interval; HMA – hypomethylating agent (i.e., azacitidine or decitabine monotherapy); NE – not estimable; OS – overall survival; PFS – progression-free survival.

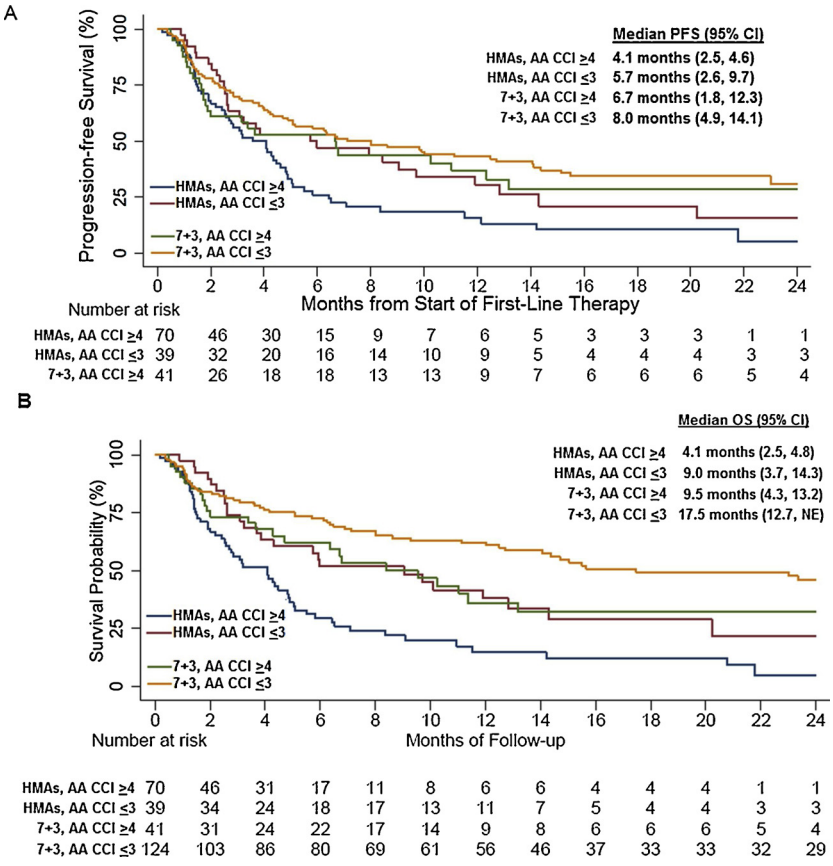

Fig. 4. Age-adjusted CCI PFS (A) and OS (B) in Elderly Patients With AML by Regimen Type, HMAs vs. 7 + 3 Key: 1 L T – first-line therapy; 2 L T – second-line therapy; 7 + 3 – cytarabine plus either daunorubicin or idarubicin; AML – acute myeloid leukemia; AA CCI – age-adjusted Charlson Comorbidity Index; CI – confidence interval; HMA – hypomethylating agent (i.e., azacitidine or decitabine monotherapy); NE – not estimable; OS – overall survival; PFS – progression-free survival.

duration of 1 L T and a median PFS of less than 8 months in either group, identifies a critical unmet need for treatment options for elderly patients with progressive or relapsed disease post-1 L T. Such therapies need to address the fitness/ability of an elderly patient population to tolerate toxicity associated with a new treatment option chemotherapy.

Our study has some limitations that should be considered. Some comorbidities may not have been captured through use of diagnosis codes. Further, reasons for the treatment decisions were not available; both patient preference and other aspects associated with physician assessments could contribute to the selection of a specific treatment. The database used for this study also lacked information on key prognostic characteristics, such as cytogenetics, chromosomal mutations, and bone marrow blast counts, which are used in the treatment decision for AML. The absence of these clinical parameters prevented comparison of survival outcomes with intensive therapy and HMAs in subgroups where results might be different from that reported in the current study. Additionally, dose of treatment was not available of therefore we were not able to determine whether some of the 7 + 3 regimens were administered at a attenuated doses, which could also impact the outcome of the study.

In conclusion, our study reveals that the choice of HMA (i.e., azacitidine or decitabine) over more intensive induction therapy in the 1 L T of elderly patients with may be influenced by an age of ≥75 years and the presence of comorbidities, including RI with CVD, and a number of comorbidities. However, patients treated with 7 + 3 had a longer PFS and OS than those treated with an HMA.

Declaration of interest

This study was funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; JB, AG, RF, and DF are employees of Takeda Pharmaceuticals. VK received an honorarium from Takeda Pharmaceuticals for this study. Xcenda received funding from Takeda Pharmaceuticals to conduct this study and develop the manuscript; EF, MB, SM, AO, and ME are employees of Xcenda, LLC.

Acknowledgments

None

Funding

This study and the manuscript development was funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

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