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Real-world treatment patterns and clinical outcomes in patients with AML unfit for first-line intensive chemotherapy*

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ABSTRACT

Acute myeloid leukemia (AML) predominantly affects the elderly, and prognosis declines with age. Induction chemotherapy plus consolidation therapy is standard of care for fit patients; options for unfit patients include hypomethylating agents (HMA), low-dose cytarabine (LDAC), targeted therapies, and best supportive care (BSC). This retrospective chart review evaluated clinical outcomes in unfit patients with AML who initiated first-line treatment or BSC 01/01/2015–12/31/2018. Overall survival (OS), progression-free survival (PFS), time-to-treatment failure (TTF), and response rates were assessed. Of 1762 patients, 1310 received systemic therapies: 809 HMA, 199 LDAC, and 302 other therapies; 452 received BSC. Median OS was 9.9, 7.9, 5.4, and 2.5 months for HMA, LDAC, other, and BSC, respectively. Median PFS was 7.5, 5.3, 4.1, and 2.1 months for HMA, LDAC, other, and BSC, respectively; median TTF was 4.9, 2.1, 2.2, and 2.1 months, respectively. Our findings highlight the unmet need for novel therapies for unfit patients.

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Acute myeloid leukemia; hypomethylating agents; low-dose cytarabine; best supportive care; unfit patients

Introduction

Acute myeloid leukemia (AML) is a heterogeneous, hematopoietic malignancy characterized by the rapid proliferation of abnormally differentiated myeloid blast cells in peripheral blood and bone marrow [1,2]. AML is uncommon, but the global incidence of AML has increased gradually in the past 28 years from 63,840 cases in 1990 to 119,570 cases in 2017 [3]. This includes 14,790 cases of AML in East Asia and 13,200 reported in China alone, while there were a total of 26,170 cases in Europe [3]. In the US in 2020, it was expected that there would be 19,940 new cases of AML [4], accounting for approximately 1% of all cancers [5].

AML predominately affects the elderly population, with a median age of 68 years at diagnosis; over 59% of patients are diagnosed at age 65 years or older [5]. Despite the greater prevalence of AML in older adults compared with the overall population, survival outcomes have not improved in this population until the recent introduction of novel targeted agents, and advanced age remains associated with a particularly poor prognosis [6–8]. Overall estimated 5-year reported survival rates range from 19 to 29% and the

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survival rates decline rapidly with age, from 30% for patients aged 25–64 to less than 10% for patients over 65 years and less than 2% for those aged over 75 years [5,9,10].

The current standard of care for patients who are able to tolerate intensive treatment is induction therapy with cytarabine and anthracycline, followed by consolidation therapy with hematopoietic stem cell transplantation (HSCT) as an option in eligible patients [7,11,12]. However, unfit patients are typically unable to tolerate intensive therapies, given their age, prevalence of comorbidities, and poor performance status [7,11]. Genetic classification is also essential for guiding treatment decisions, as unfavorable karyotypes contribute to poor prognosis [13].

Treatment options at the time of therapeutic decisions for patients in this cohort considered unfit for intensive therapy included low-intensity treatment with hypomethylating agents (HMA), low-dose cytarabine (LDAC), and best supportive care (BSC), such as hydroxyurea and transfusion support [12]. Targeted therapies including B-cell lymphoma-2 (BCL-2), FMS-like tyrosine kinase-3 (FLT3), isocitrate dehydrogenase isoform 1/2 (IDH1/2), and hedgehog inhibitors are also becoming increasingly available for patients who are ineligible for intensive treatment [6,11]. Despite the development of several prognostic models to estimate response to induction therapy and to determine the suitability of older patients for intensive therapy [8,14–17], there is currently no consensus regarding the optimal therapy for older patients [11,13,18].

Due to the aging population, the incidence of AML is rising [5,7,10]. As such, there is an unmet need to understand current treatment pathways and their respective clinical outcomes, particularly within an evolving treatment landscape. Overall survival (OS) estimates remain poor in unfit patients, and they lag behind their younger counterparts and those eligible for intensive therapy [19–23]. OS estimates reported in clinical trials range from 7.7–10.4 months for patients who receive HMA, 4.1–6.4 months for those receiving LDAC, and 3.6–3.7 months for best supportive care [19,20,24–26]. The aim of this retrospective chart review (CURRENT: Real-World Treatment Patterns and **C**linical Outcomes in **U**nfit AML Patients **R**eceiving Fi**r**st Line Systemic Treatm**ent** or Best Supportive Care) was to evaluate OS and other clinical outcomes, patient demographics, clinico-pathological characteristics, and treatment patterns of patients with AML who were considered unfit to receive intensive chemotherapy and who received first-line systemic treatment, or BSC, in real-world clinical practice.

Methods

This non-interventional, retrospective chart review was conducted in patients diagnosed with AML who were ineligible for intensive induction chemotherapy and who initiated first-line treatment or BSC between 1 January 2015 and 31 December 2018. Notification was made to the responsible ethics committees, health institutions, and/or competent authorities as required by local laws and regulations. Data collection was carried out anonymously following ethics committee approval.

Methods have been described previously (Ito *et al. Eur J Haematol*, submitted). Briefly, patients were eligible for inclusion in the study if they were $\geq$18 years old, diagnosed with primary or secondary AML, and who were unfit for intensive chemotherapy due to age, performance status, comorbidities, regional guidelines, or institutional practice based on the treating physician's assessment. Patients were required to have received first-line systemic treatment with low intensity chemotherapy together with HMAs (azacitidine or decitabine), LDAC, targeted therapy, or BSC for AML, and who received $\geq$2 practice visits to the physician during the treatment period, in addition to the initial treatment visit. Exclusion criteria included unconfirmed AML diagnosis, acute promyelocytic leukemia, and patients who received first-line treatment for AML within a clinical trial.

Patients were identified from 112 community or hospital medical centers that treated patients with AML between 2015 and 2018 across 22 countries. Each site planned enrollment of approximately 5–35 patients, and the maximum of patients per site may be defined locally. Where sites identified an excess of patients meeting the inclusion criteria, a random sampling method was provided. Patients were followed until the last recorded contact or death, whichever was applicable at the time of data collection, and all visits must have been completed prior to data extraction. Anonymized patient data were extracted from patient charts and/or site documentation and recorded *via* electronic case report forms (CRFs) that were completed by each center.

The primary endpoint was OS from diagnosis of AML. Secondary endpoints included progression-free survival (PFS), time-to-treatment failure (TTF), measurable residual disease (MRD) testing rate, and response rate per physician assessment (including complete remission [7], time to achieve CR, duration of CR, CR with incomplete hematologic recovery [CRi], partial remission [PR], and treatment failure).

Table 1. Baseline demographics and disease characteristics.

	First-line systemic therapy			
	HMA $n = 809$	LDAC $n = 199$	Other* $n = 302$	BSC $n = 452$
Gender				
Male	469 (58)	103 (52)	171 (57)	256 (57)
Female	340 (42)	96 (48)	131 (43)	196 (43)
Age at diagnosis				
Age, median (range), years	74 (35–89)	72 (44–89)	74 (38–89)	78 (20–89)
≤75 years	458 (57)	127 (64)	170 (56)	177 (39)
>75 years	351 (43)	72 (36)	131 (43)	275 (61)
Unknown	0	0	1 (<1)	0
Geographic distribution				
EEMEA	128 (16)	114 (57)	49 (16)	70 (15)
WEC	335 (41)	30 (15)	65 (22)	124 (27)
JAPAC	236 (29)	44 (22)	135 (45)	195 (43)
LATAM	110 (14)	11 (6)	53 (18)	63 (14)
Secondary AML				
Yes	268 (33)	50 (25)	93 (31)	160 (35)
No	502 (62)	139 (70)	200 (66)	272 (60)
Unknown	39 (5)	10 (5)	9 (3)	20 (4)
ECOG performance status				
0–1	375 (46)	53 (27)	123 (41)	117 (26)
≥2	257 (32)	104 (52)	150 (50)	235 (52)
Unknown	177 (22)	42 (21)	29 (10)	100 (22)
AML classification (WHO)				
AML with recurrent genetic abnormalities	35 (4)	12 (6)	21 (7)	21 (5)
AML with MDS-related changes	287 (35)	35 (18)	92 (30)	128 (28)
Therapy-related myeloid neoplasms	34 (4)	5 (3)	9 (3)	17 (4)
AML not otherwise specified	261 (32)	82 (41)	96 (32)	135 (30)
Myeloid sarcoma	2 (<1)	0	2 (1)	2 (<1)
Unknown	190 (23)	65 (33)	82 (27)	149 (33)
Molecular features identified†				
Any mutation	150 (19)	23 (12)	68 (23)	63 (14)
FLT3 mutation‡	5 (3)	0	4 (6)	2 (3)
$FLT3^{ITD}$ mutation	18 (12)	5 (22)	18 (26)	19 (30)
$FLT3^{TKD}$ mutation	2 (1)	2 (9)	1 (1)	1 (2)
IDH1 mutation	4 (3)	0	2 (3)	1 (2)
IDH2 mutation	6 (4)	1 (4)	2 (3)	0
TP53 mutation	16 (11)	1 (4)	3 (4)	7 (11)
NPM1 mutation	46 (31)	7 (30)	14 (21)	15 (24)
No mutation	357 (44)	54 (27)	78 (26)	147 (33)
Unknown molecular profile	302 (37)	122 (61)	156 (52)	242 (54)
Cytogenetic risk				
Favorable	123 (15)	20 (10)	36 (12)	38 (8)
Intermediate	288 (36)	42 (21)	91 (30)	141 (31)
Poor	214 (26)	31 (16)	92 (30)	112 (25)
Unknown	184 (23)	106 (53)	83 (27)	161 (36)
Comorbidities				
Any	630 (78)	174 (87)	238 (79)	360/425 (85)
Myocardial infarction	24 (3)	10 (5)	6 (2)	20 (4)
Angina/coronary artery disease	85 (11)	43 (22)	23 (8)	70 (15)
Congestive heart failure	66 (8)	42 (21)	32 (11)	58 (13)
Arrhythmias	71 (9)	35 (18)	29 (10)	53 (12)
Restrictive lung disease or COPD	66 (8)	17 (9)	23 (8)	41 (9)
Liver cirrhosis (C-P A, B, or C)	9 (1)	0	4 (1)	6 (1)
Elevated transaminases not related to liver cirrhosis	10 (1)	2 (1)	5 (2)	4 (1)
Renal failure or CKD stage 3, 4, or 5	22 (3)	4 (2)	6 (2)	23 (5)
Other	520 (64)	137 (69)	194 (64)	304 (67)
None	138 (17)	20 (10)	57 (19)	48 (11)
Unknown	41 (5)	5 (3)	7 (2)	21 (5)

Data are *n* (%) unless otherwise stated.
*Other includes cytarabine, aclarubicin, G-CSF (CAG regimen), enocitabine, venetoclax, or combination therapies.
†Percentages may sum up to >100% as multi-selection was permitted.
‡Not specified as $FLT3^{ITD}$ or $FLT3^{TKD}$ mutation.
AML: acute myeloid leukemia; BSC: best supportive care; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; C-P: Child Pugh; ECOG: Eastern Cooperative Oncology Group; EEMEA: Eastern Europe, Middle East, and Africa; *FLT3*: FMS-like tyrosine kinase-3; $FLT3^{ITD}$: *FLT3* mutation with the internal tandem duplication; $FLT3^{TKD}$: *FLT3* mutation in the tyrosine kinase domain; G-CSF: granulocyte-colony stimulating factor; HMA: hypomethylating agent; *IDH*: isocitrate dehydrogenase isoform; JAPAC: Japan and Asia-Pacific; LATAM: Latin America; LDAC: low-dose cytarabine; MDS: myelodysplastic syndrome; *NPM1*: nucleophosmin 1; *TP53*: tumor protein p53; WEC: Western Europe and Canada; WHO: World Health Organization.

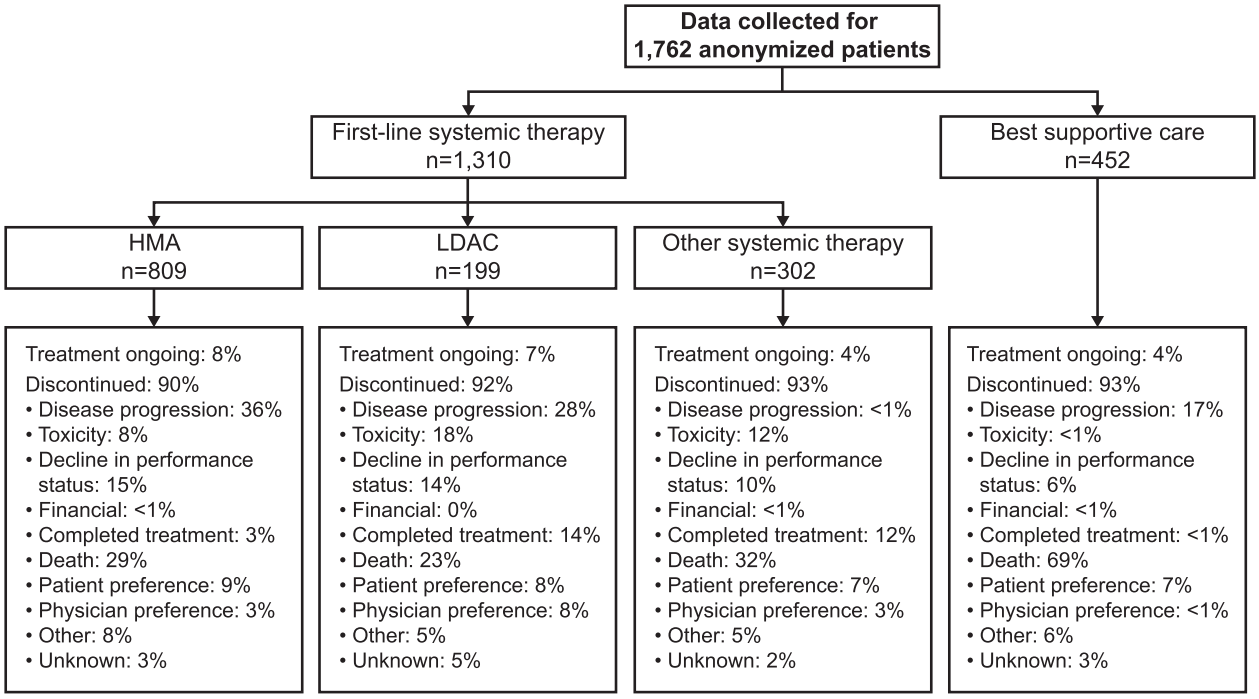


Figure 1. Patient disposition. HMA: hypomethylating agent; LDAC: low-dose cytarabine.

The target sample size was 1600 patients with AML globally. Formal statistical power considerations are not provided due to the descriptive nature of the study. However, this sample size is considered sufficient to provide reasonably precise estimates (e.g. the half-width of a two-sided 95% confidence interval [CI] for a proportion-based estimate will be within ±2.8% with $n = 1{,}200$ [using normal approximation for binomial distribution]; for treatment subgroups [$n = 300$], geographic subgroups [$n = 200$], and combinations of these [$n = 50$], the widths will be at most ±5.7%, ±6.9%, and ±13.9%, respectively). The final data cutoff was March 31, 2020. Continuous variables are described with mean, standard deviation, median, and ranges. Categorical variables are reported as counts and proportions. Time-to-event data were estimated using the Kaplan–Meier method, with median time and 95% CIs reported.

Results

Patient demographics and clinical characteristics

Overall, 1762 patients were included at the time of the final data cutoff on 31 March 2020. Just over half of identified patients were male ($n = 999$; 57%) and less than half were ≥75 years at diagnosis ($n = 829$; 47%). Secondary AML was diagnosed in 32% of patients ($n = 571$), and the majority of patients had either intermediate ($n = 562$; 32%) or poor cytogenetic risk ($n = 449$; 25%). Of the 940 patients with molecular data available, 32% had any mutation, of which *FLT3*^{ITD} ($n = 60$; 6.4%) and *NPM1* ($n = 82$; 8.7%) were the most common. First-line systemic therapy was administered in 1310 (74%) patients and 452 (26%) patients received BSC only. Baseline characteristics were generally similar between the systemic therapy and BSC cohorts (Table 1). Patients who received BSC tended to be older than patients who received first-line systemic therapy (median age 78 vs. 74 years), with a greater burden of comorbidities (85 vs 80%) and a higher Eastern Cooperative Oncology Group Performance Status (ECOG-PS, ≥2; 52 vs. 39%).

Of the 1310 patients who received first-line systemic therapy, 809 (62%) received HMA monotherapy (533 [66%] received azacitidine, 276 [34%] received decitabine) and 199 (15%) received LDAC monotherapy. There were 302 (23%) patients who received systemic therapies other than HMA and LDAC, including the cytarabine, aclarubicin, granulocyte-colony stimulating factor combination regimen (CAG), gemtuzumab ozogamicin, FLT3 inhibitors, venetoclax, and enocitabine; the most common was CAG-based combination therapy ($n = 57$; 19%). A total of 452 patients received BSC, which consisted of transfusions ($n = 377$; 83%), infection management ($n = 281$; 62%), pain relief ($n = 179$; 40%), nutritional support ($n = 123$; 27%), and other supportive measures ($n = 97$; 21%).

The use of novel agents (FLT3, BCL2, and IDH1/2 inhibitors) was low during this study period (10%). Baseline characteristics were generally similar across

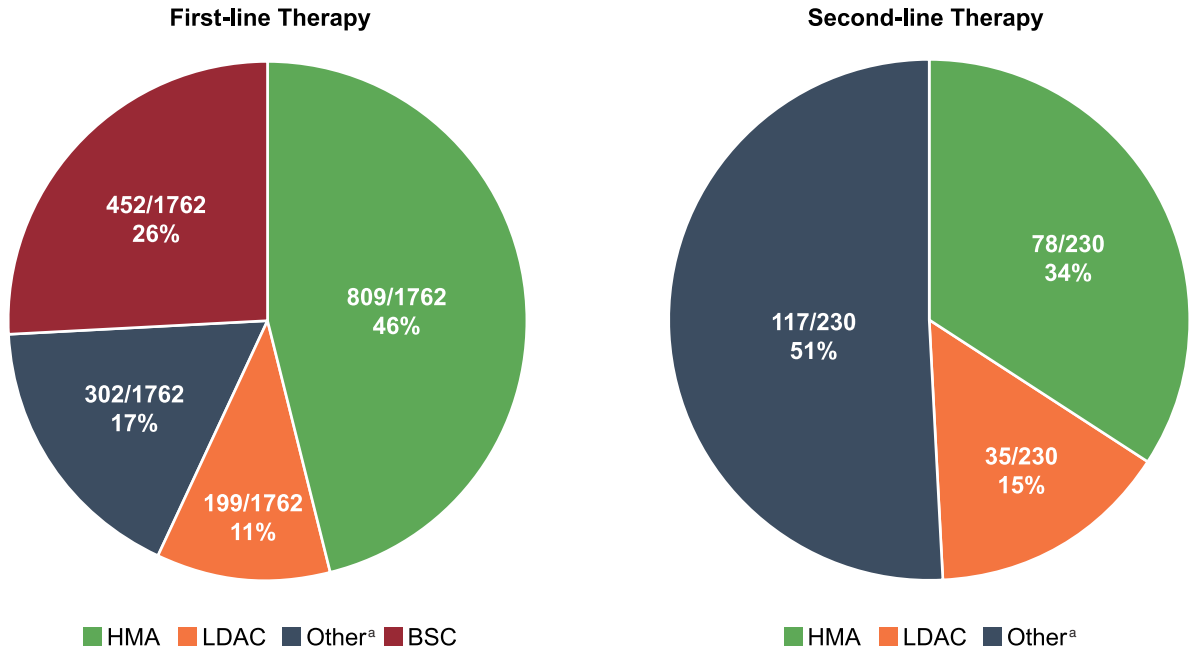


Figure 2. Overview of systemic therapies received in the first line and second line of treatment. [a]Other includes cytarabine, aclarubicin, G-CSF (CAG regimen), enocitabine, venetoclax, or combination therapies. BSC: best supportive care; CAG: cytarabine, aclarubicin, and granulocyte colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; HMA: hypomethylating agents; LDAC: low-dose cytarabine.

the systemic therapy cohorts (Table 1), although the HMA group had a lower median proportion of blast cells at baseline. The LDAC cohort also had a slightly lower median age, a lower proportion of patients >75 years, a lower rate of secondary AML, and slightly lower mutation rate (for those with available data) than the HMA and other systemic therapy cohorts. The proportion of patients with ECOG-PS ≥2 and presence of comorbidities was also slightly higher in the LDAC cohort. The median bone marrow blast percentages at baseline were 31, 50, 49, and 47% for patients who received HMA, LDAC, other systemic therapies, and BSC respectively.

The median duration of first-line systemic treatment was 5 cycles or 118 days in the HMA group, 2 cycles or 35 days in the LDAC group, and 2 cycles or 33 days in other systemic therapies group. The most common reasons for discontinuation of first-line therapy were disease progression and death (Figure 1). Of the 1310 patients who received first-line systemic therapy, 230 (18%) went on to receive second-line systemic therapy. Of these, 78 (34%) received HMAs (of whom 22% received azacitidine and 12% received decitabine), 35 (15%) received LDAC, and 117 (51%) received other systemic therapy (Figure 2).

Primary endpoint

There were 1327 (75%) deaths by the time of data cut-off. This included 587 (73%) patients who received HMA, 128 (64%) who received LDAC, 242 (80%) who received other systemic therapies as first-line treatment, and 370 (82%) who received BSC. The most common cause of death was AML progression, regardless of treatment received.

Median (95% CI) OS from diagnosis was 6.2 (5.7–7.0) months for the overall population. Median (95% CI) OS from diagnosis was 9.9 (8.9–10.8), 7.9 (6.0–9.3), 5.4 (4.6–6.7), and 2.5 (2.3–3.0) months for those who received HMA, LDAC, other systemic therapies, and BSC, respectively (Figure 3).

Secondary endpoints

Median (95% CI) PFS from diagnosis was 4.7 (4.3–5.1) months for the overall population. The median (95% CI) PFS was 7.5 (6.9–8.2), 5.3 (4.3–6.9), 4.1 (3.0–4.4), and 2.1 (1.9–2.4) months for those who received HMA, LDAC, other systemic therapies, and BSC, respectively (Figure 4(A)), and median (95% CI) TTF was 4.9 (4.2–5.7), 2.1 (1.4–2.8), 2.2 (1.3–3.5), and 2.1 (1.7–2.3)

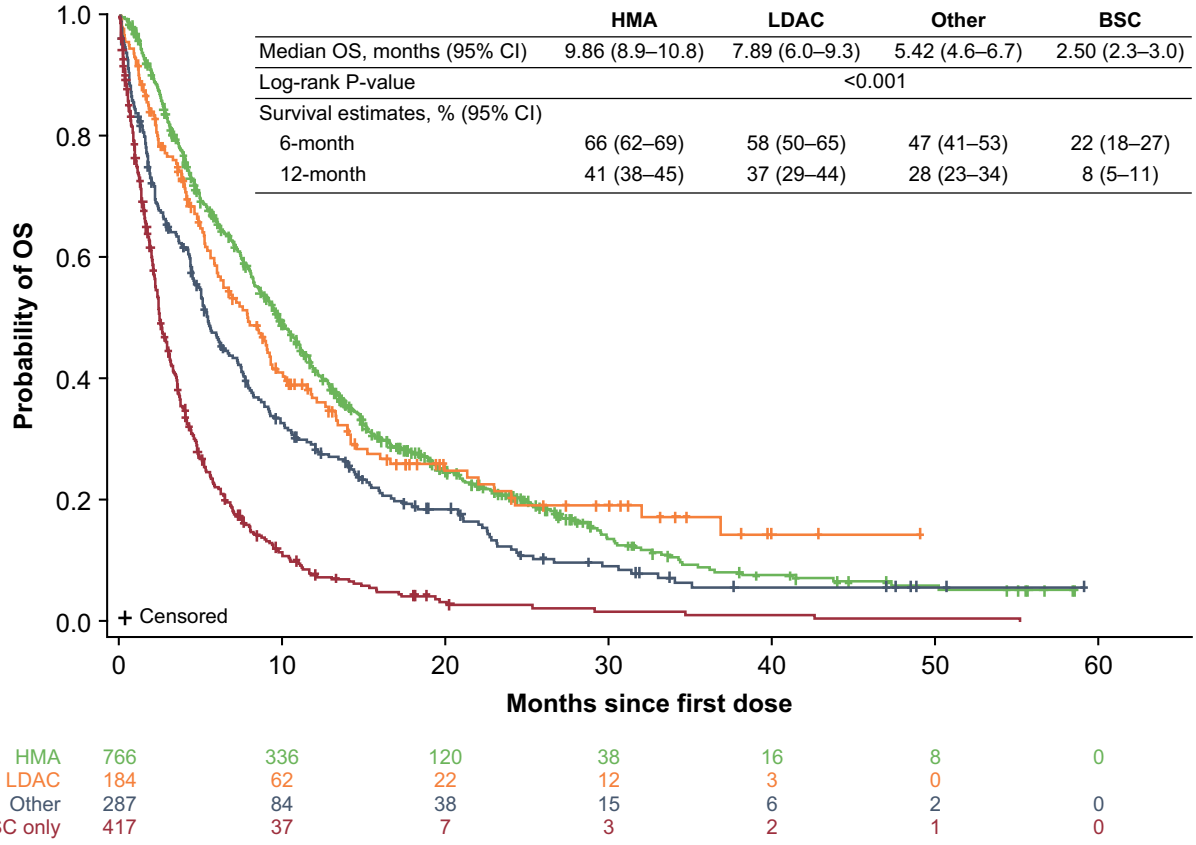


Figure 3. KM curves for OS in patients who received HMA, LDAC, other systemic therapies and BSC. BSC: best supportive care; CI: confidence interval; HMA: hypomethylating agent; KM: Kaplan–Meier; LDAC: low-dose cytarabine; OS: overall survival.

months, respectively (Figure 4(B)). For patients who received first-line systemic therapy, CR or CRi was achieved by 157 (19%) patients who received HMA, 54 (27%) who received LDAC, and 64 (21%) who received other systemic therapies (Table 2). Median time to best response was 115, 55, and 41 days, respectively, and median duration of response (CR, CRi) was 260, 266, and 196 days, respectively. MRD assessments were carried out for 124 (9%) of patients who received first-line systemic treatment, with the majority (93%) receiving 1 assessment; bone marrow was most commonly used for analysis (77%).

Discussion

This non-interventional, retrospective chart review evaluated clinical outcomes and treatment patterns among patients with AML who were unfit for intensive therapy and who received more tolerable alternatives of HMAs, LDAC, other systemic therapies, or BSC. The majority of patients received first-line systemic therapy, most commonly HMAs, with azacitidine being administered more frequently than decitabine, while BSC was selected for approximately a quarter of the patients.

The median OS observed within this study differed between treatment cohorts, ranging from 9.9 months in the HMA cohort to 2.5 months in those who received BSC. Survival outcomes were largely consistent with previous reports in clinical trials [20,26,27] and in real-world studies [18,21,22] of patients who received less intensive therapy for AML. The LDAC cohort reported a slightly longer median OS and higher CR/CRi rates to those reported in previous studies [19,24]. Although intra-study variability prohibits meaningful cross-trial comparisons, it is noteworthy that the LDAC cohort of this study had a slightly lower median age, fewer patients >75 years, a lower rate of secondary AML, and slightly lower mutation rate (for those with available data) than other cohorts, factors which may indicate that patients generally had a better prognosis at treatment initiation. A slightly reduced median OS was observed in the BSC-only cohort compared with the OS observed in clinical trials [19,20], possibly due to the more inclusive patient population in this real-world study. In addition, consistent with the literature [28], this study found that poor cytogenetic risk and *TP53* mutation are statistically associated with OS (results not shown). Rates of CR/CRi were lower among those receiving HMAs vs other systemic

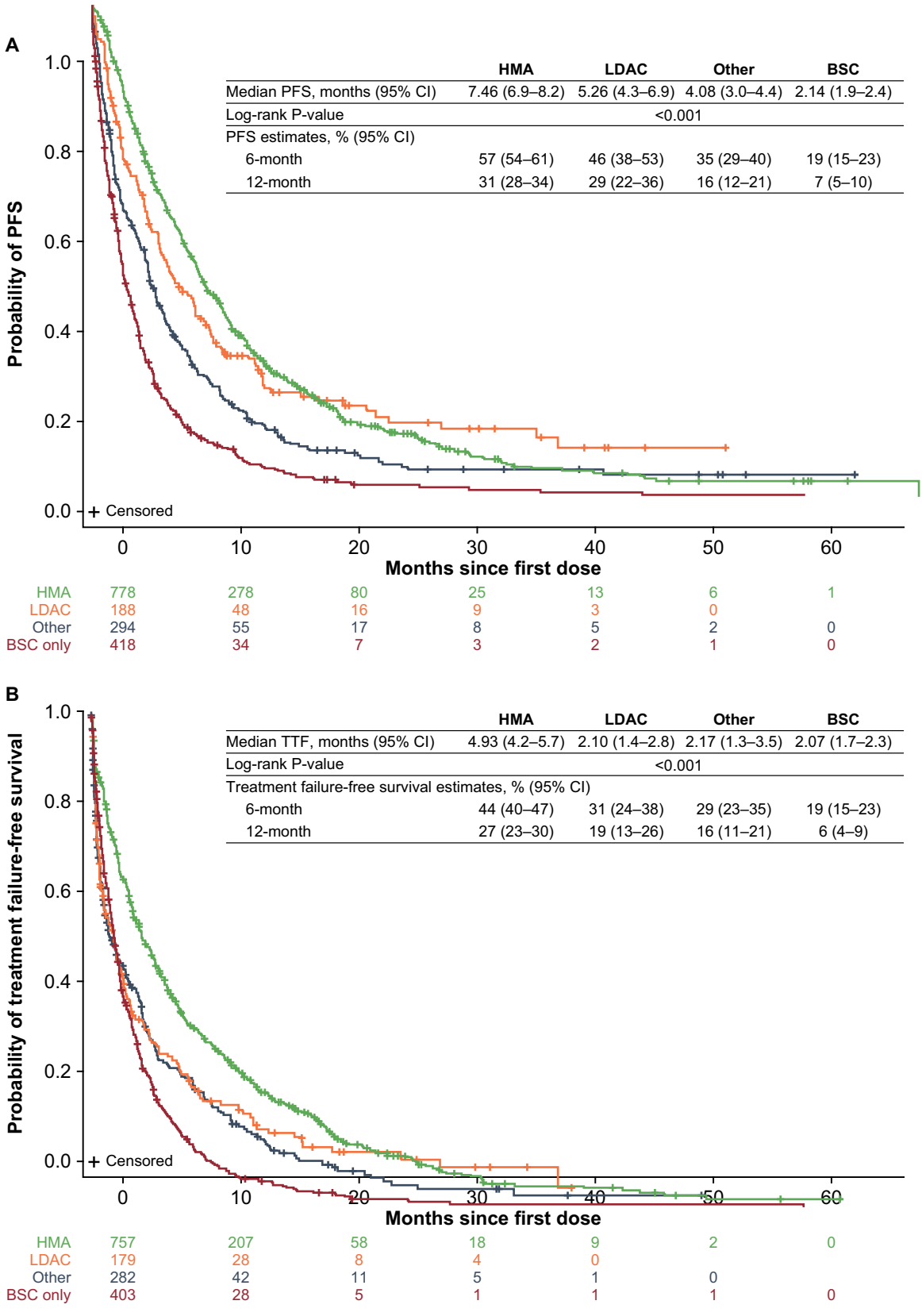


Figure 4. KM curves for (A) PFS and (B) TTF in patients who received HMA, LDAC, other systemic therapies and BSC. BSC: best supportive care; CI: confidence interval; HMA: hypomethylating agent; KM: Kaplan–Meier; LDAC: low-dose cytarabine; PFS: progression-free survival; TTF: time to treatment failure.

Table 2. Outcomes of first-line systemic treatment.

	First-line systemic therapy		
	HMA $n = 809$	LDAC $n = 199$	Other $n = 302$
Best response, *n* (%)			
CR	116 (14)	51 (26)	56 (19)
Cri	41 (5)	3 (2)	8 (3)
PR	92 (11)	18 (9)	26 (9)
SD	203 (25)	30 (15)	47 (16)
PD	108 (13)	37 (19)	68 (23)
Unknown	249 (31)	60 (30)	97 (32)
Median time from start of treatment to best response, days (range)	115 (0–989)	55 (0–229)	41 (0–360)
Median duration of CR/CRi, days (range)	260 (21–1134)	266 (61–1017)	196 (17–648)
Median time from start of treatment to disease progression, days (range)	194 (0–1283)	102 (0–1093)	96 (0–1198)

BSC: best supportive care; CR: complete response; CRi: CR with incomplete hematologic recovery; HMA: hypomethylating agent; LDAC: low-dose cytarabine; PD: disease progression; PR: partial response; SD: stable disease.

therapies in this study. Of note, 30% of patients in this study were missing response assessment data, which could limit the generalizability of response results.

In line with previous studies, this study highlights the preference for HMAs, in particular azacitidine, for patients who are considered unfit for standard intensive therapy; this was associated with a modest improvement in survival outcomes relative to LDAC, other systemic therapies, and BSC. Importantly, the variation in use of HMA or LDAC across countries may reflect differences in their approved indications and/or reimbursement. Furthermore, it should be highlighted that a quarter of patients within this study received only palliative BSC, despite the availability of more directive therapy. Depending on the geographical regions, it may be that only BSC is considered for elderly patients, based on their performance status and serious comorbidities [29]. Beyond a slightly older median age, and an imbalance of ECOG-PS $\geq$2 and comorbidities, there were few baseline patients or disease characteristics that differentiated the BSC-only cohort from the systemic therapy cohorts; the majority of patients receiving BSC in this study were located in the Japan and Asia-Pacific region. This finding was also reflected in a large retrospective US analysis that noted similarities in age, comorbidities, and high-risk disease among patients who received HMA or not treated with HMA [22].

A number of other studies have examined treatment patterns in older patients with newly diagnosed AML and assessed factors associated with the selection of intensive vs low-intensity therapy, along with their respective outcomes. A recent real-world study of 274 older patients with newly diagnosed AML in the US observed that the choice of HMA vs intensive therapy was influenced by age ($\geq$75 years) and the presence and number of comorbidities [18]; this also corroborates earlier retrospective US analyses (922 patients [21] and 8336 patients [22]) of older patients with newly-diagnosed AML that noted the rarity of intensive induction strategies administered within the older population. Less intensive therapies are more commonly selected for older patients despite improved outcomes associated with intensive therapy even in older patients with comorbidities [22,30], and recommendations that a holistic approach should be taken when selecting treatment, rather than basing treatment decisions on age alone [11,13]. The results reported here also align with the expectations for a population with a high proportion of patients who received BSC (53% of patients) [20], despite the availability of low-intensity therapies and their associated survival benefit, although median age was lower in the previous retrospective analysis [20]. Previous analyses of treatment for patients aged 60 years or over have reported comparable or greater OS for patients receiving HMA treatment than for patients receiving intensive chemotherapy, and also identified a clear benefit with HMA compared with palliative treatment [31,32]. Interestingly, one study also observed a steady increase in the usage of first line HMAs (reaching 21% in 2018) in older patients with a corresponding decrease in palliative care [31].

Since the initiation of this study, the treatment landscape has evolved alongside enhanced testing for genetic alterations and this is reflected in current treatment guidelines [7,11]. Interestingly, almost half of patients (47%) in this study did not have molecular profiling data. While targeted treatments have been associated with a moderate improvement in outcomes for those unfit for intensive therapy in clinical trials [20,23,27,33–36], prognosis is still poor and there remains a lack of consensus and standardization of optimal treatment selection for these types of patients. This may be echoed in the array of other systemic therapies recorded in this and other studies, as well as in the wide use of BSC. One important note is that the CURRENT study was conducted prior to the

wide availability of venetoclax, which has been shown to dramatically increase median OS from approximately 10 to 15 months in combination with azacitidine [37]. This finding has dramatically shifted the treatment landscape for AML, and could help to generate a consensus for venetoclax plus azacitidine as standard of care in this population. Nevertheless, it is imperative to continue to discover novel regimens to promote more favorable outcomes, and to continue to analyze and monitor their use in the real-world setting as the treatment landscape evolves.

The results of this chart review are limited by several factors which should be considered when interpreting these data. As with all real-world, retrospective studies, the design is uncontrolled and non-randomized. The findings are limited by missing data, despite attempts to mitigate this by ensuring clarity in the electronic CRF, providing sites with adequate training, and optimizing the electronic CRF to reduce variations and the need for corrections. Molecular and cytogenetic data were often not recorded, which limited assessment of their impact on outcomes. Intra- and inter-site variability may exist, including definitions of outcomes and how they are reported, and differences in standards of care by geographic region, may also influence results per country. While the extensive number of treatment combinations utilized within the 'other systemic therapies' group of this study is consistent with reports from other real-world cohorts [4,20], it does limit interpretation of these data. Also, in addition to excluding patients who received first-line therapy for AML within a clinical study, the use of targeted agents was limited in this study; this reflects that some of these agents had not been approved during the treatment period studied. With the development of more effective regimens, a greater proportion of patients (who are currently ineligible for intensive chemotherapy) may go on to receive HSCT, necessitating future studies to consider collecting data on subsequent transplant; such data were not collected in this study.

To our knowledge, this is one of the largest, global, real-world studies performed to date of treatment patterns in patients with AML who were ineligible for intensive chemotherapy. Overall, the clinical outcomes for this population were poor. OS was generally consistent with clinical trials and previous real-world studies, with a median OS of <10 months for patients who received systemic therapy and <3 months in patients who received BSC. The use of HMAs was common in this real-world cohort and was associated with a numerically longer OS, PFS, and TTF relative to LDAC and BSC. As the incidence of AML rises amid an increasingly aging population, so does the unmet clinical need for novel agents and combination therapies in unfit patients with AML, paralleled by a need to understand how the evolving treatment landscape may impact real-world clinical practice.

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Author contributions

All authors had access to relevant data, and participated in the writing, review, and approval of the manuscript. T. Miyamoto, D. Sanford, C. Tomuleasa, H.-H. Hsiao, L. J. Enciso Olivera, A. K. Enjeti, A. Gimenez Conca, T. Bernal del Castillo, L. Girshova, M. P. Martelli, B. Guvenc, A. Delgado, Y. Duan, B. Garbayo Guijarro, C. Llamas, and J.-H. Lee: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

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Data availability statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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