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Treatment patterns and healthcare resource utilization in patients with *FLT3*-mutated and wild-type acute myeloid leukemia: A medical chart study

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Abstract

Objectives: To assess real-world treatment patterns and healthcare resource utilization (HRU) among patients with *FLT3*–mutated (*FLT3*^{mut}) and *FLT3*–wild-type (*FLT3*^{wt}) acute myeloid leukemia (AML).

Methods: Data were abstracted from medical charts of patients with AML from 10 countries. Patients were grouped based on their *FLT3* mutation status, age (18-64 or ≥65), and whether they were newly diagnosed (ND) or relapsed/refractory (R/R).

Results: Charts of 1027 AML patients were included (183 *FLT3*^{mut} 18-64 ND; 136 *FLT3*^{mut} ≥65 ND; 181 *FLT3*^{mut} R/R; 186 *FLT3*^{wt} 18-64 ND; 159 *FLT3*^{wt} ≥65 ND; 182 *FLT3*^{wt} R/R). Substantial heterogeneity was observed in treatment patterns for AML. Among ND patients 18-64, the most common initial treatment was standard-to-intermediate dose cytarabine-based therapies (43.2% for *FLT3*^{mut} and 55.9% for *FLT3*^{wt}); among ND patients ≥65, the most common initial treatment was hypomethylating agent-based therapies (36.0% and 47.2%). Among R/R patients, the most common initial treatment after R/R was best supportive care only (39.8% and 24.7%). HRU was substantial across cohorts during both event-free and post-event periods.

Conclusions: Treatment patterns of AML were heterogeneous and *FLT3*^{mut} AML was treated more aggressively than *FLT3*^{wt} disease. HRU was substantial for all cohorts, particularly after relapse or treatment failure.

KEYWORDS
acute myeloid leukemia, *FLT3* mutation, healthcare resource utilization, treatment patterns

1 | INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive hematopoietic malignancy characterized by the abnormal proliferation of poorly differentiated myeloblasts in the peripheral blood and bone marrow.[1] Worldwide, AML has a prevalence that ranges from 0.6 to 11 per 100 000,[2] with higher rates in the United States (US, about 4 per 100 000)[3] and Europe (2.5-6 per 100 000)[2] compared with Asian countries (<3.2 per 100 000).[2,4] Five-year survival rates are low, ranging from 19% to 27% in the overall patient population[5,6] and falling to less than 5% in patients aged 65 years or older.[7] Approximately 30% of AML patients harbor mutations in the fms-like tyrosine kinase-3 (*FLT3*) gene, which promotes AML cell survival and proliferation via constitutive activation of the *FLT3*

signaling pathway.[8,9] The majority of patients with *FLT3* mutations have in-frame internal tandem duplications (ITD) of the juxtamembrane region of variable length, while a small portion has point mutations in the tyrosine kinase domain (TKD), typically D835Y.[8] The presence of *FLT3* mutations, particularly ITD, has been shown to be a significant prognostic factor for lower remission rates and higher relapse rates, thereby reducing survival across all age groups.[10,11]

Chemotherapy has long been the mainstay of treatment for AML.[12] Induction therapy is typically initiated soon after diagnosis to achieve remission and is followed by consolidation and maintenance therapy in an effort to maintain remission and eradicate residual malignant disease.[12] In case of relapse after initial complete remission, a second remission can sometimes be induced with additional chemotherapy. Hematopoietic stem cell transplantation (HSCT) is often used in patients in first remission who are at high risk of relapse (defined based on poor prognostic factors, such as the presence of *FLT3* mutations), or in patients in second remission.[12,13] Overall cure rates following chemotherapy with or without HSCT are only 35%-40% in patients under age 60 and 5%-15% in patients over age 60.[14]

These low cure rates have prompted the development of targeted therapies, including those with activity against *FLT3* mutations.[8] First-generation *FLT3* inhibitors are multi-target tyrosine kinase inhibitors[8] and midostaurin is currently the only one approved for the treatment, in combination with standard cytarabine-based chemotherapy, for newly diagnosed *FLT3*–mutated AML (*FLT3*^{mut} AML) in the United States,[15] Canada,[16] and Europe.[17] Second-generation *FLT3* inhibitors have higher specificity for *FLT3*[8] and a number of them are being evaluated in late-phase clinical trials or are under FDA review, including gilteritinib, crenolanib, and quizartinib.[8,18] The introduction of new treatment options are likely to have an impact on treatment patterns that therefore need to be characterized. However, while real-world treatment patterns among patients with AML have been assessed in some claims data studies, these studies mostly focused on elderly patients in the United States and did not differentiate between patients with *FLT3*^{mut} AML and *FLT3* wild-type AML (*FLT3*^{wt} AML).[19,20] The evolving AML treatment landscape is also likely to change how healthcare resources are utilized in clinical practice. Previous studies have shown that the clinical management of AML is very resource intensive, as evidenced by elevated treatment costs largely driven by hospitalizations.[23,24] However, these studies are mainly based on administrative claims data, which do not include *FLT3* mutation status, and are mostly from the United States, thus not providing a more global perspective.

To provide a more comprehensive and timely overview of how currently available treatments for *FLT3*^{mut}AML and healthcare resources are used in clinical practice around the world, this study used medical chart data from 10 countries to assess real-world treatment patterns and AML-related healthcare resource utilization (HRU) among patients with *FLT3*^{mut} and *FLT3*^{wt} AML stratified by age and disease status.

2 | PATIENTS AND METHODS

2.1 | Data source

Patient data were abstracted from medical charts by practicing hematologists and oncologists from an established physician panel in 10 countries: US, Canada, United Kingdom, France, Germany, Spain, Italy, Netherlands, Japan, and South Korea. Physicians were recruited between December 2016 and May 2017 and were eligible to participate if they had more than 3 years of practicing experience as a hematologist or an oncologist, and had seen at least one AML patient between January 1, 2013 and June 30, 2016. Eligible patients were randomly selected by the physicians based on the inclusion criteria detailed below. Physicians were asked to extract medical chart data from eligible patients into an electronic case report form, which had been pilot-tested with hematologists and oncologists to ensure clarity of the questions. To ensure a uniform sample size across cohorts (defined below), invitations to participate were staggered over time so that those sent at a later time could limit physicians to abstract data from patients in the cohorts with smaller sample sizes.

Patient data were anonymous and non-identifiable. Exemption from full review by the institutional review board was granted by the New England Institutional Review Board.

2.2 | Inclusion criteria

Patients were considered eligible for inclusion if: they had a new (ND) or relapsed/refractory (R/R) diagnosis of AML but not acute promyelocytic leukemia (APL); were at least 18 years old at the time of the AML diagnosis; had a known *FLT3* mutation status; were under the care of the participating physician from the initial AML diagnosis; and had available AML-related patient medical records, including treatments and hospitalizations.

2.3 | Study design and cohorts

For ND AML patients, the *index date* was defined as the date of first treatment after the initial AML diagnosis, between 2013 and 2015. For R/R AML patients, the *index date* was defined as the date of first relapse after the initial treatment or of being refractory to the initial treatment, between 2013 and 2015. For all patients, the *baseline period* was defined as the period from the date of the initial AML diagnosis to the index date, while the *study period* was defined as the period from the index date to the last follow-up or death (Figure 1).

Based on their *FLT3* mutation status (ie, *FLT3*^{mut} or *FLT3*^{wt} based on the genetic test closest to the index date), age, and disease status (ND or R/R) at the index date, the selected patients were grouped into the following six cohorts regardless of country of origin: cohort 1 (*FLT3*^{mut} 18-64 ND) comprising patients with ND AML harboring *FLT3* mutations who were between 18 and 64 years of age; cohort 2 (*FLT3*^{mut} ≥65 ND) comprising patients with ND AML harboring *FLT3*

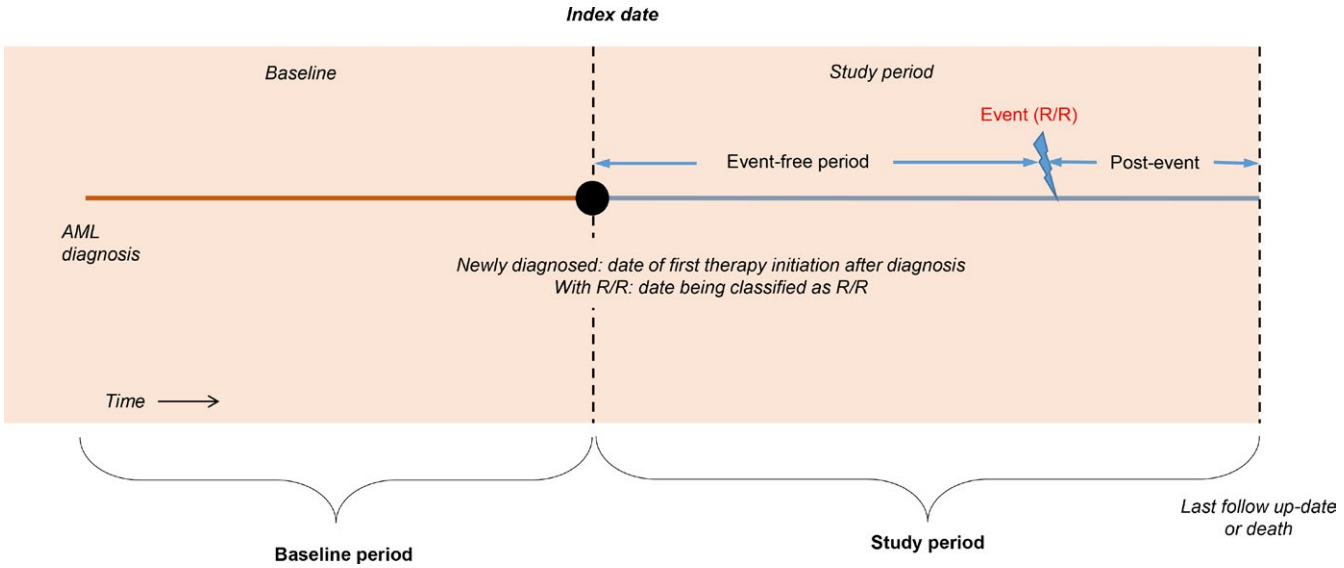

FIGURE 1 Study design schema. AML, acute myeloid leukemia; R/R, relapsed/refractory

mutations who were ≥65 years of age; cohort 3 (*FLT3*^{wt} 18-64 ND) comprising patients with ND AML without *FLT3* mutations who were between 18 and 64 years of age; cohort 4 (*FLT3*^{wt} ≥65 ND) comprising patients with ND AML without *FLT3* mutations who were ≥65 years of age; cohort 5 (*FLT3*^{mut} R/R) comprising patients with R/R AML ≥18 years old harboring *FLT3* mutations; cohort 6 (*FLT3*^{wt} R/R) comprising patients with R/R AML ≥18 years old without *FLT3* mutations.

2.4 | Study outcomes and statistical analyses

Study outcomes were assessed by cohort and included patient baseline characteristics (demographics, Eastern Cooperative Oncology Group [ECOG] performance status, AML classification [de novo AML or AML secondary to prior radiation or chemotherapy], extramedullary involvement, and physician-assessed risk status based on cytogenetic and molecular abnormalities), treatment patterns, and AML-related HRU.

To assess treatment patterns, treatment information was collected for the first three lines of therapy after the index date. Therapies were classified using the following hierarchical order: (a) cytarabine-based therapies (high-dose cytarabine [HDAC], defined as >900 mg/m^2 body surface area; standard-to-intermediate dose cytarabine [SDAC], defined as 90-900 mg/m^2 body surface area; and low dose cytarabine [LDAC], defined as <90 mg/m^2 body surface area); (b) *FLT3*-targeted agents (midostaurin, sorafenib); (c) hypomethylating agents (HMAs; including azacitidine and decitabine); (d) other nucleotide analogs (including clofarabine, cladribine, and fludarabine); (e) anthracycline without cytarabine; and (f) other chemotherapy (eg, etoposide). When combination therapies were used, they were categorized based on the component with the highest hierarchy. For example, the combination of SDAC and clofarabine was categorized only as SDAC and not as "other nucleotide analogs." In addition to the above therapies, information on HSCT (including allogeneic, reduced-intensity allogeneic, and autologous HSCT) was collected and summarized.

To evaluate adherence to treatment guidelines in clinical practice, the treatment regimens recommended by the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of AML[26] were compared to those observed in this study. Although the AML patients included in this study were not only from the United States, the comparison was conducted with the NCCN guidelines.[26] This was because the NCCN guidelines provide the most detail about specific regimens and are similar to the guidelines used in the other countries, including the European Society for Medical Oncology (ESMO),[27] Japanese Society of Hematology (JSH),[28] and European LeukemiaNet (ELN) guidelines.[29] More specifically, the therapies recommended in the NCCN guidelines[26] for ND AML patients who are 18-64 years old are SDAC + anthracycline (±*FLT3* inhibitor for *FLT3*^{mut} AML only), SDAC + anthracycline + other nucleotide analog, HDAC + anthracycline, or fludarabine/HDAC/granulocyte-colony stimulating factor (FLAG) + idarubicin; those recommended for ND AML patients aged ≥65 years are SDAC + anthracycline (±*FLT3* inhibitor for *FLT3*^{mut} AML only), SDAC + other nucleotide analog, LDAC, HMA, or best supportive care (BSC); those recommended for R/R AML patients are SDAC ± anthracycline + other nucleotide analog, SDAC + etoposide + mitoxantrone (MEC), HDAC ± anthracycline, FLAG ± idarubicin, clofarabine ± idarubicin, HMA (±*FLT3* inhibitor for *FLT3*^{mut} AML only), or BSC. In addition, enrolling patients into clinical trials is strongly preferred for R/R patients.

Acute myeloid leukemia-related HRU measures included the following: the number of inpatient admissions and inpatient days, days in intensive care unit (ICU), number of emergency department (ED) visits, number of outpatient visits, number of blood transfusions, and courses of antibiotic treatment (including antibacterial, antiviral, and antifungal treatments). All these measures were collected separately for the *event-free period* (defined as the period free of relapses for

TABLE 1 Sample size in study cohorts stratified by country

	FLT3^{mut}			*FLT3*^{wt}			Total
	18-64 ND	≥65 ND	R/R	18-64 ND	≥65 ND	R/R	
United States	58	32	51	54	42	52	289
Canada	9	3	10	10	6	10	48
United Kingdom	25	19	14	17	17	17	109
France	13	9	14	13	15	13	77
Germany	11	7	15	16	13	16	78
Spain	22	20	21	24	18	22	127
Italy	22	23	29	24	25	28	151
Netherlands	1	1	4	5	1	4	16
Japan	18	19	20	15	19	17	108
South Korea	4	3	3	8	3	3	24
Total	183	136	181	186	159	182	1027

FLT3^{mut}, fms-like tyrosine kinase-3 mutated; *FLT3*^{wt}, fms-like tyrosine kinase-3 wild type; ND, newly diagnosed; R/R, relapsed/refractory.

the four ND cohorts, and the period before the next relapse for the two R/R cohorts) and *post-event period* (defined as the period after the occurrence of a relapse or treatment failure) and summarized per month. In all the analyses, continuous variables were summarized using means, standard deviations (SD), and medians, while categorical variables were summarized using counts and proportions. All analyses were summarized descriptively without any statistical inferences made between cohorts.

3 | RESULTS

3.1 | Patient and disease characteristics

The medical records of 1,027 AML patients were abstracted by 385 hematologists and oncologists from the 10 countries included in the study. Of these patients, 183 were assigned to the *FLT3*^{mut} 18-64 ND cohort, 136 to the *FLT3*^{mut} ≥65 ND cohort, 181 to the *FLT3*^{mut} R/R cohort, 186 to the *FLT3*^{wt} 18-64 ND cohort, 159 to the *FLT3*^{wt} ≥65 ND cohort, and 182 to the *FLT3*^{wt} R/R cohort. The patient breakdown by country and cohort is reported in Table 1. The average length of the event-free period was 14.6 months (range: 9.4-17.1 months across cohorts) and that of the post-event period was 9.0 months (range: 6.7-12.6 months across cohorts).

The patients' mean age was similar between the *FLT3*^{mut} and *FLT3*^{wt} 18-64 ND cohorts (48.3 and 48.2 years), and between the *FLT3*^{mut} and *FLT3*^{wt} ≥65 ND cohorts (71.8 and 72.8 years). For the *FLT3*^{mut} and *FLT3*^{wt} R/R cohorts, the mean age was 53.2 and 56.8, respectively (Table 2). Across cohorts, there was a higher proportion of males (58.8%-69.6%) than females while approximately 76% of patients were white, with the proportion mostly driven by the larger number of North American and European countries in the patient sample (Table 2). The most common chronic comorbidities across all cohorts were hypertension (39.5%), diabetes (23.2%), and coronary heart disease (12.5%); chronic diseases were more prevalent in older patients, with the exception of hepatic insufficiency. In addition, a diagnosis of myelodysplastic syndrome (MDS) before the index date was reported in 12.6% of all patients (cohort range: 4.5%-25.4%).

In patients with *FLT3*^{mut}, 57.6% had *FLT3*–ITD only, 30.0% had *FLT3*–TKD only, and 12.4% had both *FLT3*–ITD and *FLT3*–TKD. In more than 80% of patients, the *FLT3* mutation status was detected as part of routine genetic testing for AML patients; in the remaining patients, it was detected in elective tests (testing not done as part of standard treatment protocol).

De novo AML was reported in 92.4% of all patients across cohorts; the remaining 7.6% had AML secondary to prior radiation or chemotherapy. Most patients had good-to-moderate ECOG performance status at the index date (68.5% had ECOG grade 0 or 1; 59.6-83.9% across cohorts), with *FLT3*^{mut} AML patients having worse performance status compared with *FLT3*^{wt} AML patients.

Patients with ND AML had a median time from the initial AML diagnosis to initiation of the first treatment ranging from 0.3 to 0.8 months across cohorts. R/R AML patients had a median time from the initial AML diagnosis to the time of being classified as R/R that ranged from 8.1 to 8.8 months across cohorts.

3.2 | Treatment patterns

Among ND patients aged 18-64 years with *FLT3*^{mut} and *FLT3*^{wt} AML, the two most common initial treatments were SDAC-based therapies (43.2% and 55.9%, respectively) and HMA-based therapies (13.7% and 11.8%, respectively) (Table 3). Among ND patients aged ≥65 years with *FLT3*^{mut} and *FLT3*^{wt} AML, the most common initial treatments were HMA-based therapies (36.0% and 47.2%, respectively) and SDAC-based therapies (30.1% and 30.8%, respectively). Among R/R patients with *FLT3*^{mut} and *FLT3*^{wt} AML, the most common initial treatment after the initial R/R classification was BSC only (39.8% and 24.7%, respectively), followed by SDAC-based therapies (12.7% and 19.2%, respectively), HMA-based therapies (9.4% and 16.5%, respectively), and LDAC-based therapies (9.4% and 15.4%, respectively) (Table 3).

TABLE 2 Patient baseline characteristics by cohort

	FLT3^{mut}			*FLT3*^{wt}			
	18-64 ND	≥65 ND	R/R	18-64 ND	≥65 ND	R/R	
	(N = 183)	(N = 136)	(N = 181)	(N = 186)	(N = 159)	(N = 182)	*P*-value
Age at index date, mean ± SD	48.3 ± 11.8	71.8 ± 5.6	53.2 ± 15.2	48.2 ± 12.5	72.8 ± 6.0	56.8 ± 14.6	<0.05*
Male, n (%)	119 (65.0)	80 (58.8)	126 (69.6)	115 (61.8)	95 (59.7)	119 (65.4)	0.32
Race, n (%)							0.66
White	135 (73.8)	101 (74.3)	132 (73.3)	141 (75.8)	126 (79.2)	145 (79.7)	-
Asian	33 (18.0)	27 (19.9)	29 (16.1)	31 (16.7)	25 (15.7)	26 (14.3)	-
Other	15 (8.2)	8 (5.9)	19 (10.6)	14 (7.5)	8 (5.1)	11 (6.0)	-
FLT3 status, n (%)							<0.05*
ITD only	106 (57.9)	85 (62.5)	97 (53.6)	-	-	-	-
TKD only	60 (32.8)	34 (25.0)	56 (30.9)	-	-	-	-
ITD and TKD	17 (9.3)	17 (12.5)	28 (15.5)	-	-	-	-
No *FLT3* mutation	-	-	-	186 (100.0)	159 (100.0)	182 (100.0)	
Extramedullary involvement, n (%)	74 (46.0)	60 (48.4)	87 (55.4)	55 (30.7)	33 (21.4)	62 (38.5)	<0.05*
Months since initial AML diagnosis, mean ± SD (median)	2.5 ± 10.0 (0.8)	1.2 ± 2.3 (0.5)	12.7 ± 12.8 (8.1)	1.3 ± 2.8 (0.4)	0.6 ± 1.5 (0.3)	15.0 ± 25.9 (8.8)	<0.05*
ECOG, n (%)[†]							<0.05
Grade 0-1	130 (72.6)	81 (59.6)	106 (63.1)	156 (83.9)	96 (60.4)	122 (67.1)	-
Grade 2-4	49 (27.4)	55 (40.4)	62 (37.0)	30 (16.1)	63 (39.7)	60 (33.0)	-
De novo AML, n (%)	169 (92.3)	125 (91.9)	158 (94.0)	176 (95.7)	139 (88.5)	164 (91.1)	0.21
Prior MDS, n (%)	23 (13.2)	14 (10.7)	16 (10.0)	8 (4.5)	36 (25.4)	24 (13.9)	<0.05
Risk status, n (%)[a]							<0.05*
Favorable risk	41 (24.0)	28 (21.2)	16 (10.3)	70 (38.0)	44 (28.6)	35 (20.0)	-
Intermediate risk	98 (57.3)	63 (47.7)	92 (59.0)	86 (46.7)	68 (44.2)	101 (57.7)	-
Poor risk	32 (18.7)	41 (31.1)	48 (30.8)	28 (15.2)	42 (27.3)	39 (22.3)	-
Comorbidities, n (%)							
Hypertension	55 (30.1)	64 (47.1)	66 (36.5)	59 (31.7)	84 (52.8)	78 (42.9)	<0.05*
Diabetes	42 (23.0)	41 (30.1)	31 (17.1)	27 (14.5)	61 (38.4)	36 (19.8)	<0.05*
Coronary heart disease	7 (3.8)	26 (19.1)	14 (7.7)	15 (8.1)	38 (23.9)	28 (15.4)	<0.05*
Chronic obstructive Pulmonary disease	6 (3.3)	18 (13.2)	17 (9.4)	20 (10.8)	19 (11.9)	18 (9.9)	<0.05*
Peripheral artery disease	7 (3.8)	10 (7.4)	9 (5.0)	6 (3.2)	10 (6.3)	14 (7.7)	0.33
Renal disease	10 (5.5)	9 (6.6)	7 (3.9)	5 (2.7)	10 (6.3)	9 (4.9)	0.54
Congestive heart failure	7 (3.8)	11 (8.1)	8 (4.4)	4 (2.2)	11 (6.9)	6 (3.3)	0.10

(Continues)

TABLE 2 (Continued)

	FLT3^{mut}			*FLT3*^{wt}			
	18-64 ND	≥65 ND	R/R	18-64 ND	≥65 ND	R/R	
	(N = 183)	(N = 136)	(N = 181)	(N = 186)	(N = 159)	(N = 182)	*P*-value
Stroke	5 (2.7)	9 (6.6)	9 (5.0)	4 (2.2)	8 (5.0)	3 (1.6)	0.12
Hepatic insufficiency	7 (3.8)	3 (2.2)	4 (2.2)	4 (2.2)	1 (0.6)	6 (3.3)	0.50

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; *FLT3*, fms-like tyrosine kinase-3; *FLT3*^{mut}, fms-like tyrosine kinase-3 mutated; *FLT3*^{wt}, fms-like tyrosine kinase-3 wild type; ITD, internal tandem duplication; MDS, myelodysplastic syndrome; ND, newly diagnosed; R/R, relapsed/refractory; SD, standard deviation; TKD, tyrosine kinase domain.
[a]Categorical variables may not sum to 100% due to exclusion of missing values.
*Indicates *P*-value <0.05.

TABLE 3 Patterns of initial AML therapies and stem cell transplantation by cohort

	FLT3^{mut}			*FLT3*^{wt}			
	18-64 ND	≥65 ND	R/R	18-64 ND	≥65 ND	R/R	
	(N = 183)	(N = 136)	(N = 181)	(N = 186)	(N = 159)	(N = 182)	*P*-value
Initial drug therapies, n (%)							
HDAC	25 (13.7)	14 (10.3)	5 (2.8)	18 (9.7)	17 (10.7)	21 (11.5)	<0.05*
SDAC	79 (43.2)	41 (30.1)	23 (12.7)	104 (55.9)	49 (30.8)	35 (19.2)	<0.05*
LDAC	11 (6.0)	9 (6.6)	17 (9.4)	4 (2.2)	6 (3.8)	28 (15.4)	<0.05*
FLT3 inhibitors[a]	7 (3.8)	3 (2.2)	6 (3.3)	2 (1.1)	2 (1.3)	1 (0.5)	0.17
HMA[b]	25 (13.7)	49 (36.0)	17 (9.4)	22 (11.8)	75 (47.2)	30 (16.5)	<0.05*
Other nucleoside analogs[c]	21 (11.5)	5 (3.7)	17 (9.4)	17 (9.1)	1 (0.6)	9 (4.9)	<0.05*
Anthracycline without cytarabine	9 (4.9)	9 (6.6)	17 (9.4)	3 (1.6)	5 (3.1)	9 (4.9)	<0.05*
BSC	3 (1.6)	3 (2.2)	72 (39.8)	10 (5.4)	4 (2.5)	45 (24.7)	<0.05*
Other	3 (1.6)	3 (2.2)	7 (3.9)	6 (3.2)	0 (0.0)	4 (2.2)	0.22
Stem cell transplantation, n (%)	50 (29.2)	18 (13.6)	41 (23.6)	45 (24.3)	13 (8.5)	32 (18.1)	<0.05*

AML, acute myeloid leukemia; BSC, best supportive care; *FLT3*, fms-like tyrosine kinase-3; *FLT3*^{mut}, fms-like tyrosine kinase-3 mutated; *FLT3*^{wt}, fms-like tyrosine kinase-3 wild type; HDAC, high-dose cytarabine; HMA, hypomethylating agents; LDAC, low-dose cytarabine; ND, newly diagnosed; R/R relapsed/refractory; SDAC, standard-to-intermediate dose cytarabine.
*Indicates *P*-value <0.05.
[a]*FLT3* inhibitors include midostaurin and sorafenib.
[b]HMAs include azacitidine and decitabine.
[c]Other nucleoside analogs include clofarabine, cladribine, and fludarabine.

Overall, across cohorts, patients with *FLT3*^{mut} AML tended to receive more aggressive treatment compared with patients with *FLT3*^{wt} AML (Table 3). Specifically, HDAC-based therapies were used by more ND patients aged 18-64 years who had *FLT3*^{mut} AML vs *FLT3*^{wt} AML (13.7% vs 9.7%); HMA-based therapies were used by fewer ND patients aged ≥65 years who had *FLT3*^{mut} AML vs *FLT3*^{wt} AML (36.0% vs 47.2%).

When comparing the observed treatments with those recommended by the NCCN,[24] more than 50% of ND patients aged 18-64, more than 28% of ND patients aged ≥65 years, and more than 39% of patients with R/R AML did not receive guideline-recommended treatments, with substantial heterogeneity in treatment patterns for AML (Table S1). HSCT was administered more often to younger patients, with 26.7% of patients with ND AML aged 18-64 receiving HSCT compared with 10.9% of those aged ≥65 years. Among patients with R/R AML, 20.8% received HSCT. Furthermore, patients with *FLT3*^{mut} AML received HSCT more often than patients with *FLT3*^{wt} AML (22.9% vs 17.5%).

3.3 | Healthcare resource utilization

In the overall patient sample, monthly AML-related HRU measures (inpatient admissions, inpatient days, ICU days, outpatient visits, ED visits, blood transfusions, and antibiotic treatment courses) were greater during the post-event period compared with the event-free period, with the exception of outpatient visits

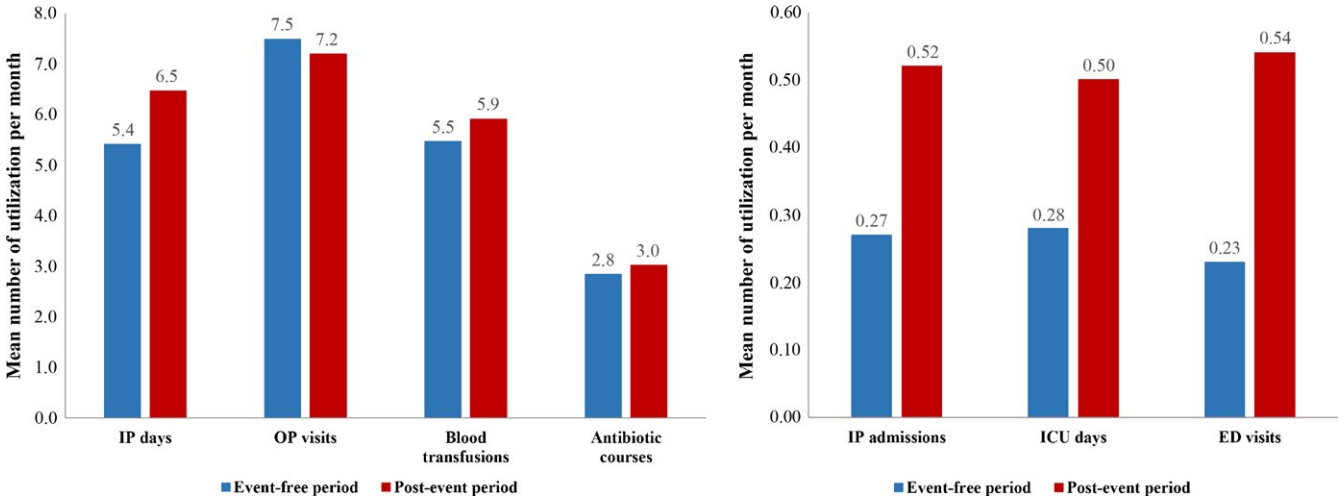

FIGURE 2 Healthcare resource utilization of patients with AML by event-free[1] vs post-event periods[2]. AML, acute myeloid leukemia; ED, emergency department; ICU, intensive care unit; IP, inpatient; OP, outpatient. [1]The event-free period was defined as the period free of relapses for the four ND cohorts, and the period before the next relapse or treatment failure for the two R/R cohorts. [2]The post-event period was defined as the period after the occurrence of a relapse or treatment failure after the index date

(Figure 2). More specifically, in the event-free period vs the post-event period across all cohorts, the mean number of inpatient admissions per month was 0.27 vs 0.52; the mean number of inpatient days per month was 5.4 vs 6.5; the mean number of ICU days per month was 0.28 vs 0.50; and the mean number of ED visits per month was 0.23 vs 0.54. The post-event period was also associated with more blood transfusions and antibiotic treatments compared to the event-free period (Figure 2). Other HRU measures which increased from the pre-event to post-event period included diagnostic imaging per month (0.68 vs 1.39) and hospice experience (2.2% vs 24.6%) (Table S2).

At the cohort level, monthly AML-related hospitalizations, ICU visits, and ED visits are generally greater during the post-event period compared with the event-free period. Outpatient visits were more frequent during the event-free period than during the post-event period for R/R AML patients (8.5 vs 7.2), but were similar for ND AML patients (6.9 vs 7.1 for the 18-64 age range; 7.0 vs 7.3 for the ≥65 age range) (Figure S1). Moreover, in both the event-free and the post-event periods, fewer inpatient admissions were observed for ND AML patients who were 18-64 years old compared with ND AML patients who were ≥65 years old and all patients with R/R AML. On the other hand, ND AML patients who were 18-64 years old had more ICU days, blood transfusions, and antibiotic treatments compared with all other patients in both the event-free and post-event periods (Figure S1). The range of observed values in individual HRU measures was large among patients across all cohorts.

4 | DISCUSSION

This study sought to assess real-world treatment patterns and HRU among adult patients with *FLT3*^{mut} and *FLT3*^{wt} AML. Importantly, the study population included patient charts from 10 different countries, providing a global perspective of how patients with AML are treated and healthcare resources utilized in the real world.

The results of this study showed that treatment patterns were heterogeneous across cohorts, with many different treatment regimens observed within each cohort. In ND patients, the treatment for *FLT3*^{mut} AML tended to be more aggressive than that for *FLT3*^{wt} AML across cohorts, consistent with the poorer prognosis associated with *FLT3* mutations.[10,11,30] Substantial HRU was observed across cohorts, and patients who were older or had R/R AML had more AML-related hospitalizations than younger ND patients; some of these HRU items are often associated with significant medical costs—eg, hospitalizations (especially ones that involve ICU stays) and blood transfusion.[23,25,31,32] Overall, all HRU measures except outpatient visits showed an increase after the occurrence of a relapse or treatment failure, most likely due to hospitalizations or the initiation of additional treatments.

The heterogeneity of treatment patterns and large variations in HRU across and within cohorts may be due to differences in patient populations, clinical practices, and treatment availability across countries. As new *FLT3*-targeted therapies are approved around the world, treatment patterns and HRU among patients with *FLT3*^{mut} AML are likely to evolve. In the present study, the first-generation *FLT3* inhibitor midostaurin was found to be rarely used across cohorts. Since midostaurin was approved after the data used in this study were collected, it is likely that the rare instances in which the use of midostaurin was observed occurred within a clinical trial setting. However, as more *FLT3* inhibitors are made available, their use among patients with *FLT3*^{mut} AML is expected to increase. In the RATIFY trial, which led to the approval of midostaurin in ND patients with *FLT3*^{mut} AML, the use of midostaurin with induction chemotherapy was associated with a statistically significant prolongation of overall survival (74.7 months for midostaurin + induction chemotherapy vs 25.6 months for

placebo + induction chemotherapy).[33] In addition, while efficacy data from Phase 3 trials of second-generation *FLT3* inhibitors in ND *FLT3*^{mut} AML patients are not yet available, data from Phase 1 or 2 trials suggest a significant response rate in R/R *FLT3*^{mut} AML patients.[34,35]

As a result of the evolving treatment landscape for AML, along with increased testing for genetic mutations, treatment guidelines are likely to undergo changes, further promoting a wider use of *FLT3* inhibitors in clinical practice. In the present study, the treatments most commonly used by ND AML patients were found to be consistent with the NCCN guidelines,[26] but a considerable proportion of patients received non-recommended combination treatments. A lack of standardization of treatment has also been reported in other studies regarding treatment decisions for elderly patients with AML.[19,20] Additionally, these studies made the argument that palliative care is used too frequently among older patients without considering the tolerability of intensive treatments and weighing factors such as age, genetic and cytogenetic profiles, and overall health. Future studies are warranted to better understand the factors underlying treatment decisions for *FLT3*^{mut} AML in order to improve the standardization of clinical practices based on optical treatment regimens and promote physician adherence to the regimens recommended in guidelines.

Intensive induction therapies tend to be more commonly used in younger patients,[20-22] consistent with the finding of this study that only approximately 40% of patients aged 65 years or older received first-line SDAC or HDAC. Despite receiving less intensive therapy, older patients have been reported to have more inpatient admissions.[20-22] In one US study, 77.0% of Medicare beneficiaries had 0.63 AML-related inpatient visits per month and 6.63 AML-related inpatient days per month, in the same range as the estimates reported in the current study.[22] More transfusions per month have also been reported in older AML patients.[20] Despite differences in patient populations, study designs, and methodologies, all these studies point to substantial HRU among patients with AML, especially, as found in this study, in the presence of *FLT3* mutations and after a relapse or treatment failure.

Overall, the heterogeneity of treatment patterns reported in this study suggests the need for more effective and standardized treatment strategies and better-defined treatment guidelines for AML patients, particularly those harboring *FLT3* mutations. As second-generation *FLT3* inhibitors are approved and existing first-generation inhibitors become more widely used in clinical practice, further studies are warranted to assess any changes in treatment patterns and HRU over time.

The results of this study should be interpreted in light of some limitations. First, the results may not be generalizable to patients from countries not included in this study as the standard of care and clinical practices may differ. Second, the US-based NCCN guidelines[26] were used as the treatment pattern benchmark to assess adherence to guidelines even though the study sample comprised patient data from different countries. While the NCCN guidelines[26] are similar to those from other countries, some differences exist and these should be taken into consideration when interpreting the results of this study. For example, while the NCCN guidelines[26] provide a list of specific treatment regimens, including options for both patients who can and cannot tolerate aggressive therapies, other guidelines provide fewer and less specific treatment options. The ELN guidelines note that no specific regimen has emerged as the standard of care for R/R AML patients, and recommend the repeated use of induction therapy in patients fit for intensive therapy and BSC in all other patients. The ESMO guidelines[27] are similarly unspecific and recommend allogeneic transplant or BSC for R/R AML patients, adding that patients who are in their first relapse may use intensive re-induction. In the present study, the treatment combinations used to define guideline-recommended regimens were broader than those detailed in all the guidelines mentioned above, thus providing a conservative estimate of the percentages of patients who did not receive guideline-recommended treatments. Third, only patients with HRU available for extraction were included in this study. As a result, HRU may have been underestimated if the information pertaining to HRU measures was received by a different physician or not recorded in the patient chart. Fourth, despite applying randomization to the patient selection process, selection bias may exist in this study as some participating physicians may have selected patients whom they had recently seen or had better outcomes. Lastly, as with any retrospective observational study, there is the potential for missing or inaccurate data recorded in the medical charts or for errors introduced during data entry.

5 | CONCLUSIONS

This study found considerable heterogeneity in *FLT3*^{mut} AML treatment patterns, with some treatment combinations used in clinical practice but not recommended by treatment guidelines. *FLT3*^{mut} patients tended to receive more aggressive treatment compared with *FLT3*^{wt} patients. Moreover, HRU was substantial across all cohorts, but particularly after the occurrence of relapse or treatment failure. With the emergence of several new targeted therapies with considerable efficacy, including first- and second-generation *FLT3* inhibitors, further studies are warranted to assess how, and to what extent, treatment patterns and HRU change over time in real-world clinical practice.

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CONFLICT OF INTEREST

James D. Griffin has received consultancy fees from Astellas Pharma and Novartis. Hongbo Yang, Yan Song, and David Kinrich are

employees of Analysis Group, Inc, which has received consultancy fees from Astellas Pharma to conduct this study. Manasee V. Shah is an employee of Astellas Pharma, Inc; Cat N. Bui was an employee of Astellas Pharma during the conduct of this study. No restrictions were placed by the sponsor on study design, data collection and interpretation, manuscript writing, and decision to submit this manuscript for publication.

DATA ACCESSIBILITY

Access to anonymized individual participant level data will not be provided for this trial as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas."

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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