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ORIGINAL RESEARCH

Treatment Patterns and *FLT3* Mutation Testing Among Patients with Acute Myeloid Leukemia in China: A Retrospective Observational Study

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Introduction: For acute myeloid leukemia (AML), prognosis is particularly poor in patients harboring FMS-like tyrosine kinase 3 (*FLT3*) gene mutations, though routine screening for these mutations at diagnosis has been shown to be insufficient. The understanding of the impact of *FLT3* mutations on treatment decisions is limited.

Methods: In this retrospective, observational study, we investigated the key epidemiological characteristics, treatment patterns and responses among adult patients with newly diagnosed (ND) AML in China, who initiated treatment from January 1, 2015, to December 31, 2019, or progressed to relapsed/refractory (R/R) AML by December 31, 2020.

Results: Of the 853 ND AML patients included, 63.4% were screened for *FLT3* status, and 20.1% tested positive ($FLT3^{MUT}$) at initial diagnosis. Of 289 patients who progressed to R/R AML during the study period, 24.9% were screened at the diagnosis of R/R AML, and 19.4% tested positive; 20.5% of screened patients changed *FLT3* status at first diagnosis of R/R AML. Initial treatment regimens or treatment responses did not seem to differ in patients with ND AML by *FLT3* mutation status. In patients with R/R AML, there was an apparent difference in second-line treatment choices by *FLT3* mutation status; however, the number of *FLT3*-mutated patients were limited to demonstrate any meaningful distinction. *FLT3*-mutated R/R AML was associated with shorter relapse time.

Conclusion: Study findings showed that there was a lack of routine testing for *FLT3* mutations at first diagnosis of R/R AML, and initial treatment decisions did not differ by *FLT3* mutation status. Given the clinical burden of $FLT3^{MUT}$, likelihood of *FLT3* status changes, and emerging FLT3 inhibitors, further routine *FLT3* screening is needed to optimize treatment of R/R AML.

Keywords: acute myeloid leukemia, epidemiology, real-world, retrospective study

Introduction

Acute myeloid leukemia (AML) is the predominant form of leukemia in adults, both globally and in China.[1–3] It is characterized by the rapid proliferation of undifferentiated myeloblasts and a poor prognosis, particularly for older individuals, with most patients relapsing after initial treatment.[4,5] For patients with newly diagnosed (ND) AML, initial treatment comprises induction chemotherapy to reduce leukemic cell numbers to below detectable levels, followed by consolidation therapy to eliminate any remaining leukemic cells and reduce the risk of relapse.[6,7]

Allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is indicated for use either as first-line therapy in patients achieving remission following chemotherapy, for whom the estimated probability of relapse without allo-HSCT would be >35–40%, or as second-line treatment following relapse after initial chemotherapy.[8] However, relapse after allo-HSCT is relatively common (25–55%), with survival rates after 4 years ranging between 20% and 35%.[9] As an alternative therapeutic

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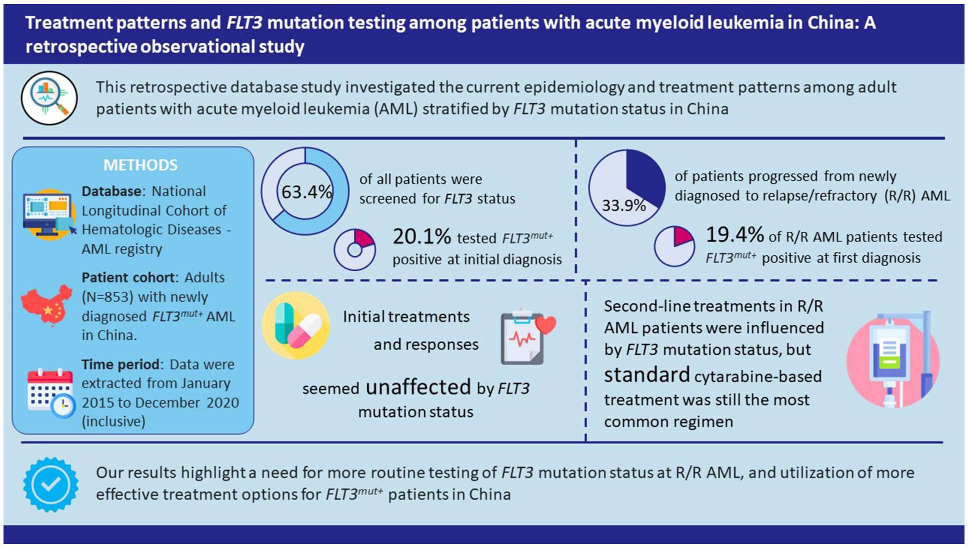
Graphical Abstract



pathway, several key genetic mutations have been shown to be closely associated with the pathogenesis of AML and poorer prognoses in AML patients,[10,11] with their inhibition linked to improved clinical outcomes in relapsed/refractory (R/R) AML patients.[12] Recent advances in next-generation sequencing technology have enhanced our understanding of these mutations underlying AML and the genomic heterogeneity between patients,[5] providing an opportunity for more personalized, less intensive therapies and the development of agents that directly target the affected pathways.

Approximately 30% of patients with AML harbor mutations in the FMS-like tyrosine kinase 3 (*FLT3*) gene;[10] one of the most common types of *FLT3* mutations is an internal tandem duplication (*FLT3*-ITD), which may be present in 25% of patients.[13] A recent study of 171 Chinese patients reported the incidence of *FLT3*-ITD to be 18.1% and found it to be associated with a significantly reduced rate of complete remission (CR).[14] *FLT3*-ITD, as well as the less common point mutations within the activation loops of the *FLT3* tyrosine kinase domain (*FLT3*-TKD), are associated with an increased risk of relapse and reduced survival rates.[15,16] It is therefore recommended that patients with ND AML are screened for *FLT3* mutations, so that they can receive targeted treatment with FLT3 inhibitors.[17] While clinical trials for next-generation FLT3 inhibitors are ongoing, two FLT3 inhibitors, midostaurin and gilteritinib, have been approved by the US Food and Drug Administration (FDA), for ND AML and R/R AML, respectively.[5] At the time of this study, only gilteritinib has received regulatory approval in China (in 2021).[18] Both midostaurin and gilteritinib have been shown to significantly increase CR rate and overall survival compared to treatment with standard chemotherapy.[19,20]

Despite the emergence and ongoing development of FLT3 inhibitors, and recommendations from clinical guidelines, the occurrence of routine screening for *FLT3* mutations in patients with AML is still limited.[21] Although previous studies across multiple countries have noted that $FLT3^{MUT}$ patients were treated more aggressively than wild-type *FLT3* patients,[22] further trends in treatment pattern by *FLT3* mutation status were not identified.

In this real-world, single-center study, we investigated epidemiologic characteristics, treatment patterns, clinical outcomes in patients with AML in China. We also sought to determine the prevalence of *FLT3* mutation testing and stratify outcomes by *FLT3* mutation status.

Materials and Methods

Study Design and Patients

This was a retrospective, longitudinal, observational cohort study based on historical data from the National Longitudinal Cohort of Hematologic Diseases (NICHE)-AML registry, of the Institute of Hematology and Blood Diseases Hospital (IHBDH), the leading hospital for the China Alliance for Blood Diseases. The study included patient data recorded from January 1, 2015, to December 31, 2020. No a priori hypotheses were tested.

All eligible patients were aged ≥18 years at the time of initial diagnosis and initiated on treatment for ND AML between January 1, 2015, and December 31, 2019; of these patients, those who subsequently progressed to R/R AML (from the initial treatment for ND AML) during this period (plus 1 year of follow-up to December 31, 2020) were identified. Patients were split by disease progression status (ND and R/R AML), whether *FLT3* mutation testing was performed, and, if so, the result of the test (wild-type *FLT3* [$FLT3^{WT}$] and mutated *FLT3* [$FLT3^{MUT}$]).

Eligible patients also had at least 1 year of follow-up at the data cut (December 31, 2020); however, patients with less than 1 year of follow-up were eligible if the reason for loss of follow-up was death. Patients were excluded if they had acute promyelocytic leukemia or were participating in clinical trials.

The study was conducted in accordance with the Declaration of Helsinki and International Conference of Harmonisation guidelines. The study was approved by the institutional review board committee of the IHBDH. The review board committee confirmed that informed consent was not needed from participants, and all data were anonymized prior to the current study.

Treatment

This was a non-interventional, real-world registry study and patients did not receive treatment as part of the study. However, historical medical data extracted from the NICHE-AML registry also included information regarding treatments received by patients, and the corresponding treatment responses.

Endpoints

The primary objectives were to investigate the key epidemiological characteristics among patients with AML in China and to understand the treatment patterns and responses among patients stratified by ND, R/R, and *FLT3* mutation status. Specifically, the primary endpoints were as follows: cross-sectional distribution of patients with ND AML, relapsed AML, and refractory AML (patients who were classified as having refractory AML at any point during the study) at the time of data cut (December 31, 2020); rate of progression from ND to R/R AML during study period; proportion of patients who received *FLT3* mutation testing at initial diagnosis and at first diagnosis of R/R disease; and prevalence of patients harboring *FLT3* mutations among all tested patients.

Other primary endpoints were the first-line and R/R treatment patterns and responses, including distribution of therapies being used; use of stem-cell transplantation; and the proportion of patients achieving a CR or CR with incomplete hematologic recovery (CRi).

Secondary and exploratory objectives included descriptions of patient baseline demographics and disease characteristics at initial diagnosis.

Statistical Analysis

Continuous variables were calculated as mean with standard deviation (SD) and median with interquartile range (IQR); categorical variables were calculated as counts and proportions. Summary descriptive statistics collected were the length of follow-up and the number of follow-up visits per person for AML treatment at the IHBDH.

The progression rate from ND to relapsed and refractory AML was determined from the available data, with the total number of patients with ND AML forming the denominator. Data were calculated for the following six study groups constructed according to R/R status and *FLT3* mutation status: (1) $FLT3^{WT}$ at initial diagnosis; (2) $FLT3^{MUT}$ at initial diagnosis; (3) unknown *FLT3* mutation status at initial diagnosis; (4) $FLT3^{WT}$ at R/R disease; (5) $FLT3^{MUT}$ at R/R disease; and (6) unknown *FLT3* mutation status at R/R disease.

All measurements were summarized descriptively, and no statistical comparisons were made across study groups. All analyses were conducted using a complete case analysis approach and patients with missing values in relation to patient and disease characteristics were omitted from the corresponding statistic. Regarding treatment information, ongoing treatments without complete data for treatment response and number of treatment cycles were also omitted; the absence of treatment name, dosage, and administration date were considered an indicator that a patient did not receive treatment at the corresponding line.

Due to the nature of the NICHE-AML registry database, all patients included in the current study were initially classed as ND and a subset of patients progressed to R/R during the follow-up period. The index date for patients with ND AML was defined as the initiation date of the first therapy; for patients with R/R disease after the initial treatment, the index date was the date of confirmation of R/R AML. To maximize the achievable sample size in the study groups, a patient could contribute to multiple study groups, eg, patients with ND AML who progressed to R/R AML during follow-up would contribute to both the ND and R/R study groups.

Results

Patient and Disease Characteristics

A total of 1002 patients were identified from the NICHE-AML registry with ND AML and who initiated treatment or had progressed to R/R AML at treatment initiation during the study period. Of these, 853 patients were eligible and were enrolled in the study (Figure 1). In total, 541 (63.4%) patients received *FLT3* mutation testing at initial AML diagnosis: 432 patients were diagnosed with *FLT3*^{WT}, 109 with *FLT3*^{MUT}, and 312 with unknown *FLT3* mutation status at enrolment (Table 1a).

During the study period, 289 (33.9%) patients progressed from ND to R/R AML, including 234 (27.4%) who relapsed after initial treatment and 55 (6.4%) who were refractory to initial treatment (Tables 1b and 2). Seventy-two (24.9%) patients with R/R AML received *FLT3* mutation testing at first diagnosis of R/R AML, of whom 58 had *FLT3*^{WT} and 14 had *FLT3*^{MUT} disease; the *FLT3* mutation status was unknown for the remaining 217 patients with R/R AML (Table 2).

By study end, the cross-sectional distribution of patients with ND, relapsed, and refractory (at any point during the study) AML was 66.1% (564/853), 25.4% (217/853), and 8.4% (72/853), respectively.

FLT3 Mutation Testing

The proportion of ND AML patients tested for *FLT3* mutation status increased year-on-year, from 29% in 2016 to 87% in 2017, 89% in 2018, and 96% in 2019. A similar pattern of increased *FLT3* mutation testing was observed for patients

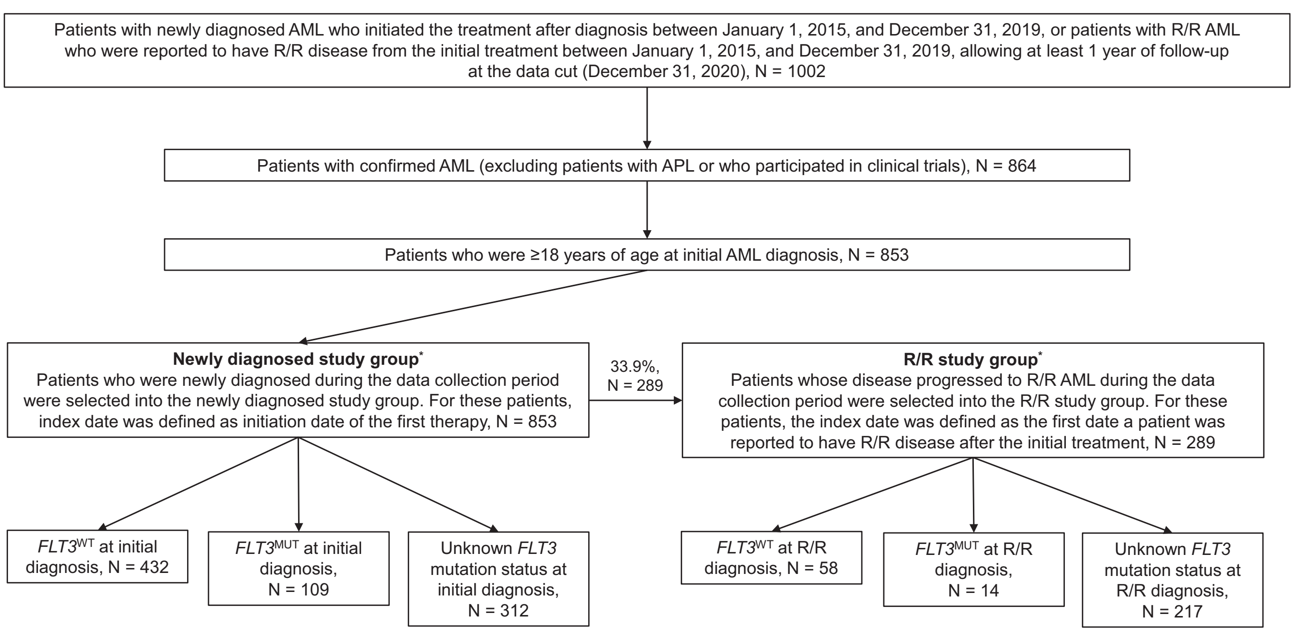


Figure 1 Flow of patients through the study. *All patients had newly diagnosed AML at entry to the NICHE-AML historical database.
Abbreviations: AML, acute myeloid leukemia; *FLT3*, FMS-like tyrosine kinase-3; MUT, mutated; R/R, relapsed/refractory; WT, wild type.

Table 1 Demographics and Disease Characteristics of Patients with (a) ND and (b) R/R AML in the NICHE-AML Registry

(a)				
Characteristic	**All ND AML Patients N = 853**	***FLT3*^WT^ N = 432**	***FLT3*^MUT^ N = 109**	**Unknown *FLT3* Mutation Status[a] N = 312**
Follow-up duration, days	573.4 (475.9)	494.8 (364.2)	399.8 (328.1)	742.9 (592.6)
Age at diagnosis, y	42.5 (12.8)	43.1 (12.8)	44.0 (12.5)	41.3 (12.8)
Male, n (%)	448 (52.5)	244 (56.5)	51 (46.8)	153 (49.0)
Known mutation status at diagnosis, n (%)	541 (63.4)	432 (100)	109 (100)	-
FLT3	109 (20.1)	0	109 (100)	-
NPM1	109 (20.1)	66 (15.3)	43 (39.4)	-
CEBPA	103 (19.0)	89 (20.6)	14 (12.8)	-
IDH1	38 (7.0)	32 (7.4)	6 (5.5)	-
Other acquired mutation	533 (98.5)	428 (99.1)	105 (96.3)	-
Cytogenetic status, n (%)	832 (97.5)	421 (97.5)	105 (96.3)	306 (98.1)
Abnormal karyotype	416 (50.0)	235 (55.8)	42 (40.0)	139 (45.4)
FAB classification,[23] n (%)	650 (76.2)	345 (79.9)	77 (70.6)	228 (73.1)
M0	3 (0.5)	2 (0.6)	0	1 (0.4)
M1	6 (0.9)	2 (0.6)	1 (1.3)	3 (1.3)
M2	253 (38.9)	158 (45.8)	20 (26.0)	75 (32.9)
M4	113 (17.4)	54 (15.7)	12 (15.6)	47 (20.6)
M5	265 (40.8)	126 (36.5)	44 (57.1)	95 (41.7)
M6	6 (0.9)	1 (0.3)	0	5 (2.2)
M7	1 (0.2)	0	0	1 (0.4)
Type of AML				
De novo	849 (99.5)	428 (99.1)	109 (100)	312 (100)
Secondary	4 (0.5)	4 (0.9)	0	0
Risk stratification[7]	746 (87.5)	427 (98.8)	108 (99.1)	211 (67.6)
Favorable	283 (37.9)	200 (46.8)	82 (75.9)	1 (0.5)
Intermediate	423 (56.7)	227 (53.2)	26 (24.1)	170 (80.6)
Adverse	40 (5.4)	0	0	40 (19.0)
(b)				
Characteristic	**All R/R AML Patients N = 289**	***FLT3*^WT^ N = 58**	***FLT3*^MUT^ N = 14**	**Unknown *FLT3* Mutation Status[b] N = 217**
Follow-up duration, days	562.7 (438.3)	606.2 (371.7)	479.2 (261.3)	556.4 (463.2)
Age at diagnosis, y	43.6 (13.5)	43.5 (13.1)	44.4 (15.4)	43.6 (13.6)
Male, n (%)	154 (53.3)	32 (55.2)	9 (64.3)	113 (52.1)

(*Continued*)

Table 1 (Continued).

Known mutation status at diagnosis, n (%)	183 (63.3)	45 (77.6)	9 (64.3)	129 (59.4)
FLT3	29 (15.8)	3 (6.7)	4 (44.4)	22 (17.1)
NPM1	30 (16.4)	8 (17.8)	3 (33.3)	19 (14.7)
CEBPA	45 (24.6)	20 (44.4)	1 (11.1)	24 (18.6)
IDH1	15 (8.2)	2 (4.4)	2 (22.2)	11 (8.5)
Other acquired mutation	182 (99.5)	44 (97.8)	9 (100)	129 (100)
Cytogenetic status, n (%)	285 (98.6)	56 (96.6)	14 (100)	215 (99.1)
Abnormal karyotype	135 (47.4)	21 (37.5)	2 (14.3)	112 (52.1)
FAB classification,[23] n (%)	229 (79.2)	56 (96.6)	11 (78.6)	162 (74.7)
M0	0	0	0	0
M1	2 (0.9)	2 (3.6)	0	0
M2	87 (38.0)	30 (53.6)	1 (9.1)	56 (34.6)
M4	34 (14.8)	5 (8.9)	2 (18.2)	27 (16.7)
M5	103 (45.0)	19 (33.9)	7 (63.6)	77 (47.5)
M6	2 (0.9)	0	1 (9.1)	1 (0.6)
M7	0	0	0	0
Type of AML				
De novo	287 (99.3)	58 (100)	14 (100)	215 (99.1)
Secondary	2 (0.7)	0	0	2 (0.9)
Risk stratification[7c]	254 (87.9)	55 (94.8)	14 (100)	185 (85.3)
Favorable	88 (34.6)	31 (56.4)	5 (35.7)	52 (28.1)
Intermediate	152 (59.8)	23 (41.8)	9 (64.3)	120 (64.9)
Adverse	14 (5.5)	1 (1.8)	0	13 (7.0)

Notes: Data are mean (SD), unless otherwise stated. [a]Genetic testing results were not available for patients with unknown *FLT3* mutation status at initial AML diagnosis; [b]Genetic testing results at initial diagnosis were summarized among patients with relevant information at initial diagnosis; [c]Each patient was classified into only one risk category.

Abbreviations: AML, acute myeloid leukemia; CEBPA, CCAAT enhancer binding protein alpha; FAB, French-American-British; *FLT3*, FMS-like tyrosine kinase-3; IDH, isocitrate dehydrogenase; MUT, mutated; ND, newly diagnosed; NPM1, nucleophosmin 1; R/R, relapsed or refractory; SD standard deviation, WT, wild-type, y, years.

with R/R AML, although the overall proportion tested remained lower than for ND AML (3% in 2016, 19% in 2017, 16% in 2018, and 53% in 2019).

FLT3 Mutations

Among patients with any *FLT3*^{MUT} at initial diagnosis, the proportions with *FLT3*-ITD, *FLT3*-TKD, and unspecified *FLT3* mutations were 48.6%, 29.4%, and 23.9%, respectively. The corresponding proportions among patients with any *FLT3*^{MUT} at first diagnosis of R/R disease were 64.3%, 42.9%, and 7.1% (Table 2).

Among patients who received *FLT3* testing at both initial diagnosis and first diagnosis of R/R AML, 5.6% and 9.3% of patients lost and gained *FLT3*^{MUT} at first diagnosis of R/R AML, respectively. Additionally, 5.6% of patients switched from *FLT3*-ITD to *FLT3*-TKD or vice versa at first diagnosis of R/R AML.

Table 2 Prevalence, Method, and Outcome of *FLT3* Mutation Testing for Patients with AML

Key Epidemiologic Characteristic, n (%)	All ND AML Patients N = 853	All R/R AML Patients N = 289
Progression from ND to R/R AML	289 (33.9)	–
Relapsed after initial treatment	234 (27.4)	–
Refractory to initial treatment	55 (6.4)	–
FLT3 mutation testing		
At initial AML diagnosis	541 (63.4)	–
At first R/R diagnosis	–	72 (24.9)
NGS testing method	541 (100)	72 (100)
Other testing method	0	0
FLT3^{MUT} positivity among tested patients[a]		
At initial AML diagnosis	109 (20.1)	–
FLT3-ITD mutation	53 (48.6)	–
FLT3-TKD mutation	32 (29.4)	–
Unspecified *FLT3* mutation	26 (23.9)	–
At first R/R AML diagnosis	–	14 (19.4)
FLT3-ITD mutation	–	9 (64.3)
FLT3-TKD mutation	–	6 (42.9)
Unspecified *FLT3* mutation	–	1 (7.1)
FLT3 testing at both initial AML and first R/R diagnoses		54 (18.7)
Lost *FLT3* mutation at first R/R	–	3 (5.6)
Gained *FLT3* mutation at first R/R	–	5 (9.3)
FLT3-ITD vs *FLT3*-TKD mutation switch at first R/R	–	3 (5.6)
From *FLT3*-ITD to *FLT3*-TKD	–	1 (33.3)
From *FLT3*-TKD to *FLT3*-ITD	–	2 (66.7)

Notes: [a]Patients could harbor both *FLT3*-ITD and *FLT3*-TKD mutations, therefore, the percentages of each *FLT3* mutation type may not add up to 100%.
Abbreviations: AML, acute myeloid leukemia; *FLT3*, FMS-like tyrosine kinase-3; ITD, internal tandem duplication; MUT, mutated; ND, newly diagnosed; NGS, next generation sequencing; R/R, relapsed or refractory; TKD, tyrosine kinase domain.

Treatment Patterns and Responses

Newly Diagnosed and Relapsed/Refractory AML

The most common regimen (70.6%; 602/853) for first-line induction therapy in patients with ND AML was cytarabine plus daunorubicin. Following first-line induction therapy, 87.1% (743/853) of patients received consolidation therapy, most commonly high-dose cytarabine (63.1%; 469/743) (Table 3a). On average, patients received one treatment cycle per induction regimen and one to three treatment cycles per consolidation regimen. For patients with R/R AML, induction therapy with cytarabine plus daunorubicin was the most common regimen (73.7%; 213/289), while high-dose cytarabine comprised the most common consolidation therapy (58.3%; 134/230) (Table 3b).

Following first-line induction, 88.0% (751/853) of patients with ND AML achieved CR or CRi; 91.8% (682/743) maintained CR/CRi following consolidation therapy. Among patients with ND AML who received HSCT (7.4%, 63/

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Table 3 (a) First-Line Treatments Recorded for Patients with ND AML and (b) Treatments Recorded Prior to First Diagnosis of R/R AML in Patients with R/R AML

(a)

Therapy	All Patients with ND AML (N = 853)		*FLT3*[WT] at Initial Diagnosis (N = 432)		*FLT3*[MUT] at Initial Diagnosis (N = 109)		Unknown *FLT3* Mutation Status (N = 312)	
	Patients,[a] n (%)	Mean (SD) Ara-C Dose (mg/m^2), Cycles	Patients, n (%)	Mean (SD) Ara-C Dose (mg/m^2), Cycles	Patients, n (%)	Mean (SD) Ara-C Dose (mg/m^2), Cycles	Patients, n (%)	Mean (SD) Ara-C Dose (mg/m^2), Cycles
Induction	**853 (100)**		**432 (100)**		**109 (100)**		**312 (100)**	
DA[b]	602 (70.6)	166.1 (289.5), 1.0 (0.1)	341 (78.9)	154.3 (232.3), 1.0 (0.0)	91 (83.5)	147.8 (222.4), 1.0 (0.1)	170 (54.5)	199.3 (401.5), 1.0 (0.0)
IA[c]	133 (15.6)	118.8 (16.5), 1.1 (0.3)	92 (21.3)	117.9 (15.7), 1.1 (0.3)	26 (23.9)	119.9 (18.6), 1.1 (0.4)	15 (4.8)	122.8 (18.1), 1.0 (0.0)
HAD	126 (14.8)	233.1 (362.9), 1.0 (0.2)	4 (0.9)	120.7 (8.6), 1.0 (0.0)	2 (1.8)	119.3 (3.1), 1.0 (0.0)	120 (38.5)	238.7 (370.9), 1.0 (0.2)
MA	61 (7.2)	107.4 (22.8), 1.0 (0.0)	30 (6.9)	106.6 (25.6), 1.0 (0.0)	5 (4.6)	126.2 (10.3), 1.0 (0.0)	26 (8.3)	104.7 (19.7), 1.0 (0.0)
Other[d]	140 (16.4)	–	83 (19.2)	–	25 (22.9)	–	40 (12.8)	–
Consolidation	**743 (87.1)**		**371 (85.9)**		**97 (89.0)**		**275 (88.1)**	
HiDAC	469 (63.1)	6004.0 (323.3), 2.6 (0.6)	245 (66.0)	6021.1 (322.7), 2.6 (0.7)	62 (63.9)	6042.8 (235.0), 2.6 (0.7)	162 (58.9)	5964.4 (348.5), 2.7 (0.6)
MA	236 (31.8)	495.4 (979.4), 1.9 (0.8)	78 (21.0)	140.5 (303.3), 1.4 (0.6)	14 (14.4)	229.9 (445.7), 1.4 (0.5)	144 (52.4)	659.5 (1134.4), 2.1 (0.9)
DA	216 (29.1)	582.8 (1083.4), 1.6 (0.5)	92 (24.8)	138.1 (250.6), 1.8 (0.5)	20 (20.6)	119.0 (15.1), 1.7 (0.5)	104 (37.8)	1131.6 (1416.8), 1.5 (0.5)
MiDAC	124 (16.7)	2346.1 (799.6), 1.9 (0.5)	71 (19.1)	2314.8 (811.5), 2.0 (0.6)	13 (13.4)	2395.0 (805.6), 1.8 (0.4)	40 (14.5)	2386.9 (785.5), 1.9 (0.4)
HA	108 (14.5)	112.9 (36.2), 1.7 (0.6)	52 (14.0)	113.1 (48.8), 1.7 (0.5)	7 (7.2)	119.3 (10.6), 1.7 (0.5)	49 (17.8)	111.8 (19.8), 1.8 (0.6)
Ara-C+HDAC	67 (9.0)	5851.6 (526.5), 2.0 (0.7)	41 (11.1)	5921.0 (404.8), 1.8 (0.7)	8 (8.2)	6044.8 (149.9), 1.9 (0.8)	18 (6.5)	5651.0 (729.2), 2.2 (0.7)
Decitabine	62 (8.3)	-, 2.5 (1.5)	33 (8.9)	-, 2.5 (1.6)	5 (5.2)	-, 3.4 (1.7)	24 (8.7)	-, 2.1 (1.0)
IA	62 (8.1)	183.8 (325.9), 1.1 (0.2)	47 (12.7)	167.1 (266.5), 1.0 (0.2)	8 (8.2)	116.5 (18.5), 1.0 (0.0)	7 (2.5)	351.3 (663.1), 1.2 (0.5)
AA	60 (8.1)	105.8 (45.3), 1.5 (0.5)	34 (9.2)	113.1 (52.5), 1.5 (0.5)	6 (6.2)	115.8 (23.1), 1.7 (0.5)	20 (7.3)	90.1 (32.7), 1.5 (0.5)
Other[d]	234 (31.5)	-	117 (31.5)	-	20 (20.6)	-	75 (27.3)	-
HSCT								
Allogeneic	62 (7.3)	-	32 (7.4)	-	12 (11.0)	-	18 (5.8)	-
Autologous	1 (0.1)	-	1 (0.2)	-	0	-	0	-

(b)								
Therapy	**All Patients with R/R AML (N = 289)**		***FLT3*****^{WT} at R/R Diagnosis (N = 58)**		***FLT3*****^{MUT} at R/R Diagnosis (N = 14)**		**Unknown *FLT3* Mutation Status (N = 217)**	
	Patients,[a] n (%)	**Mean (SD) Ara-C Dose (mg/m^2), Cycles**	**Patients, n (%)**	**Mean (SD) Ara-C Dose (mg/m^2), Cycles**	**Patients, n (%)**	**Mean (SD) Ara-C Dose (mg/m^2), Cycles**	**Patients, n (%)**	**Mean (SD) Ara-C Dose (mg/m^2), Cycles**
Induction	**289 (100)**		**58 (100)**		**14 (100)**		**217 (100)**	
DA[b]	213 (73.7)	182 (355.3), 1.0 (0.0)	48 (82.8)	201.8 (332.5), 1.0 (0.0)	10 (71.4)	121.1 (8.1), 1.0 (0.0)	155 (71.4)	180.6 (373.8), 1.0 (0.0)
IA[c]	50 (17.3)	116.6 (15.3), 1.2 (0.4)	7 (12.1)	112.0 (6.0), 1.2 (0.5)	2 (14.3)	121.7 (8.0), 1.0 (0.0)	41 (18.9)	117.2 (16.6), 1.2 (0.4)
HAD	43 (14.9)	199.3 (308.8), 1.0 (0.2)	3 (5.2)	104.4 (8.2), 1.0 (0.0)	2 (14.3)	111.0 (9.7), 1.0 (0.0)	38 (17.5)	208.7 (323.2), 1.1 (0.2)
MA	30 (10.4)	109.8 (20.1), 1.0 (0.0)	6 (10.3)	110.9 (17.9), 1.0 (0.0)	1 (7.1)	104.1 (-), 1.0 (-)	23 (10.6)	109.7 (21.5), 1.0 (0.0)
D-AA	16 (5.5)	48.5 (16.7), 1.1 (0.3)	0	-	0	-	16 (7.4)	48.5 (16.7), 1.1 (0.3)
Other[d]	33 (11.4)	-	4 (6.9)	-	1 (7.1)	-	26 (12.0)	-
Consolidation	**230 (79.6)**		**55 (94.8)**		**12 (85.7)**		**163 (75.1)**	
HiDAC	134 (58.3)	5979.1 (325.1), 2.7 (0.6)	35 (63.6)	5980.4 (315.4), 2.7 (0.6)	8 (66.7)	5985.1 (301.4), 2.8 (0.4)	91 (55.8)	5977.9 (332.5), 2.6 (0.7)
MA	80 (34.8)	528.0 (1015.6), 1.8 (0.8)	14 (25.5)	273.6 (662.1), 1.7 (0.9)	4 (33.3)	112.6 (9.2), 1.4 (0.5)	62 (38.0)	592.0 (1079.9), 1.8 (0.7)
DA[b]	68 (29.6)	655.5 (1146.5), 1.6 (0.6)	15 (27.3)	250.3 (589.8), 1.6 (0.5)	0	-	53 (32.5)	768.1 (1238.0), 1.6 (0.6)
MiDAC	43 (18.7)	2175.4 (724.6), 1.9 (0.5)	10 (18.2)	1961.5 (172.2), 2.1 (0.4)	1 (8.3)	4165.8 (-), 2.0 (-)	32 (19.6)	2185.4 (759.5), 1.8 (0.5)
HA	34 (14.8)	121.8 (37.7), 1.7 (0.6)	9 (16.4)	148.5 (50.7), 1.9 (0.3)	1 (8.3)	117.8 (-), 2.0 (-)	24 (14.7)	111.0 (26.0), 1.6 (0.6)
Decitabine	20 (8.7)	-, 1.9 (1.1)	3 (5.5)	-, 1.0 (0.0)	1 (8.3)	-, 3.0 (-)	16 (9.8)	-, 1.8 (1.1)
Ara-C+HDAC	18 (7.8)	5915.5 (397.5), 1.8 (0.6)	2 (3.6)	5613.8 (284.9), 1.0 (0.0)	1 (8.3)	6095.8 (-), 1.0 (-)	15 (9.2)	5932.4 (406.3), 1.9 (0.6)
AA	17 (7.4)	106.3 (52.8), 1.6 (0.5)	3 (5.5)	175.4 (49.4), 1.8 (0.4)	0	-	14 (8.6)	88.1 (36.7), 1.5 (0.5)
IA[c]	14 (6.1)	135.5 (61.1), 1.0 (0.0)	4 (7.3)	187.5 (50.1), 1.0 (0.0)	0	-	10 (6.1)	114.7 (53.7), 1.0 (0.0)
Other[d]	60 (26.1)	-	11 (20.0)	-	1 (8.3)	-	34 (20.9)	-
HSCT	-							
Allogeneic	12 (4.2)	-	1 (1.7)	-	2 (14.3)	-	9 (4.1)	-
Autologous	0	-	0	-	0	-	0	-

Notes: [a]Treatment information was summarized for each regimen and categorized by therapy type. This column summarizes the number of patients who ever received a specific treatment regimen. A patient receiving multiple treatment regimens under one treatment type would be counted for each received treatment regimen; therefore, the percentages under each treatment type may not add up to 100%; [b]DA regimen included DA 7+3, DA 5+2, and other DA. DA 7+3 refers to cytarabine daily for 7 days and daunorubicin daily for 3 days. DA 5+2 refers to cytarabine daily for 5 days and daunorubicin daily for 2 days; [c]IA regimen included IA 7+3, IA 5+2, and other IA. IA 7+3 refers to cytarabine daily for 7 days and idarubicin daily for 3 days. IA 5+2 refers to cytarabine daily for 5 days and idarubicin daily for 2 days; [d]Other refers to a combined group of individual regimens used by <5% of patients.

Abbreviations: AA, cytarabine and aclarubicin; AML, acute myeloid leukemia; Ara-C, cytarabine; Ara-C+HDAC, cytarabine and histone deacetylase; DA, daunorubicin and cytarabine; D-AA, decitabine, cytarabine, and aclarubicin; *FLT3*, FMS-like tyrosine kinase-3; HA, homoharringtonine and cytarabine; HAD, homoharringtonine, cytarabine, and daunorubicin; HSCT, hematopoietic stem-cell transplantation; HiDAC, high-dose cytarabine; IA, idarubicin and cytarabine; MA, cytarabine and mitoxantrone; MiDAC, mid-dose cytarabine; MUT, mutated; ND, newly diagnosed; SD, standard deviation; WT, wild type.

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853), 85.7% (54/63) achieved CR/CRi (Table 4a). Among all patients with ND AML who received first-line treatment, 27.4% (234/853) relapsed following CR/CRi.

Overall, patients with R/R AML received a median of two lines of therapy, with 82.0% (237/289) patients receiving second-line therapy (Table S1). The most common second-line regimens in the R/R AML setting were cytarabine plus mitoxantrone (24.5%; 58/237), decitabine, cytarabine plus aclarubicin (22.8%; 54/237), cytarabine plus

Table 4 First-Line Treatment Response Among (a) Patients with Newly Diagnosed AML and (b) All Patients with R/R AML, and Those with R/R AML and *FLT3*^{WT}, *FLT3*^{MUT}, and Unknown *FLT3* Mutation Status

(a)					
Therapy	**All newly Diagnosed Patients (N = 853)**				
	Patients Who Received Treatment(s), n (%)	**Treatment Response, n (%)**		**Relapsed, n (%)**	**Refractory, n (%)**
		CR/CRi Not Yet Achieved/ Observed	**Ever Achieved CR/CRi**		
Induction therapy	853 (100)	102 (12.0)	751 (88.0)	234 (27.4)	55 (6.4)
Consolidation therapy	743 (87.1)	61 (8.2)	682 (91.8)		
HSCT	63 (7.4)	9 (14.3)	54 (85.7)		
(b)					
Therapy	**All R/R diagnosed patients (N = 289)**				
	Patients who received treatment (s), n (%)	**Treatment response, n (%)**		**Time from treatment initiation to first relapse after initial treatment (days), mean (SD) [median (IQR)]**	**Time from first documented CR/CRi to first relapse after initial treatment (days), mean (SD) [median (IQR)]**
		CR/CRi not yet achieved/ observed	**Ever achieved CR/CRi**		
Induction therapy	289 (100)	59 (20.4)	230 (79.6)	358.0 (241.5) [306.5 (254.2)]	314.3 (242.6) [252.0 (268.0)]
Consolidation therapy	230 (79.6)	29 (12.6)	201 (87.4)		
HSCT	12 (4.2)	4 (33.3)	8 (66.7)		
Therapy	***FLT3*^{WT} (N = 58)**				
	Patients who received treatment (s), n (%)	**Treatment response, n (%)**		**Time from treatment initiation to first relapse after initial treatment (days), mean (SD), [median (IQR)]**	**Time from the first documented CR/CRi to the first relapse after the initial treatment (days), mean (SD) [median (IQR)]**
		CR/CRi not yet achieved/ observed	**Ever achieved CR/CRi**		
Induction therapy	58 (100)	3 (5.2)	55 (94.8)	366.9 (220.3) [331.5 (235.8)]	321.8 (220.1) [291.0 (212.8)]
Consolidation therapy	55 (94.8)	4 (7.3)	51 (92.7)		
HSCT	1 (1.7)	0 (0)	1 (100)		

(*Continued*)

Table 4 (Continued).

Therapy	*FLT3*^MUT at R/R (N = 14)				
	Patients who received treatment (s), n (%)	Treatment response, n (%)		Time from treatment initiation to first relapse after initial treatment (days), mean (SD), [median (IQR)]	Time from first documented CR/CRi to first relapse after initial treatment (days), mean (SD), [median (IQR)]
		CR/CRi not yet achieved/ observed	Ever achieved CR/CRi		
Induction therapy	14 (100)	2 (14.3)	12 (85.7)	320.0 (172.5) [294.0 (123.8)]	271.0 (174.3) [242.0 (126.0)]
Consolidation therapy	12 (85.7)	1 (8.3)	11 (91.7)		
HSCT	2 (14.3)	2 (100)	0 (0)		
Therapy	**Unknown *FLT3* mutation status at R/R (N = 217)**				
	Patients who received treatment (s), n (%)	Treatment response, n (%)		Time from treatment initiation to first relapse after initial treatment (days), mean (SD), [median (IQR)]	Time from first documented CR/CRi to first relapse after initial treatment (days), mean (SD), [median (IQR)]
		CR/CRi not yet achieved/ observed	Ever achieved CR/CRi		
Induction therapy	217 (100)	54 (24.9)	163 (75.1)	357.8 (252.7) [293.0 (283.0)]	314.9 (254.3) [235.0 (292.0)]
Consolidation therapy	163 (75.1)	24 (14.7)	139 (85.3)		
HSCT	9 (4.1)	2 (22.2)	7 (77.9)		

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; HSCT, hematopoietic stem-cell transplantation; *FLT3*, FMS-like tyrosine kinase-3; HSCT, hematopoietic stem-cell transplantation; MUT, mutated; R/R, relapsed/refractory; SD, standard deviation; WT, wild type.

aclarubicin (16.9%; 40/237), daunorubicin plus cytarabine (13.5%; 32/237), homoharringtonine plus cytarabine (12.2%; 29/237), decitabine (11.4%; 27/237) and fludarabine, cytarabine plus granulocyte-colony stimulating factor (11.0%; 26/237). Third- and fourth-line therapy were received by, respectively, 41 (14.2%) and 15 (5.2%) patients in the R/R AML setting.

For patients who relapsed during the study period after achieving CR/CRi with first-line therapy, median (IQR) times from treatment initiation and first documented CR/CRi to the first relapse were 306.5 (254.2) and 252.0 (268.0) days, respectively (Table 4b). Approximately half (48.9%; 116/237) of patients with R/R AML achieved CR/CRi following second-line therapy, and 26.8% (11/41) and 26.7% (4/15) achieved CR/CRi following third- and fourth-line therapy.

Treatment Regimens and Patterns by FLT3 Mutation Status

Initial treatment regimens recorded for patients with ND AML did not appear to be influenced by *FLT3* mutation status: 78.9% (341/432) and 83.5% (91/109) of patients with *FLT3*^WT and *FLT3*^MUT received cytarabine plus daunorubicin induction therapy, respectively (Table 3a). However, differences in treatment patterns for patients with ND AML were noted between those with known and unknown *FLT3* mutation status: specifically, a higher proportion of patients with confirmed *FLT3*^MUT received cytarabine plus daunorubicin induction therapy than those with an unknown *FLT3* mutation status (83.5% [91/109] vs 54.5% [170/312]; Table 3a). For patients with ND AML, there were no notable differences in treatment responses between patients with *FLT3*^{MUT} or *FLT3*^{WT} AML, or for patients with unknown *FLT3* mutation status at initial diagnosis.

Following R/R AML diagnosis, there were apparent differences in the choice of second-line treatment regimens according to *FLT3* mutation status; however, the number of patients with *FLT3*^{MUT} AML included was low (n = 14), and it is therefore unclear whether these differences are meaningful. Among patients with R/R AML who relapsed after achieving CR/CRi with first-line therapy, those with *FLT3*^{MUT} AML had a shorter median (IQR) time from treatment initiation to first relapse than patients with *FLT3*^{WT} AML (294.0 [123.8] vs 331.5 [235.8] days) and shorter median (IQR) time from CR/CRi to first relapse (242.0 [126.0] vs 291.0 [212.8] days) (Table 4b).

Discussion

This study presents a real-world investigation of the current epidemiology and treatment patterns among adult patients with AML stratified by *FLT3* mutation status in China. In our analysis of patient records from the NICHE-AML registry of the IHBDH in China, approximately one-third of patients progressed from ND to R/R AML during the study period, and the prevalence of *FLT3*^{MUT} was approximately 20% among both patients with ND AML and those with R/R AML. The presence of *FLT3*^{MUT} did not appear to influence the choice of initial treatment selected for patients in this registry, with DA and HiDAC being the mainstay induction and consolidation regimens, respectively, consistent with clinical practice guidelines in China for AML.[6] For patients with R/R AML, there was an apparent difference in the second-line treatment regimens for patients with *FLT3*^{WT} and *FLT3*^{MUT}, although the most common regimens in both cases were still cytarabine-based, which are standard in this setting.[24,25]

In the NICHE-AML registry, testing for *FLT3* mutation status increased from 2016 to 2019. These findings reflect the recommendations included in AML clinical practice guidelines in China, which have suggested routine testing for *FLT3* mutation at the time of disease diagnosis since 2017.[26] The increased occurrence of *FLT3* mutation testing could also reflect the availability of FLT3-inhibitor agents. Approximately half (48.6%) of the patients with *FLT3*^{MUT} at ND AML diagnosis harbored a *FLT3*-ITD mutation, while this percentage increased to 64.3% for patients who progressed to R/R AML; the corresponding proportions for those with *FLT3*-TKD were 29.4% in ND AML and 42.9% in R/R AML. However, it should be noted that the type of *FLT3* mutation was unspecified for almost one-quarter (23.9%) of patients at ND diagnosis. The proportions of ND AML patients with either *FLT3*-ITD or *FLT3*-TKD in the NICHE-AML registry were both higher than anticipated from the published literature.[13,14] In addition, there appears to be mounting evidence in favor of repeated mutational testing at diagnosis and at each relapse, since the emergence and type of mutation can greatly influence outcomes and, therefore, the choice of treatment.[27] Our results further support the need for repeated testing, as we observed that at first diagnosis of R/R AML, 5.6% and 9.3% of patients lost and gained *FLT3*^{MUT}, respectively, with a further 5.6% of patients switching between *FLT3* mutations.

We observed differences in the clinical outcomes of patients with AML depending on *FLT3* mutation status. In particular, *FLT3*^{MUT} carriers had a shorter time to relapse than those with *FLT3*^{WT}, from both initial diagnosis and CR/CRi; this is consistent with previous studies that have reported worse clinical outcomes for patients with a *FLT3* mutation, particularly *FLT3*-ITD.[11]

A key strength of this study is the information system at IHBDH, one of the largest hematology centers in China that provides the highest level of care to patients with AML, which has been established for more than 20 years and includes comprehensive data; from this, the NICHE-AML dataset provided an adequate sample size of 853 patients with median follow-up of 425 days. While the registry comprises patients from IHBDH, a single hospital in Northern China, patients are referred there from other regions, thus the cohort covers a large geographical area.

Nevertheless, our study has a number of limitations, some of which are inherent to retrospective studies, which should be considered when interpreting the data. Guidelines for the diagnosis of AML in China in 2017 have included testing for *FLT3*-ITD mutations;[26] however, *FLT3* testing may have had limited availability for patients who initiated on treatment between 2015 and 2017. The mean age of patients at initial diagnosis (42.5 years) was younger than the median age of diagnosis in US populations,[28] and all patients received intensive treatment; as older patients may have different disease trajectories and/or could only receive supportive care, the generalizability of these findings to AML patients may be limited outside of China. The study variables available for analysis were restricted to those recorded in the registry, and some relevant data, such as reasons for treatment discontinuation or switching, were not included and could not be retrieved retrospectively. The data are limited to patients with R/R AML owing to the small sample size; as such, these results should be interpreted with caution. Due to the observational nature of the study, no formal hypothesis testing was performed and all analyses were descriptive. The NICHE-AML registry comprises only passive follow-up data relating to hospital visits to IHBDH and lacks systematic follow-up data for survival, disease progression and longitudinal treatment patterns, and treatments received at other hospitals. It should be noted that a thorough review was also performed to exclude patients with long gaps between visits or a short follow-up period; however, this approach might introduce bias, as patients' adherence may be associated with certain characteristics such as socioeconomic status and age. Genetic/molecular marker testing has formed part of the standard of care at IHBDH since 2017; therefore, the proportion of patients who underwent *FLT3* mutation testing in the present study may be higher than that in general practice in China, as testing occurs routinely only in larger hematological centers. Despite this, the proportion of patients with known *FLT3* mutation status at first diagnosis of R/R AML was still relatively low, at approximately one quarter, and observations relating to this population should thus be considered provisional. While we observed that *FLT3* testing increased during the study period, by 2019 only approximately half of patients were being tested at diagnosis with R/R AML, versus essentially all patients being tested at ND AML.

Conclusion

In conclusion, we found that one-fifth of patients tested harbored an *FLT3* mutation and that *FLT3*$^{\mathrm{MUT}}$ was associated with poorer clinical outcomes. However, we also observed that many patients with AML were not tested for *FLT3* mutations, particularly at first diagnosis of R/R AML. Furthermore, treatment regimens were not significantly influenced by *FLT3* status; this may be attributed to the fact that the first FLT3 inhibitor, gilteritinib, only received regulatory approval in China in 2021.[18] Taken together, our results highlight a need for more routine testing of *FLT3* mutation status at R/R AML, and utilization of more targeted treatment options for those patients possessing *FLT3* mutations (eg, FLT3 inhibitor agents) in China.

Abbreviations

Allo-HSCT, allogeneic hematopoietic; AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; FDA, US Food and Drug Administration; *FLT3*, FMS-like tyrosine kinase 3; *FLT3*-ITD, FMS-like tyrosine kinase 3 internal tandem duplication; *FLT3*$^{\mathrm{MUT}}$, FMS-like tyrosine kinase 3 mutated; *FLT3*-TKD, FMS-like tyrosine kinase 3 tyrosine kinase domain; *FLT3*^{WT}, FMS-like tyrosine kinase 3 wild-type; IHBDH, Institute of Hematology and Blood Diseases Hospital; IQR, interquartile range; ND, newly diagnosed; NICHE, National Longitudinal Cohort of Hematologic Diseases; R/R, relapsed/refractory; SD, standard deviation.

Data Sharing Statement

Researchers may request access to anonymized participant-level data, trial-level data and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

Compliance with Ethics Guidelines

The study was conducted in accordance with the Declaration of Helsinki and International Conference of Harmonisation guidelines. The study was approved by the institutional review board committee of the IHBDH. The review board committee confirmed that informed consent was not needed from participants, and all data were anonymized prior to the current study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Li-Jen Cheng and Prabhuram Krishnan are employees of Astellas Pharma Singapore Pte. Ltd. Christopher H. Young is an employee of Astellas Pharma US Inc. Jia Zhong and Eric Q. Wu are employees of Analysis Group, Inc., an HEOR CRO company contracted by Astellas to undertake analysis. Jianxiang Wang participated in an advisory board for AbbVie. The authors report no other conflicts of interest in this work.

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