Original Article | Clinical Studies

FLT3 inhibitor maintenance after allogeneic stem cell transplantation in *FLT3*-mutated acute myeloid leukemia (AML) patients

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Background: The somatic mutation of fms-like tyrosine kinase 3 (*FLT3*) in acute myeloid leukemia (AML) is associated with increased risk of relapse and lower survival rates. FLT3i as maintenance after allogeneic hematopoietic stem cell transplant (allo-HSCT) are under study to prevent disease relapse, but real-world data are lacking.

Methods: We performed a single center, retrospective cohort study and analyzed patients who had *FLT3*-mutated AML and underwent allogeneic-HSCT between January 2011 to June 2022 at the University of Chicago. We identified 23 patients who received FLT3i maintenance therapy post-allo-HSCT and compared their outcomes against 57 patients who did not. Primary outcome was disease-free survival (DFS). Secondary outcomes include overall survival (OS) and relapse rate.

Results: FLT3i maintenance therapy was started at a median 59 days (range, 29–216 days) after allo-HSCT with median duration of 287 days (range, 15–1,194 days). Maintenance therapy was well tolerated. Overall, the improvement in DFS rates for patients after they were placed on FLT3i maintenance therapy was not significant [hazard ratio (HR) for relapse or death =0.65, 95% confidence interval (CI): 0.32–1.31, P=0.23]. However, when adjusted for the conditioning regimen and donor status, the differences were statistically significant with improvement in DFS and OS for patients on FLT3i maintenance (HR for OS =0.42, 95% CI: 0.18–0.95, P=0.04).

Conclusions: When adjusting for conditioning regimen and donor status, there was a significant improvement in DFS and OS for patients who received FLT3i maintenance therapy compared to those who did not. Randomized prospective studies may provide more insight.

Keywords: Fms-like tyrosine kinase 3 (*FLT3*); FLT3 inhibitor (FLT3i); maintenance; acute myeloid leukemia (AML); relapse

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Introduction

Mutations of the fms-like tyrosine kinase 3 (*FLT3*) gene are one of the most common recurring molecular genetic abnormalities in acute myeloid leukemia (AML), occurring in approximately 25–30% of patients with newly diagnosed AML (1). They most often occur as in-frame internal tandem duplications (ITD) but point mutations in the tyrosine kinase domain (TKD) and at the activation loop residue D835 also occur (2). Although *FLT3-ITD* mutated patients have comparable rates of initial complete remission (CR) compared to those without these mutations, they have an increased risk of relapse and lower survival rates (3). For instance, the German AML Cooperative Group found that *FLT3-ITD* mutated patients have an event-free survival (EFS) of 7.4 versus 12.9 months (P=0.007) compared to wild-type AML (4). Thus, the development of FLT3 inhibitor (FLT3i) has emerged to improve overall treatment outcomes.

One such FLT3i is midostaurin, a first-generation, type-I multi-kinase inhibitor. Midostaurin was initially developed as a protein kinase C inhibitor but was also found to have inhibitory activity against FLT3 (5). In phase I/II studies, midostaurin demonstrated blast reduction in relapsed/refractory AML, though no patients attained CR which suggested that midostaurin was not sufficient as monotherapy (5). However, the phase III RATIFY trial in 2017 demonstrated that the addition of midostaurin to intensive induction therapy significantly improved median overall survival (OS) (74.7 versus 25.6 months, P=0.009) when compared to placebo in newly diagnosed *FLT3*-mutated AML patients (6). This led to Food and Drug Administration (FDA) approval of midostaurin as part of induction therapy and is now the current standard of care in addition to intensive chemotherapy during induction followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT) (6). More recently, a second-generation tyrosine kinase inhibitor with higher specificity against *FLT3-ITD* and TKD mutations, gilteritinib, was granted FDA approval after it showed increased survival and higher rates of remission in patients with relapsed or refractory *FLT3*-mutated AML compared to salvage chemotherapy in the ADMIRAL trial (7).

Despite the improvement in outcomes with combination chemotherapy, the relapse rate (RR) among patients with *FLT3*-mutated AML remains high (3). This raises the question of the utility of FLT3i in maintenance therapy after allo-HSCT. Some studies suggest that maintenance therapy with FLT3i can improve post-HSCT outcomes by eliminating minimal residual disease (MRD) during consolidation therapy (6,8,9). The SORMAIN trial demonstrated that maintenance therapy after allo-HSCT with FLT3i sorafenib, another first-generation type-I multi-kinase inhibitor, reduced the risk of relapse and death (10). A recent multi-center randomized phase III trial in China also investigated the use of sorafenib as maintenance post-HSCT and found it reduced the incidence of relapse (11).

Though these trials have yielded promising results, more real-world data are needed in this area. We therefore investigated our experiences in a single institution retrospective study of FLT3i maintenance therapy after allo-HSCT. We present this article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1941/rc).

Highlight box

Key findings

- Our retrospective study showed benefits of using fms-like tyrosine kinase 3 inhibitor (FLT3i) maintenance after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients who had *FLT3*-mutated acute myeloid leukemia (AML).

What is known and what is new?

- Patients with *FLT3*-mutated AML have higher risk of relapse and lower survival rates.
- This manuscript adds real-world data on patients who had *FLT3*-mutated AML and underwent allo-HSCT between January 2011 and June 2022 at a single tertiary referral hospital.
- When adjusting for conditioning regimen and donor status, there was a significant improvement in overall survival and disease-free survival for patients who received FLT3i maintenance compared to those who did not receive FLT3i maintenance.

What is the implication, and what should change now?

- Prospective randomized trials are needed to further determine the benefits and optimal duration of FLT3i maintenance.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective data analysis was under the approved consents by IRB at The University of Chicago Biological Sciences Division/University of Chicago Medical Center. These patients who underwent stem cell transplantation were all consented for research data analysis.

We performed a single center, retrospective cohort study and analyzed patients who had *FLT3*-mutated AML and

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Table 1 Baseline characteristics

Characteristics	No maintenance	Maintenance
Total patients	57 [71]	23 [29]
Age (years)	52 [21–72]	47 [28–71]
Gender		
Female	30 [53]	9 [39]
Male	27 [47]	14 [61]
Karnofsky Performance status		
≥90	48 [84]	19 [83]
<90	9 [16]	4 [17]
HCT–CI score		
0–2	35 [61]	13 [57]
3 or more	22 [39]	10 [43]
Disease status		
Remission (CR1/CR2/> CR2)	49 [86]	20 [87]
Relapsed or refractory	8 [14]	3 [13]
Donor type		
MRD	23 [40]	8 [35]
MUD	16 [28]	1 [4]
Haplo-cord	18 [32]	14 [61]
Conditioning regimen		
Myeloablative	17 [30]	14 [61]
RIC	40 [70]	9 [39]

Data are presented as median [range] or n [%]. CR1, first complete remission; CR2, second complete remission. HCT-CI, hematopoietic stem cell transplantation co-morbidity index; CR, complete remission; MRD, matched related donor; MUD, matched unrelated donor; Haplo-cord, combination of CD34 selected haplo-identical stem cell infusion followed by umbilical cord stem cell infusion (12); RIC, reduced intensity conditioning.

underwent allo-HSCT between January 2011 and June 2022 at the University of Chicago. Transplant data were stored in RedCap storage system and manually reviewed. Chart review through Epic electronic medical record was systematically analyzed for each unique patient. This resulted in 80 evaluable patients who were *FLT3*-mutated and underwent allo-HSCT; 23 received FLT3i maintenance therapy, and 57 did not. We included all the patients in the defined time period. We relied solely on manual review of clinician documentation through Epic to determine start dates and duration of FLT3i maintenance, in addition to patient outcomes and adverse events. A systematic search including the terms "FLT3, midostaurin, sorafenib, gilteritinib, maintenance" were included using the Epic search function to help thoroughly review each patient's chart. We searched for each of the terms separately to maximize our yield, and to ensure these patients were all on FLT3i maintenance and not just on FLT3i for induction therapy. Pathology data from bone marrow biopsies and next-generation sequencing (NGS) were also reviewed.

Drug dosing

Patients received one of three different FLT3i as maintenance based on availability, insurance, off-label use of an FDA approved drug, and treating physician's preference. Sorafenib was used before midostaurin and gilteritinib were approved. Per chart review, dosing of FLT3i for maintenance therapy was: midostaurin (50 mg, twice a day), sorafenib (200–400 mg, twice a day), and gilteritinib (40–120 mg, daily).

Study outcomes and statistical methods

The primary outcome was disease-free survival (DFS). Secondary outcomes were OS, RR, and impact on graft-versus-host disease (GVHD). Univariate and multivariate Cox (7) regression models were fit to examine the association between administration of FLT3i maintenance and the occurrence of events. Time was measured from the day of transplant. Since FLT3i were added at variable times after transplant, its addition was treated as a time-dependent covariate in the Cox regression analysis, i.e., set to 0 initially and changed to 1 if and when the patient received FLT3i. The hazard ratio (HR) reflects the increase in the hazard rate at any time for those on FLT3i at that time versus those not on FLT3i.

Results

Baseline characteristics were similar in both groups (*Table 1*) with the exception of donor type and conditioning regimen. FLT3i maintenance therapy, which included midostaurin (n=7), sorafenib (n=6), and gilteritinib (n=10), was started at a median 59 days (range, 29–216 days) after allo-HSCT with a median treatment duration of 287 days (range, 15–1,194 days). Overall, there was no statistically significant improvement in the DFS rate in patients who received FLT3i maintenance therapy (HR for relapse or death =0.65,

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Table 2 Hazard ratios

Clinical endpoints	Hazard ratio (95% CI)	P value
DFS	0.65 (0.32–1.31)	0.23
OS	0.56 (0.26–1.15)	0.12
RR	0.62 (0.26–1.41)	0.25
OS*	0.42 (0.18–0.95)	0.04

*, when adjusted for conditioning regimen and donor status. Hazard ratios listed comparing patients on FLT3i maintenance versus no FLT3i maintenance. CI, confidence interval; DFS, disease-free survival; OS, overall survival; RR, relapse rate; FLT3, fms-like tyrosine kinase 3; FLT3i, FLT3 inhibitor.

Table 3 GVHD

GVHD	Incidence	Cumulative (%)
aGVHD		
Grade I	11	13.75
Grade II	21	26.25
Grade III	5	6.25
Grade IV	1	1.25
All grade aGVHD	38	47.50
Grade II–IV	27	33.75
cGVHD		
Mild	9	11.25
Moderate	3	3.75
Severe	3	3.75
All grade	15	18.75
Moderate to severe	6	7.50

GVHD, graft-versus-host disease; aGVHD, acute GVHD; cGVHD, chronic GVHD.

95% CI: 0.32–1.31, P=0.23) compared to those who did not (*Table 2*). There was also no significant improvement in OS for those on FLT3i maintenance (HR =0.56, 95% CI: 0.26–1.15, P=0.12). However, when adjusted for the conditioning regimen and donor type, the differences were statistically significant with improvement in OS for patients on FLT3i maintenance (HR =0.42, 95% CI: 0.18–0.95, P=0.04) compared to those who did not receive FLT3i maintenance therapy. The difference in DFS was also significant after adjustment (HR =0.46, 95% CI: 0.21–0.99, P=0.04). Further subgroup analyses were therefore undertaken to more clearly identify which individuals benefited from FLT3i maintenance. Although the numbers are small, the OS benefit was most pronounced in the MAC group [HR =0.31, 95% CI: 0.11–0.89, P=0.03 (n=31)] as opposed to the RIC subgroup [HR =0.78, 95% CI: 0.27–2.24, P=0.64 (n=49)]. Similarly, the effect was greater and statistically significant in patients who had haplo-cord donors [HR =0.32, 95% CI: 0.12–0.81, P=0.01 (n=32)] as opposed to MRD/MUD [HR =0.67, 95% CI: 0.20–2.27, P=0.52 (n=48)].

Decrease in RRs was also not statistically different for those who received versus didn't receive FLT3i maintenance (HR =0.62, 95% CI: 0.26–1.41, P=0.25). Seven of 23 patients (30%) who received FLT3i maintenance relapsed at an average of 323 days post-transplant (standard deviation 249 days) compared to 33 of 57 patients (58%) who did not receive maintenance and relapsed at an average of 255 days post-transplant (standard deviation 310 days). Although the HR was not significant, it is notable that fewer patients relapsed on FLT3i maintenance (30% *vs.* 58%).

GVHD

Patients on FLT3i maintenance had a nonsignificant increased risk of developing acute GVHD (HR =1.37, 95% CI: 0.67–2.79, P=0.38). Similarly, these patients also demonstrated an increased risk of chronic GVHD as well but not statistically significant (HR =2.25, 95% CI: 0.81–6.25, P=0.12). We graded severity of acute GVHD and chronic GVHD per the European Society for Blood and Marrow Transplantation (EBMT) handbook 7th edition (13,14) (*Table 3*). Thirty-eight of 80 patients (48%) developed grade II–IV acute GVHD while 15 of 80 (19%) developed chronic GVHD.

Safety

FLT3i maintenance was generally well tolerated and did not increase the risk of acute GVHD nor chronic GVHD nor non-relapse mortality in a statistically significant manner. Out of 23 patients who received FLT3i maintenance, 48% (n=11) experienced adverse events: 55% (n=6) of these were related to gastrointestinal toxicities and 27% (n=3) from cytopenia. Of the 11 patients who experienced adverse effects, 64% (n=7) led to cessation of therapy (5 from gastrointestinal toxicities, 1 from cytopenia, 1 from transaminitis). Thus, 30% of all 23 patients on FLT3i maintenance (n=7) discontinued maintenance therapy due to adverse events. Therapy was discontinued for these patients at a median of 146 days (range, 20–411 days) from

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starting FLT3i maintenance.

Discussion

In our retrospective study, univariate analyses did not yield statistically significant improvements in DFS and OS. However, when adjusted for the conditioning regimen and donor type, the difference in OS was significant with improvement for patients who received FLT3i maintenance (HR =0.42, 95% CI: 0.18–0.95, P=0.04) compared to those who had not, and similarly for DFS. Of note, 61% of patients on FLT3i maintenance had received a myeloablative conditioning (MAC) regimen compared to 30% not on maintenance, and more patients on FLT3i maintenance (61% versus 32%) received cord-based transplants as well. MAC is most suitable for young, fit patients, and Scott *et al.* found that MAC results in higher OS than reduced intensity conditioning (RIC) though not statistically significant (15). However, MAC does have statistically significant lower RR than RIC. More recently, there has been a long-term follow-up of the BMT CTN 0901 clinical trial in 2021 which demonstrated superior OS for patients who received MAC compared to those who received RIC in a statistically significant manner in patients with AML and myelodysplasia (MDS) (HR =1.54, 95% CI: 1.07–2.2, P=0.03) (16). Patients who received RIC also had a significantly higher risk of relapse as well (HR =4.06, 95% CI: 2.59–6.35, P<0.001) (15). Regarding stem cell source, Dholaria *et al.* found that cord-blood transplants are generally associated with lower leukemia-free survival (LFS) and OS compared to non-cord transplants (17). Thus, myeloablative therapies and donor type may be confounding variables in determining the true impact of FLT3i maintenance therapy on OS and DFS in this study.

We could not differentiate results amongst the three different FLT3i drugs given our small sample size of 23 patients who received FLT3i maintenance. FLT3i maintenance was started between days 29 and 216 after transplant, with a median of 59 days. In this setting, anyone who relapsed or died early did not get a chance to receive FLT3i maintenance therapy. In other words, those on FLT3i maintenance had to survive long enough to receive it, thus creating a lead-time bias. Treating FLT3i maintenance as a time-dependent covariate in the Cox regression modeling avoided this bias. We also acknowledge that the sample size was not large enough to enable more extensive adjusted analyses.

In recent years, there have been other studies evaluating the maintenance role of FLT3i. In the SORMAIN trial, 83 adult patients with *FLT3-ITD* AML in complete hematologic remission after allo-HSCT were randomly assigned to receive sorafenib (n=43) or placebo (n=40). With a median follow-up of 41.8 months, the HR for relapse or death in the sorafenib group versus placebo was 0.39 (95% CI: 0.18–0.85, P=0.13). The 24-month relapse-free survival (RFS) was 53.5% with placebo versus 85.0% with sorafenib. Unfortunately, the utility of sorafenib has been limited by its drug toxicities. Fifty percent of the patients who received sorafenib required dose reduction, and 21% of patients had to stop given adverse effects (8). In 2022, a follow-up analysis of the phase III ADMIRAL trial has shown promise using another FLT3i, gilteritinib, as maintenance therapy after allo-HSCT. Of their 64 patients who were treated with gilteritinib, 40 patients continued maintenance therapy with gilteritinib with a median duration of 9.7 months. A *post hoc* analysis of data from the ADMIRAL trial reports cumulative 24-month RRs were 0% in patients whose response before HSCT was CR (n=4) or CR/CRh (CR with partial hematologic recovery) (n=9) and 19% for patients who had a pretransplant response of CRc (complete composite remission) (n=20). Only 7 of 40 (18%) patients had dose decreases due to adverse events. Thus, gilteritinib was well tolerated and sustained remission (18). Most recently in March 2023, the MORPHO phase III prospective trial evaluating gilteritinib as maintenance therapy in this setting announced the trial did not meet the primary objective of lowering RFS (NCT02997202) (19).

Despite advancements in FLT3i, primary and acquired resistance to these drugs remain an issue (20). The most common resistance-causing mutation occurs at the FLT3 gatekeeper F691 and AL D835 residues. These mutations directly or indirectly impair drug binding and efficacy (21). Specifically for gilteritinib, activating mutations in the Ras/MAPK pathway seem to be a very common resistance mechanism (22). Thus, finding a way to suppress these pathways may help combat resistance and increase efficacy of these medications.

Conclusions

In summary, post-transplant maintenance therapy with FLT3i is feasible and may improve DFS and OS. Prospective randomized trials should now examine this possibility in these patients who currently have a high rate of relapse.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-23-1941/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1941/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective data analysis was under the approved consents by IRB at The University of Chicago Biological Sciences Division/University of Chicago Medical Center. These patients who underwent stem cell transplantation were all consented for research data analysis.

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