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Research Paper

Real-world patterns of maintenance therapy after allogeneic transplant in older adults with acute myeloid leukemia: A Medicare cohort study

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A R T I C L E I N F O

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A B S T R A C T

Introduction: Older adults represent the majority of patients with acute myeloid leukemia (AML), and an increasing proportion receive allogeneic hematopoietic cell transplantation (alloHCT). Mutations in the *FMS*-like tyrosine kinase 3 gene (*FLT3*) confer high relapse risk, and post-transplant maintenance with FLT3 tyrosine kinase inhibitors (FLT3-TKIs) is guideline-recommended. However, real-world utilization, adherence, and tolerability of FLT3-TKIs in older adults remain poorly characterized.
Materials and methods: Using 100% Medicare claims (Parts A/B/D and Medicare Advantage encounter data), we conducted a retrospective cohort study of beneficiaries ≥65 years old with AML who received alloHCT between January 1, 2016 and June 30, 2024, and initiated FLT3-TKI maintenance (gilteritinib, midostaurin, or sorafenib) within 100 days post-transplant. Baseline demographics, comorbidities, prior therapy, and health care resource utilization (HCRU) were captured from 2010 through the index date. Adherence was assessed using proportion of days covered (PDC). Dose modification, FLT3-TKI switching, and post-transplant HCRU were evaluated descriptively. Centers for Medicare & Medicaid Services suppression rules were applied throughout.
Results: Of 7403 eligible older adults with AML undergoing alloHCT, 150 (2.0%) initiated FLT3-TKI maintenance (gilteritinib: 54.7%, midostaurin: 24.0%, sorafenib: 21.3%). Mean age was 70.5 years, and 59.3% had Charlson Comorbidity Index ≥4. Utilization of post-transplant FLT3-TKIs was sustained from 2020 onwards at approximately 20% of eligible patients annually. Overall adherence was modest, with a mean PDC of 47% and very few patients achieving PDC ≥80%. Higher mean PDC was observed in patients ≥70 years of age, those with fewer comorbidities, those previously treated with low-intensity chemotherapy, and those who received gilteritinib as maintenance. Among patients treated with gilteritinib, two-thirds had no evidence of dose change, and no patients switched to an alternative FLT3-TKI. Across all patients, post-alloHCT HCRU was predominantly outpatient visits, with low hospitalization rates across FLT3-TKIs.
Discussion: In this first real-world analysis of post-alloHCT FLT3-TKI maintenance in older adults, utilization was low and adherence was modest, although not impaired by age alone. Gilteritinib demonstrated the highest adherence and appeared to have favorable tolerability. Strategies to improve adherence and prospective data in older adults are needed to maximize the benefits of FLT3-TKI maintenance in this population.

1. Introduction

With a median age at diagnosis of 69 years, acute myeloid leukemia (AML) is primarily a disease of older adults [1]. Historically, outcomes for older adults with AML were dismal. Between 2015 and 2021, the estimated five-year survival rate for patients >60 years old with AML was 20% [1,2]; however, outcomes in this population are improving [2]. Allogeneic hematopoietic cell transplantation (alloHCT), traditionally restricted to only young and fit patients, now represents a potentially curative therapy in this population. Advances in reduced intensity conditioning, alternatives to older sibling donors, and improvements in supportive care have broadened alloHCT eligibility to many older adult candidates [3]. Over the past decade, the use of alloHCT in patients with AML who are >70 years old has significantly increased, with associated

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improvement in survival outcomes [2,3].

A key prognostic factor in AML is the presence of activating mutations in the *FMS*-like tyrosine kinase 3 (*FLT3*) gene, particularly internal tandem duplications (ITDs) [4]. *FLT3*-ITD mutations are the most common genetic aberration in AML, found in approximately 20% of all newly diagnosed cases [5]. Patients with *FLT3*-ITD AML have high relapse rates and a poor prognosis [6,7], and are recommended to undergo alloHCT in first complete remission [8]. Although alloHCT can be a curative therapy for these patients, relapse remains the leading cause of post-alloHCT mortality [9]. Multiple studies have examined the benefits of giving prophylactic maintenance via oral FLT3 tyrosine kinase inhibitors (FLT3-TKIs) for one to two years post-alloHCT to minimize relapse. Relative to placebo, maintenance therapy reduces the risk of post-transplant relapse and mortality [10–13]. As such, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend maintenance therapy with FLT3-TKIs for all patients with *FLT3*-mutated AML in complete remission post-transplant, regardless of age [14].

Despite these recommendations, the real-world use and adherence of oral maintenance therapies is poorly understood [3]. This is particularly true for older adults, who were either excluded or underrepresented in the key prospective trials studying FLT3-TKI maintenance therapy [10–13]. Further, the burden of polypharmacy, drug-drug interactions, and medication-associated toxicity is increased in older adults [15,16], and the real-world tolerability of maintenance FLT3-TKIs (gilteritinib, midostaurin, and sorafenib) in this population is unknown. While all FLT3-TKIs are listed in the NCCN Guidelines® [14], they have distinct toxicity profiles, with gilteritinib most commonly associated with cytopenias, elevated liver enzymes, and neuropathy; midostaurin with cytopenias, abdominal pain, nausea, and diarrhea; and sorafenib with fatigue, diarrhea, and rash [17]. This study aims to describe the real-world use, adherence, and tolerability (assessed indirectly through dose modifications or agent switching) of FLT3-TKIs among Medicare beneficiaries ≥65 years old, and to assess for differences among the three available FLT3-TKIs.

2. Methods

2.1. Ethics

As this study was retrospective and utilized anonymized medical and prescription claims data, ethical approval was not required.

2.2. Data source

This study used data from Medicare beneficiaries covered by Parts A/B/D or Medicare Advantage (Part C) identified using the following 100% Centers for Medicare & Medicaid Services (CMS) Medicare claims

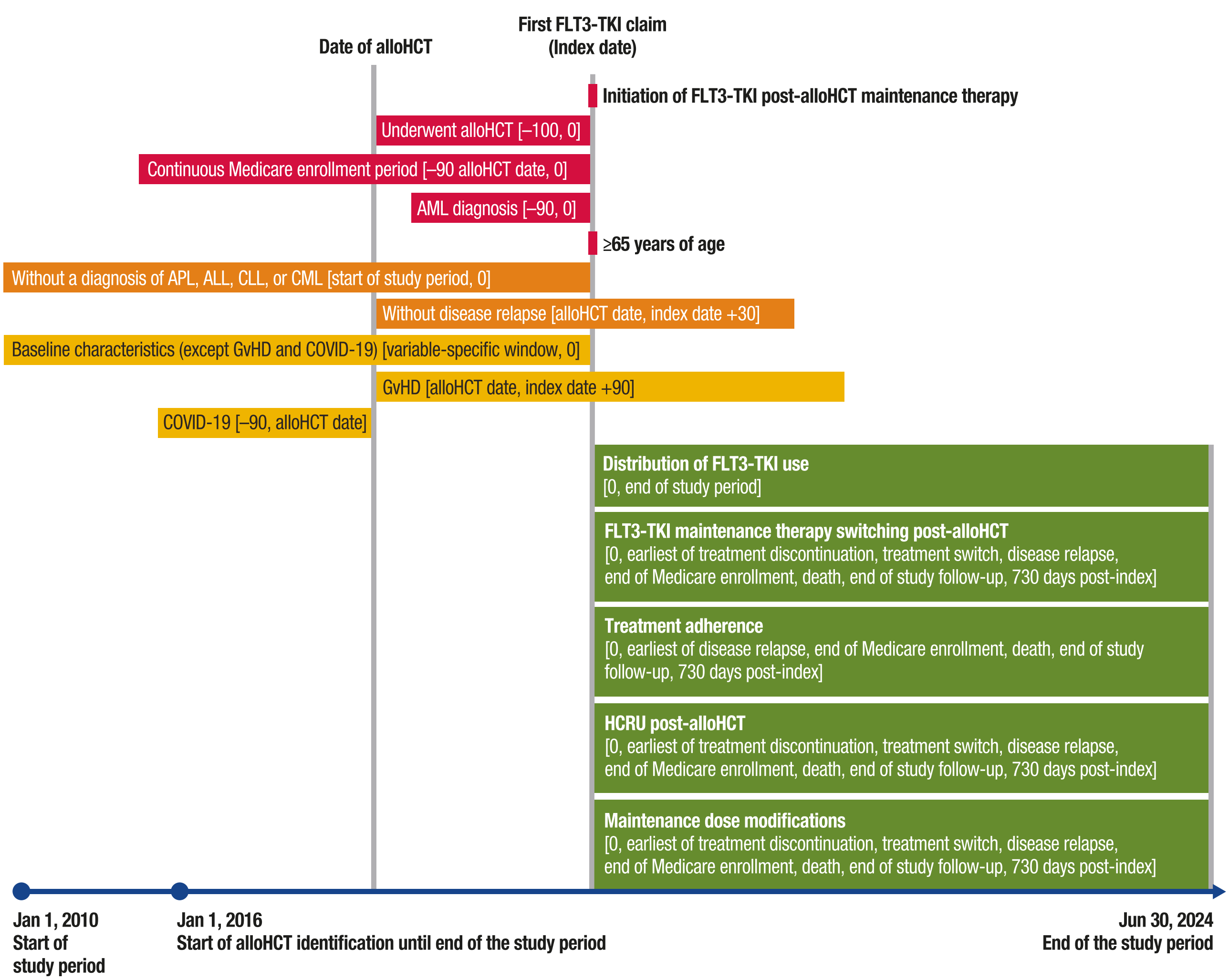

Fig. 1. Study schematic.
ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; FLT3, *FMS*-like tyrosine kinase 3; GvHD, graft versus host disease; HCRU, health care resource utilization; TKI, tyrosine kinase inhibitor.

databases: Research Identifiable Files, Part D Event, Medicare Advantage Encounter data, and Master Beneficiary Summary File. The index period was between January 1, 2016 through June 30, 2024; data from Medicare beneficiaries covered by Part C were collected from 2017 to 2021.

2.3. Study design

This was a retrospective study of patients with AML ≥65 years old who were enrolled in Medicare and initiated FLT3-TKI maintenance therapy with gilteritinib, midostaurin, or sorafenib following alloHCT. The date of alloHCT was defined as the date of the procedure, or the seventh day of hospitalization for alloHCT if no procedure code was available. The index date was defined as the first claim for gilteritinib, midostaurin, or sorafenib observed within the first 100 days following alloHCT (Fig. 1). Baseline patient characteristics were described based on the data available from January 1, 2010 up to the day before the index date. Comorbidities, based on Charlson Comorbidity Index (CCI), observed within one year before the index date were reported. Patients were followed in the Medicare database for health care encounters and prescription fills for all three FLT3-TKIs until relapse, death, or end of the follow-up period.

2.4. Study population

Eligible patients were ≥65 years old as of the index date and had received ≥1 alloHCT between January 1, 2016 and June 30, 2024. Inclusion criteria required: (1) evidence of AML, defined as ≥1 inpatient or ≥2 outpatient claims (spaced ≥30 days apart) with an AML diagnosis within 90 days prior to or on the index date; (2) initiation of maintenance therapy with gilteritinib, midostaurin, or sorafenib within 100 days following the alloHCT date; and (3) continuous enrollment in the health plan for a minimum of 90 days prior to the alloHCT admission through the index date. Patients were excluded if they had ≥1 inpatient or ≥2 nondiagnostic outpatient claims with a diagnosis of acute promyelocytic leukemia (APL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), or chronic myeloid leukemia (CML) prior to the index date or if they had evidence of relapse between the alloHCT date and 30 days following the index date.

2.5. Study end points

FLT3-TKI adherence was reported as proportion of days covered (PDC), which was defined using the following formula: (the last fill + days' supply – index date + 1 day) / the total number of days in the follow-up period. Full treatment adherence was defined as a PDC ≥80% as per standard oncology definitions [18,19]. FLT3-TKI dose modifications (dose increase or decrease) were considered as a change of a minimum clinically allowable dose after examination of the distribution of the calculated average daily dose. The average daily dose was calculated using the following formula: (dose strength × quantity) / days' supply. The smallest unit of strength (dose unit) was defined for each of the three FLT3-TKIs after review of the distribution values of the calculated dose variable. Dose modifications were evaluated from the index date until the earliest of treatment discontinuation, treatment switch, relapsed or refractory (R/R) disease, end of Medicare enrollment, death, end of study follow-up, or 730 days after the index date. Patients with missing days, supply, or quantity were excluded.

2.6. Statistical analyses

Patient demographics, comorbidities, disease characteristics, and health care resource utilization (HCRU) were summarized using descriptive statistics during the baseline period. Patterns of FLT3-TKI use and adherence were summarized by the index FLT3-TKI for the overall patient population and for subgroups of interest. Association between continuous variables was evaluated with Pearson correlations with a significance level of 0.05.

In accordance with CMS privacy regulations, variables with frequencies of <11 patients and summary statistics for continuous variables based on <50 patients cannot be reported and are denoted with an asterisk (*). Values that did not meet these thresholds but contributed to the calculation of a suppressed value are presented as estimates (e.g., ">11 patients"). To comply with CMS data suppression rules, results for midostaurin and sorafenib were combined when necessary.

3. Results

3.1. Patients

We identified 112,141 patients who underwent ≥1 alloHCT from January 1, 2016 through June 30, 2024. Among those, 7403 patients had AML, were ≥65 years old, and maintained continuous Medicare enrollment. A total of 150 patients initiated maintenance therapy with a FLT3-TKI (gilteritinib, midostaurin, or sorafenib) within 100 days following alloHCT and were included in the final analysis (Supplementary Fig. 1). Of those 150 patients, 82 (54.7%) received gilteritinib, 36 (24.0%) received midostaurin, and 32 (21.3%) received sorafenib as post-alloHCT maintenance therapy.

3.2. Baseline demographics and clinical characteristics

The mean (standard deviation [SD]) age was 70.5 (3.5) years, and 78 patients (52.0%) were ≥70 years old; 50.0% were female (Table 1). The mean (SD) CCI was 4.5 (2.6) and 89 patients (59.3%) had a CCI ≥4. Common comorbidities included chronic pulmonary disease (26.7%), diabetes with or without chronic complication (22.7%), cerebrovascular disease (21.3%), and congestive heart failure (21.3%). Comorbidity profiles and CCI were similar among FLT3-TKIs.

Prior to alloHCT, nearly half of the patients (82; 54.7%) received high-intensity chemotherapy (HIC), and 54 patients (36.0%) received low-intensity chemotherapy (LIC), while 9.3% had unknown status. Prior HIC was more common in patients receiving midostaurin or sorafenib versus gilteritinib (66.2% vs 45.1%), while prior LIC was more common for gilteritinib versus midostaurin or sorafenib (50.0% vs 19.1%). Most patients (119; 79.3%) had received a FLT3-TKI prior to alloHCT, with similar proportions across groups. Across the full cohort, roughly half of patients (81; 54.0%) had history of R/R AML prior to transplant, with similar proportions across FLT3-TKI groups. The mean (SD) time from alloHCT to initiation of FLT3-TKI maintenance therapy was 56.2 (24.2) days, with similar durations observed across groups. Nineteen patients (12.7%) developed acute graft versus host disease (GvHD).

3.3. FLT3-TKI utilization over time

Following 2020, the use of FLT3-TKI maintenance was sustained, with similar percentages in 2020 (17.3%), 2021 (20.7%), 2022 (20.0%), and 2023 (16.0%) (Table 2). Across all patients, the most common FLT3-TKI was gilteritinib (82; 54.7%); the remainder of patients received midostaurin or sorafenib (68; 45.3%). Gilteritinib use increased over time, with most patients initiating therapy between 2020 and 2023; 13.4% of patients initiated gilteritinib in 2020, increasing to 29.3% in 2021, and 23.2% in 2023. By contrast, <11 patients initiated midostaurin or sorafenib in each index year from January 1, 2016 to June 30, 2024.

Given that patients with a history of R/R AML prior to transplant are at higher risk of post-transplant relapse, we hypothesized that the use of FLT3-TKI maintenance would be higher in this population. This did appear to be true initially; in 2020 and 2021, 18.5% and 22.2% of patients with a history of R/R AML prior to transplant received FLT3-TKI maintenance, compared with 15.9% and 18.8% of patients without a

Table 1
Patient and treatment characteristics.

	Overall ($N = 150$)	Gilteritinib ($n = 82$ [54.7%])	Midostaurin or sorafenib ($n = 68$ [45.3%])
Demographic characteristics			
Age, mean (SD), years	70.5 (3.5)	71.1 (3.5)	69.7 (NC)
<70, n (%), years	72 (48.0)	35 (42.7)	37 (54.4)
≥70, n (%), years	78 (52.0)	47 (57.3)	31 (45.6)
Female, n (%)	75 (50.0)	44 (53.7)	31 (45.6)
Clinical characteristics			
CCI score, mean (SD)	4.5 (2.6)	4.4 (2.4)	4.7 (NC)
<4, n (%)	61 (40.7)	35 (42.7)	26 (38.2)
≥4, n (%)	89 (59.3)	47 (57.3)	42 (61.8)
CCI comorbidities, n (%)			
Chronic pulmonary disease	40 (26.7)	22 (26.8)	18 (26.5)
Diabetes with or without chronic complication	34 (22.7)	14 (17.1)	20 (29.4)
Cerebrovascular disease	32 (21.3)	18 (22.0)	14 (20.6)
Congestive heart failure	32 (21.3)	19 (23.2)	13 (19.1)
Mild liver disease	31 (20.7)	18 (22.0)	13 (19.1)
Peripheral vascular disease	30 (20.0)	17 (20.7)	13 (19.1)
Myocardial infarction	20 (13.3)	*	*
Diabetes with chronic complication	17 (11.3)	*	*
Rheumatic disease	11 (7.3)	*	*
Dementia	*	*	*
Hemiplegia or paraplegia	*	*	*
Metastatic solid tumor	*	*	*
Peptic ulcer disease	*	0	*
AIDS/HIV	0	0	0
Moderate or severe liver disease	*	*	*
Other comorbidities of interest, n (%)			
GvHD post-alloHCT	19 (12.7)	11 (13.4)	*
COVID-19 infection prior to alloHCT	54 (36.0)	35 (42.7)	19 (27.9)
Patients with a history of R/R prior to alloHCT, n (%)	81 (54.0)	45 (54.9)	36 (52.9)
Treatment characteristics			
Use of FLT3-TKI prior to alloHCT, n (%)	119 (79.3)	64 (78.0)	55 (80.9)
Prior chemotherapy,[a] n (%)			
HIC	82 (54.7)	37 (45.1)	45 (66.2)
LIC	54 (36.0)	41 (50.0)	13 (19.1)
Time from alloHCT to initiation of FLT3-TKI maintenance therapy, mean (SD), days	56.2 (24.2)	55.5 (24.4)	57.0 (NC)

Demographics were described from Jan 1, 2010 to the day before the index date (day −1).
CCI was described from one year before the index date (day −1). GvHD was described from alloHCT to 90 days after the index date (inclusive). COVID-19 infection was described from 90 days before the alloHCT date.
Baseline characteristics were described from Jan 1, 2010 to the day before the index date (day −1). The date of AML diagnosis is the date of first observed AML diagnosis during the baseline period.
Results denoted by an asterisk (*) were blinded in accordance with CMS blinding requirements.
alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CCI, Charlson Comorbidity Index; CMS, Centers for Medicare & Medicaid Services; FLT3, *FMS*-like tyrosine kinase 3; GvHD, graft versus host disease; HIC, high-intensity chemotherapy; LIC, low-intensity chemotherapy; NC, not calculated; R/R, relapsed or refractory; SD, standard deviation; TKI, tyrosine kinase inhibitor.
[a] For some patients, the use of HIC or LIC was not identified and therefore the proportions in this category do not add up to 100%.

Table 2
Distribution of FLT3-TKI over the years overall and in patients with or without a history of R/R AML prior to alloHCT.

Index year distribution, n (%)	Overall ($N = 150$)	Gilteritinib ($n = 82$)	Midostaurin or sorafenib ($n = 68$)	Patients with a history of R/R AML prior to alloHCT ($n = 81$)	Patients without a history of R/R AML prior to alloHCT ($n = 69$)
2016–2018	*	0	*	*	*
2019	14 (*)	*	*	*	*
2020	26 (17.3)	11 (13.4)	*	15 (18.5)	11 (15.9)
2021	31 (20.7)	24 (29.3)	*	18 (22.2)	13 (18.8)
2022	30 (20.0)	21 (25.6)	*	15 (18.5)	15 (21.7)
2023	24 (16.0)	19 (23.2)	*	11 (13.6)	13 (18.8)
2024[a]	*	*	*	0	*

Demographics were described from Jan 1, 2010 to the day before the index date (day −1).
Results denoted by an asterisk (*) were blinded in accordance with CMS blinding requirements.
alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CMS, Centers for Medicare & Medicaid Services; FLT3, *FMS*-like tyrosine kinase 3; R/R, relapsed or refractory; TKI, tyrosine kinase inhibitor.
[a] Up to Jun 30, 2024.

history of R/R AML, respectively. By 2022 and 2023, however, a similar proportion of patients in both groups received maintenance therapy.

3.4. Treatment adherence

Across all patients, the adherence for FLT3-TKI maintenance therapy following alloHCT, as measured by the mean PDC, was 47%. PDC varied across FLT3-TKIs (Fig. 2). Patients treated with gilteritinib demonstrated the highest adherence (mean PDC: 54%), whereas mean PDC was 43% for midostaurin, and 35% for sorafenib. Full treatment adherence (PDC ≥80%) was poor overall. Among all patients, very few (>7.3%) were considered treatment-adherent, with a slightly improved rate of 15% in the subset treated with gilteritinib. The percentages of treatment-adherent patients in the midostaurin and sorafenib treatment groups were not available.

In subgroup analyses, older patients, those with fewer comorbidities, those who had received prior LIC, and those without a history of R/R disease prior to alloHCT showed greater adherence (Fig. 3). Patients ≥70 years of age had a higher mean PDC versus those <70 years (mean PDC: 51% vs 43%). For both age groups, mean PDC was numerically higher for gilteritinib (<70 years: 49%; ≥70 years: 58%) versus midostaurin (<70 years: 41%; ≥70 years: 45%) or sorafenib (<70 years: 35%; ≥70 years: 34%). Patients with a CCI score <4 generally had a higher mean PDC than those with a CCI score ≥4 (52% vs 45%), and for both CCI categories, mean PDC was numerically higher for gilteritinib (CCI <4: 60%; CCI ≥4: 50%) versus midostaurin (CCI <4: 41%; CCI ≥4: 45%) or sorafenib (CCI <4: 40%; CCI ≥4: 31%). The correlation between PDC and CCI score was not significant ($P = 0.49$).

The mean PDC among patients who were previously treated with HIC was numerically lower than for those who had not received HIC (45% vs 50%). Among patients who had received prior HIC, patients treated with gilteritinib were more adherent to maintenance therapy (57%) compared with those who received midostaurin (42%) or sorafenib (29%). By contrast, mean PDC for patients who were previously treated with LIC was numerically higher than for those who had not received LIC (53% vs 44%). Patients with prior history of LIC who received gilteritinib or sorafenib had a mean PDC of 55% each, and those who

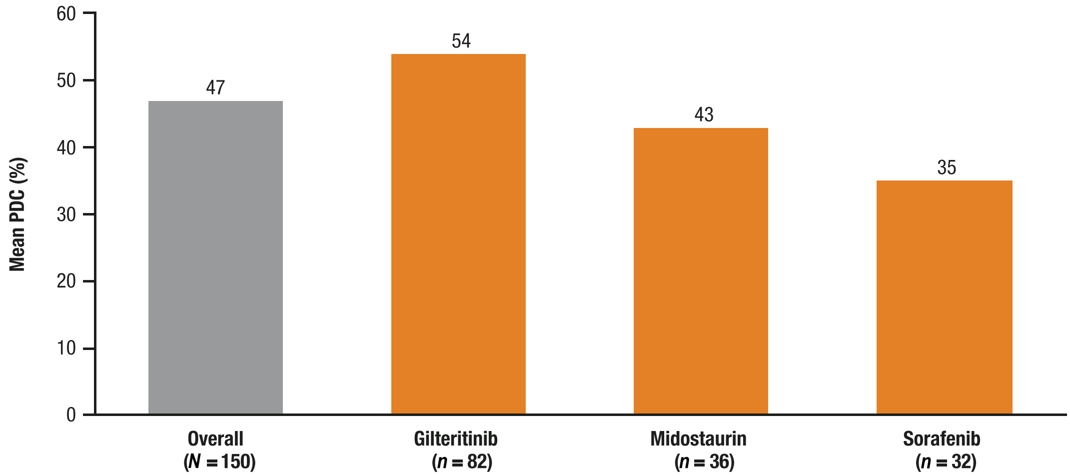

Fig. 2. Treatment adherence in the overall cohort.
PDC was evaluated from the index date until the earliest of R/R, end of Medicare enrollment, death, end of study follow-up, or 730 days after the index date.
PDC, proportion of days covered; R/R, relapsed or refractory.

received midostaurin had a mean PDC of 43%.

Adherence was higher in patients without a history of R/R AML prior to alloHCT, with a mean PDC of 52% versus 41% for those who did have a history of R/R disease. Among patients treated with gilteritinib, adherence was higher in those without versus with a history of R/R disease (59% vs 48%), and a similar trend was observed for sorafenib (45% vs 24%). By contrast, patients treated with midostaurin showed similar adherence between groups, with a mean PDCs of 44% and 43% in patients with and without an R/R history, respectively.

3.5. FLT3-TKI dose modifications and agent switching

To better understand the tolerability of FLT3-TKI maintenance therapies, we examined patterns in dose modification and switching from one FLT3-TKI to another. Because data for midostaurin and sorafenib were largely suppressed due to small sample sizes, this analysis focused on the most commonly used FLT3-TKI, gilteritinib. Of the 74 patients treated with gilteritinib that had available dose information, 67.6% had no evidence of dose change, while 32.4% experienced a dose modification. Among those with a dose modification, <50% had a dose decrease, and >50% had a dose increase (numbers suppressed due to small sample sizes). The mean (SD) age and CCI were similar for both patients whose gilteritinib dose was maintained or increased and for those whose dose was decreased, at 70.4 (3.5) versus 71.0 (3.5) years, and 5.0 (3.1) versus 5.2 (2.4) years, respectively.

Switching from one FLT3-TKI to another varied among FLT3-TKIs. No patients who initiated gilteritinib switched to another FLT3-TKI during the study period. Fewer than 32% of patients who initiated midostaurin switched to gilteritinib, while <38% of those who initiated sorafenib switched to either gilteritinib or midostaurin.

3.6. Health care resource utilization in patients receiving FLT3-TKI maintenance

Finally, we sought to examine HCRU in older adults receiving FLT3-TKI maintenance therapy after transplant. The mean (SD) HCRU follow-up was 659.38 (686.91) days; patients receiving sorafenib had a longer HCRU follow-up (1069.03 [1023.24] days) versus gilteritinib (541.01 [489.35] days) and midostaurin (564.86 [575.93] days). Following transplant, outpatient physician visits were the most frequently used service, with an average of 3.20 visits per patient per month (PPPM), followed by outpatient hospital visits at 1.37 PPPM. Post-transplant hospitalizations were relatively infrequent, at 0.07 PPPM. This pattern was consistent across patients receiving all three FLT3-TKIs (Table 3).

HCRU was numerically higher in younger patients, those with more comorbidities, and those with a history of R/R disease prior to alloHCT (Supplementary Table 1). Relative to patients ≥70 years of age, those <70 years had more post-alloHCT hospitalizations (0.05 vs 0.10 PPPM) and outpatient physician visits (2.92 vs 3.46 PPPM). Patients with CCI ≥4 had generally higher HCRU across all categories compared with those with CCI <4, including number of hospitalizations (0.11 vs 0.01 PPPM), hospitalization with intensive care unit (ICU) stays (0.03 vs 0 PPPM), and outpatient physician visits (4.60 vs 1.13 PPPM). Compared with patients who did not have a history of R/R disease, those with R/R disease prior to alloHCT had more post-alloHCT hospitalizations (0.03 vs 0.11 PPPM), ICU stays (0.01 vs 0.03 PPPM), and outpatient physician visits (2.61 vs 3.73 PPPM). By contrast, HCRU was similar between patients who had previously been treated with HIC versus LIC.

4. Discussion

For patients with *FLT3*-mutated AML receiving alloHCT, post-transplant maintenance therapy with FLT3-TKIs can prevent relapse and extend survival [10–13]; however, the real-world use and tolerability of FLT3-TKIs remains largely underexplored, particularly in older adults. This retrospective cohort study addresses this gap by providing real-world data on utilization and adherence of FLT3-TKI maintenance therapy in patients with AML who are ≥65 years old.

Although *FLT3* mutation testing results were not available and the exact number of mutation-positive patients is unknown, from a total of 7403 patients with AML in the study, we estimate that approximately 20% (or 1481 patients) had *FLT3*-ITD mutations [5]. Furthermore, based on previous studies, we estimate that approximately two-thirds of patients (or 987 patients) with *FLT3*-ITD mutations would undergo alloHCT [20]. Nevertheless, only 150 patients (15% of those estimated 987 patients) were reported to initiate FLT3-TKI maintenance post-alloHCT, indicating that despite both supporting clinical trial data [10–13] and NCCN Guidelines [14], the real-world use of FLT3-TKIs in older adults remains markedly low. Factors contributing to low FLT3-TKI utilization could include uncertainty about generalizability of trial data to older adults, clinician hesitancy regarding tolerability in older adults with comorbidities, concerns about polypharmacy and drug-drug interactions, or fragmentation between transplant and hematology teams during the post-transplant transition period.

Based on the results of this study, however, FLT3-TKI use is increasing over time, with approximately 20% of older adult transplant recipients receiving maintenance in the past five years. Gilteritinib was

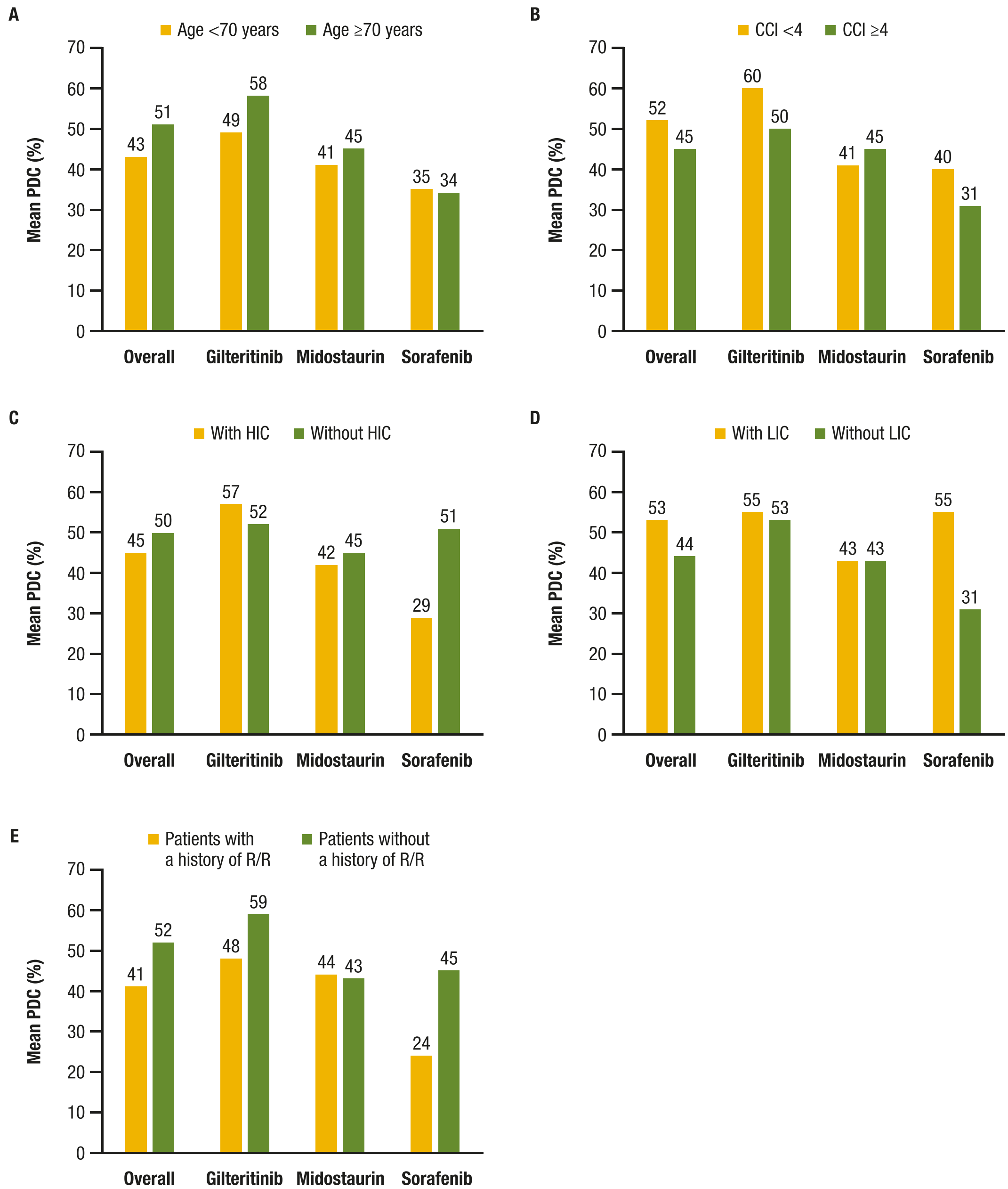

Fig. 3. Treatment adherence by (A) age, (B) CCI, and history of (C) HIC, (D) LIC, and (E) R/R disease prior to alloHCT.
PDC was evaluated from the index date until the earliest of R/R, end of Medicare enrollment, death, end of study follow-up, or 730 days after the index date. alloHCT, allogeneic hematopoietic cell transplantation; CCI, Charlson Comorbidity Index; HIC, high-intensity chemotherapy; LIC, low-intensity chemotherapy; PDC, proportion of days covered; R/R, relapsed or refractory.

the most commonly used FLT3-TKI among patients in this study (54.7%), despite receiving US Food and Drug Administration approval in December 2018 [21], later than midostaurin (April 2017) [22] and sorafenib (2005) [23], suggesting that time from approval was not the primary driver of FLT3-TKI choice. The current findings mirror those of another recent retrospective cohort study investigating real-world treatment patterns of FLT3-TKI maintenance in younger adults, in which FLT3-TKI utilization rose to 50% between 2017 and 2022 and over half (51.8%) of patients received gilteritinib [24].

Although NCCN Guidelines recommend the use of FLT3-TKI maintenance in patients of all ages [14], the trials on which these recommendations are based predominantly focus on younger and fitter patients. The four randomized trials evaluating FLT3-TKI maintenance enrolled patients with median ages ranging from 35 to 54 years [10–13]. By contrast, in this real-world study, the median age was 70.5 years. Comorbidities were also common in this population, with a mean CCI of 4.5. Further, many common comorbidities reported, including pulmonary dysfunction, diabetes, cerebrovascular disease, and heart failure, are also associated with inferior outcomes following alloHCT [25]. By contrast, among the four published FLT3-TKI maintenance trials, only one reported comorbidity data; in that study, nearly half of patients (44%) had no significant comorbidities [13]. Thus, relative to clinical trial populations, this real-world patient cohort was both considerably older and featured more comorbidities.

In this real-world population, FLT3-TKI adherence was modest, with a mean PDC of 47% across all patients. In a similar claims-based study of FLT3-TKI maintenance in younger adults (median age: 52 years), the median PDC was 57% [26], suggesting that increased age and comorbidities in the present cohort did not markedly decrease adherence. Medication adherence is particularly important for older transplant

Table 3
Health care resource utilization post-allogeneic hematopoietic cell transplantation.

Mean (SD)	Overall (N = 150)	Gilteritinib (n = 82 [54.7%])	Midostaurin (n = 36 [24.0%])	Sorafenib (n = 32 [21.3%])
Duration of follow-up, days	659.38 (686.91)	541.01 (489.35)	564.86 (575.93)	1069.03 (1023.24)
Hospitalizations, PPPM	0.07 (0.19)	0.07 (0.19)	0.07 (0.12)	0.09 (0.25)
Length of hospital stay among patients with ≥1 inpatient stay, days	8.52 (27.51)	9.60 (34.21)	5.89 (11.61)	8.72 (20.44)
Hospitalization with prior ED visit, PPPM	0.04 (0.12)	0.03 (0.10)	0.03 (0.07)	0.05 (0.18)
Hospitalization with ICU days, PPPM	0.02 (0.07)	0.03 (0.08)	0.03 (0.07)	0.01 (0.02)
Outpatient hospital visits, PPPM	1.37 (2.77)	1.17 (1.98)	1.68 (3.08)	1.53 (3.71)
Ambulatory surgery centers, PPPM	0.003 (0.02)	0.005 (0.03)	0	0
Outpatient ED visits, PPPM	0.01 (0.02)	0.002 (0.01)	0.01 (0.03)	0.005 (0.02)
Outpatient physician visits, PPPM	3.20 (5.45)	3.33 (5.96)	3.41 (4.27)	2.62 (5.35)
Other outpatient visits,[a] PPPM	0.10 (0.23)	0.11 (0.23)	0.13 (0.30)	0.05 (0.10)

HCRU follow-up period was defined from the index date to the earliest of treatment discontinuation, treatment switch, R/R, end of Medicare enrollment, death, end of study follow-up, or 730 days after the index date.
ED, emergency department; HCRU, health care resource utilization; ICU, intensive care unit; PPPM, per patient per month; R/R, relapsed or refractory; SD, standard deviation.
[a] Other outpatient visits not otherwise categorized above as well as visits to skilled nursing facilities, home health aid, and hospice.

candidates, who are frequently impacted by polypharmacy prior to transplant. Prior studies report a median of 8.5 medications per patient in older adults prior to alloHCT, with 28% to 35% taking ≥7 medications [27,28]. Pretransplant polypharmacy in older adults predicts poor overall survival and is associated with longer post-alloHCT hospitalizations [15]. The potential burden of polypharmacy is likely even greater following transplant; in addition to treatments for comorbidities, transplant patients require medications for immunosuppression, antimicrobial prophylaxis, and supportive care. Thus, although FLT3-TKIs may reduce relapse in this population, substantial polypharmacy makes FLT3-TKI adherence challenging.

In the present study, patients with greater comorbidity showed decreased FLT3-TKI adherence, potentially reflecting the burden of polypharmacy, including drug-drug interactions. By contrast, older age was associated with increased adherence. This is consistent with previous studies on oral cancer treatments in older patients, which report that age-related factors, such as comorbidities or functional limitations, but not age itself, hinder treatment adherence [29,30]. There are several potential mechanisms for this finding. Comprehensive geriatric assessment, which includes physical function, mental health, cognition, polypharmacy, comorbidities, and social support, is increasingly standard in determining alloHCT candidacy in older adults [31,32]. Thus, adults ≥70 years of age likely represent a highly selected subgroup, which may facilitate both the oncologist's willingness to initiate maintenance FLT3-TKI and patient's ability to adhere to therapy and tolerate side effects [33]. Indeed, in our cohort, older age was associated with fewer post-transplant hospitalizations and outpatient physician visits, further supporting the increased fitness in this population. Our findings underscore a key role for careful patient selection by the treating physician, and further reinforce that older age alone should not be the sole barrier to transplant.

Interestingly, although a history of R/R disease prior to alloHCT is associated with a higher risk of post-alloHCT relapse [34], in this analysis, pre-alloHCT R/R disease was associated with decreased adherence. This finding is in contrast to a prior claims-based analysis in younger adults that showed increased FLT3-TKI adherence in patients with a history of R/R disease [26], and suggests that factors beyond disease risk may be the primary drivers of adherence in this population.

Adherence was also impacted by FLT3-TKI selection, with higher rates observed in patients receiving gilteritinib. Gilteritinib maintenance was generally well tolerated, with most patients either maintaining or increasing their starting dose, and no cases of switching to an alternative FLT3-TKI, both of which are potential surrogates for tolerability. The mean age and CCI were similar for patients for whom the dose of gilteritinib was either maintained or increased (potentially indicating tolerability) compared with patients for whom the dose was decreased (potentially indicating concern for toxicity or adverse reaction), suggesting that gilteritinib tolerability was not impacted by either age or comorbidity. Reasons for dose decrease or FLT3-TKI switching are unknown, but may include disease relapse, treatment-associated toxicity, or the development of other post-alloHCT complications, such as GvHD [10,11,13].

Given the apparent clinical benefit of FLT3-TKI maintenance in this population, the implementation of effective adherence practices, such as the use of pillboxes or medication reminder tools, are warranted. To address the substantial burden of polypharmacy in older patients, regular deprescribing of unnecessary medications and pharmacist-led intervention programs, both proven effective in alloHCT patients of all ages, are also worth considering [35–37].

In addition to patient adherence, the low rate of FLT3-TKI maintenance utilization in our cohort suggests that strategies to improve FLT3-TKI prescribing by oncologists are warranted as well. At the provider level, education regarding the tolerability of FLT3-TKI maintenance in older adults may counter hesitancy driven by age or comorbidity concerns. At the system level, standardized post-transplant care pathways that incorporate automated review of FLT3 mutation status and patient eligibility for FLT3-TKI may also improve utilization. Future research should evaluate barriers to prescribing from both patient and physician perspectives to better understand whether low utilization reflects clinical ineligibility, toxicity concerns, cost barriers, or gaps in complex care coordination.

As a claims-based analysis, this study has several potential limitations. The dataset used lacked some key clinical features, including AML risk stratification, mutation status, pre-alloHCT complete remission and measurable residual disease status, and transplant characteristics. This study also only assessed secondary adherence, as pharmacy claims for a filled prescription do not guarantee that patients took their medication as prescribed. In addition, claims data cannot capture toxicity data associated with specific therapies, limiting our understanding of FLT3-TKI tolerability.

Overall, this is the first retrospective cohort study evaluating real-world treatment patterns and tolerability of FLT3-TKI maintenance in older adults, a population previously underrepresented in clinical trials. Our findings show that FLT3-TKI maintenance utilization and adherence was modest but not limited by age alone. Additional real-world studies are needed to better understand patient- and disease-specific factors associated with adherence, as well as the impact of FLT3-TKI utilization on relapse and survival outcomes in older adult populations.

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Author contributions

Conceptualization: All authors.

Methodology: All authors.
Data curation: CY, PK, and PP.
Formal analysis: CY, PK, and PP.
Investigation: VEK, AB, CY, DM, and PP.
Writing – original draft: All authors.
Writing – review and editing: All authors.

Data sharing statement

All data generated or analyzed during this study, which support the findings of this study, are included within this article and its supplementary information files. Researchers interested in further analyses not present in the manuscript may contact the corresponding author.

Declaration of competing interest

VEK reports grant support from an NIH K12 award to research population-level care patterns in AML (not related to the current work), consulting fees from Astellas, Omeros (not related to the current work), and Servier, speaking fees from Association of Northern California Oncologist and The Cancer Network AML FaceOff, and unpaid committee membership to ASH, ASTCT, and the BMT Clinical Trials Network. **AB**, **CY**, and **DN** are employees of Astellas. **PK** reports no conflicts of interest. **PP** is an employee of Astellas and receives support for attending Astellas internal meetings and conferences.

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Appendix A. Supplementary data

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