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Research paper

Clinical and economic analysis of patients with acute myeloid leukemia by *FLT3* status and midostaurin use at a Comprehensive Cancer Center*

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ABSTRACT

Introduction: Identification of cytogenetic and molecular abnormalities has become vital for the appropriate treatment of acute myeloid leukemia (AML). One of the most common molecular alterations in AML is the constitutive activation by internal tandem duplication of FMS-like tyrosine kinase 3 (*FLT3*).
Methods: This observational, retrospective, cohort study at the Huntsman Cancer Institute (HCI) had two time periods: 1) a historical pre-midostaurin time period which consisted of the *FLT3* mutated (FLT3m) and *FLT3* wild type (FLT3wt) cohorts from January 1, 2007, to December 31, 2016, and 2) a post-midostaurin cohort which consisted of the *FLT3* mutated midostaurin-user cohort (early mido) from May 01, 2017 to December 31, 2018.
Results: In total, 39 patients were included in the FLT3m cohort, 61 in the FLT3wt cohort, and seven in the early mido cohort. FLT3m patients spent fewer days in the hospital during the first consolidation regimen and received fewer consolidation cycles compared to FLT3wt patients. Overall survival (OS) was similar between FLT3m and FLT3wt patients. For patients without hematopoietic stem cell transplant, OS was significantly shorter for FLT3m patients compared to FLT3wt patients. Mean AML related inpatient charges and physician charges for FLT3m patients were significantly higher than FLT3wt patients.
Conclusion: The *FLT3* mutation is historically associated with a shorter time to transplant and increased total health care charges. More information is needed to evaluate the real-world treatment strategies for FLT3-mutated patients in the presence of FLT3 inhibitors and the impact of these treatment strategies on clinical and economic outcomes.

1. Introduction

Acute myeloid leukemia (AML) is a cancer of the hematopoietic stem and progenitor cells typically caused by inherited or acquired genetic mutations [1]. It is estimated that there will be 21,450 new cases of AML in 2019, making it one of the most common types of leukemia [2]. Prognosis of AML diagnosis is poor, with a five-year survival rate of approximately 27% [3]. The lifetime risk of developing AML is 0.5% [3].

In order to stratify risk and select appropriate treatment regimens for AML, identifying cytogenetic and molecular abnormalities has become vital. One of the most common molecular alterations in AML is the constitutive activation by internal tandem duplication of *FLT3*, a tyrosine kinase receptor. Studies have shown that the *FLT3* mutation is seen in 25%–30% of AML cases, and patients with this genetic mutation have poorer clinical outcomes and increased relapse rates [4,5].

Induction therapy with chemotherapy is the backbone of treatment for AML. Following CR, patients proceed to consolidation therapy. A

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large meta-analysis demonstrated that patients with cytogenetic intermediate- or high-risk AML benefited from hematopoietic stem cell transplant (HSCT) [6]. Several recent studies have further shown improved benefits for FLT3 mutated patients that receive HSCT as soon as possible following first complete remission [7–10].

Midostaurin (Rydapt; Novartis Pharmaceuticals, Inc.) became the first medication approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with *FLT3*-mutation positive AML in April, 2017 [11]. Midostaurin is indicated in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation therapy. Results from randomized clinical trials have shown that the use of midostaurin with HSCT can significantly improve both overall survival (OS) and event-free survival (EFS) in for FLT3m patients [12]. Understanding the economic and clinical impact of a *FLT3* mutation requires ongoing research and investigation. The primary objective of this study was to compare the real-world clinical and economic outcomes of patients with AML by *FLT3* mutation status. Secondarily, early data on midostaurin use in *FLT3* mutated AML patients is described.

2. Methods

2.1. Study design

This observational cohort study evaluated AML patients by *FLT3* mutation status and midostaurin use at the Huntsman Cancer Institute (HCI). HCI is a National Cancer Institute (NCI) designated Comprehensive Cancer Center, member of the National Comprehensive Cancer Network (NCCN), and the major cancer center in the Intermountain West that provides care to Utah and surrounding states. AML patients were identified retrospectively using the Huntsman Cancer Institute Tumor Registry (HCI-TR) using ICD-9-CM and ICD-10-CM codes indicative of AML. Patients with AML identified through the HCI-TR were linked to electronic health record data from the University of Utah Enterprise Data Warehouse (EDW).

2.2. Patient population

The index date was defined as the date of AML diagnosis. Patients were required to be 18 years or older at the time of diagnosis. Patients were also required to have a second encounter at least 30 days from the index date encounter unless death was recorded. Included patients received induction chemotherapy with an anthracycline and cytarabine (7 + 3) and had *FLT3* status documented. Patients were categorized as *FLT3*-mutated based on the presence of an ITD or TKD *FLT3* mutation.

This study included patients from two distinct time periods: 1) a historical pre-midostaurin time period from January 1, 2007, to December 31, 2016, which consisted of the *FLT3*-mutated (FLT3m) and *FLT3* wild type (FLT3wt) cohorts, and 2) a post-midostaurin cohort which consisted of the *FLT3*-mutated midostaurin-user cohort (early mido) from May 01, 2017, to December 31, 2018.

2.3. Study variables

2.3.1. Baseline characteristics

Patient demographic and clinical characteristics at diagnosis were obtained. These characteristics included age, sex, race, payer type, region, classification of AML by the French-American-British (FAB) and the World Health Organization (WHO) classification systems, AML risk classification (defined by the International Working Group and European Leukemia Net), presentation of extramedullary disease, and presence of CNS disease at diagnosis.

2.3.1.1. Clinical outcomes. A complete response (CR) was defined as a bone marrow biopsy result of < 5% blasts or by provider documentation of response. Likewise, relapse was defined as a bone marrow biopsy result of > 5% blasts or appearance of extramedullary disease, or by provider documentation. EFS was calculated from first CR to first relapse or death and censored at last known date of follow-up. OS measured time from diagnosis to death with patients censored at last known date of follow-up. For each cohort, treatment patterns and time to treatment were also collected.

2.3.1.2. Economic outcomes. Health care charges were calculated using pharmacy and medical hospital claims information from the EDW. Health care resource utilization represented the total of inpatient admissions, duration of inpatient admissions, outpatient visits, and emergency rooms visits. Health care charges and resource utilization were categorized as AML-related or all-cause, and as inpatient or outpatient related. Health care charges and utilization were also stratified by the type of charges including facility/technical, physician/professional, and pharmacy. Lastly, health care charges and utilization were analyzed by type of treatment. AML-related charges were associated with a primary, secondary, or tertiary diagnosis of AML during the survival. All health care charge data were adjusted for inflation to 2017 values using the Bureau of Labor Statistics Consumer Price Index for Medical Care.

2.4. Data analysis

The main summary measures include means, standard deviations (SD), medians, interquartile range (IQR) for continuous variables and frequency and percentages for categorical variables. Treatment patterns, survival status, health care utilization, and charges were compared between historical pre-midostaurin FLT3m and FLT3wt patients using Wilcoxon rank-sum tests, chi-square, and Fisher's exact tests as appropriate.

An *a priori* alpha level of 0.05 was used for all analyses. Demographic and clinical characteristics of AML patients were summarized using descriptive statistics. This included means, standard deviations, medians and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. SAS version 9.4 was used for all statistical analyses

Response rates for induction, consolidation, HSCT, and salvage were reported as counts and percentages. Response rates were compared between FLT3m and FLT3wt groups using Wilcoxon rank sum tests.

Survival analyses were conducted using Kaplan-Meier methodology from index date until death or censored at last follow-up. Survival was stratified by FLT3m and FLT3wt groups and compared by univariate Cox regression models (hazard ratios, confidence intervals, and p-values). In addition, Cox proportional hazard models were also developed to assess associations between prognostic factors (baseline demographic and clinical characteristics and *FLT3* status) and EFS and OS. Proportional hazards assumption to verify if survival curves had hazard functions that are proportional over time, was also tested.

Mean charges with standard deviation and median charges with interquartile range (25%–75%) were estimated for FLT3m and FLT3wt groups. Median health care utilization with interquartile range was also calculated for the above groups. As charge and utilization data were non-normal, Wilcoxon rank-sum test and Kruskal Wallis test were used to compare utilization and charges between FLT3m and FLT3wt groups, respectively.

Patients with absent demographic characteristics (e.g., race, insurance, region) or clinical characteristics (e.g., FAB classification, WHO classification, risk based on cytogenetic and molecular abnormalities) were categorized as 'Unknown.' All available patient information was included for survival analysis, utilization and charge analyses.

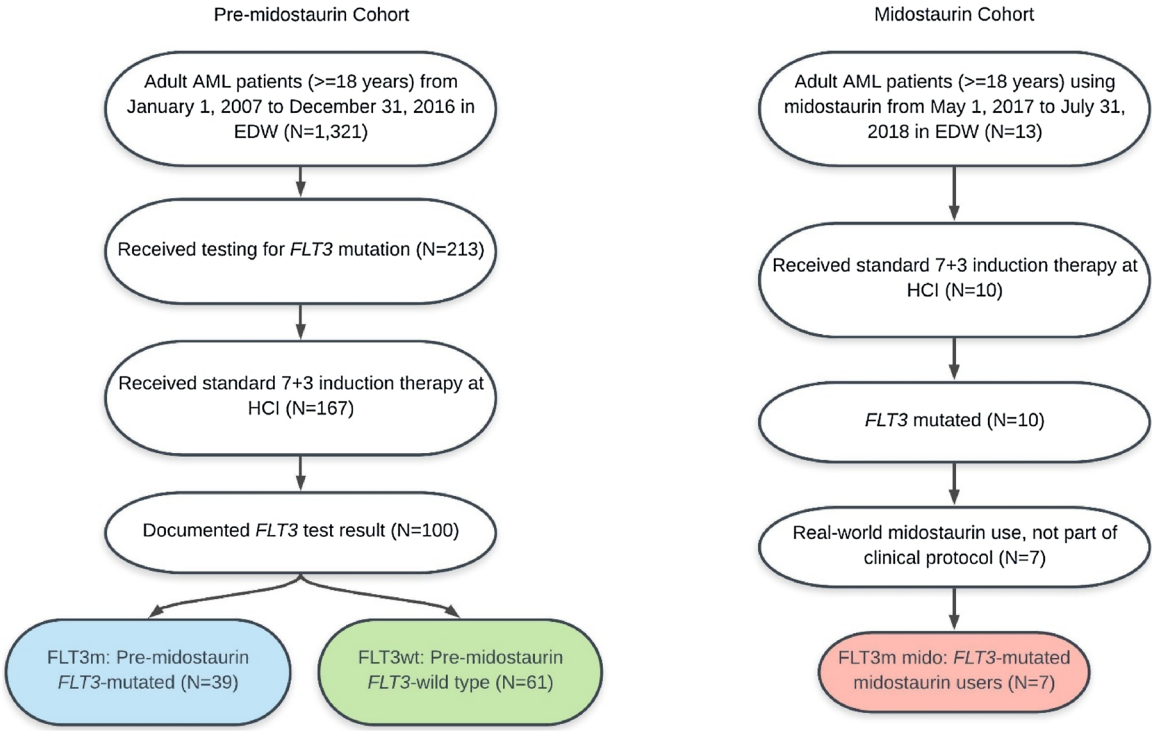

Fig. 1. Patient Flow Diagram.

3. Results

3.1. Baseline characteristics

The total number of adult AML patients at HCI between January 1, 2007, and December 31, 2016, was 1321. After including only patients who received *FLT3* testing and 7 + 3 induction therapy at HCI, the sample size decreased to 167 patients. Preliminary demographic characteristics and treatment pattern data for all excluded AML patients can be found in the supplemental material (Supplementary Tables 1 and 2). Of the total pre-midostaurin sample, 39 patients were FLT3m (ITD or TKD mutations), 61 patients were FLT3wt (neither ITD nor TKD mutation), and the remaining 67 patients did not have a *FLT3* test result reported (Fig. 1). Results from the cohort of patients with unknown FLT3 results can also be found in the supplementary material (Supplementary Tables 3 and 4). A separate cohort of nine *FLT3*-mutated patients treated at HCI following midostaurin approval was evaluated. Two of these patients did not receive midostaurin due to participation in a clinical trial and were excluded. The remaining seven *FLT3*-mutated patients who were administered midostaurin are included in the study (Fig. 1).

The mean age of the sample at index was 52 years. A majority of the total sample were younger than 60 years of age (72%) and were white (83%). Approximately half of the total sample were males (51%). A higher percentage of FLT3m patients were females (56%) compared to the FLT3wt group (44%). All patients in the midostaurin group were younger than 60 years. Six of the seven midostaurin patients (86%) were males. The risk classification of the FLT3m group had a distribution of 51% adverse risk and 49% intermediate risk. The FLT3wt group had 16% adverse risk, 49% intermediate risk, and 33% favorable risk. There were four early mido patients classified with adverse risk, and three classified with intermediate risk (Table 1).

3.2. Treatment patterns and response

3.2.1. Induction therapy

All patients included in the study received 7 + 3 induction therapy. The median time from diagnosis to the start of induction therapy was 2, 2, and 4 days for the FLT3m, FLT3wt, and early mido groups, respectively. Median time from start of induction to treatment response was 14 days. The CR rates following induction therapy were 90%, 77%, and 86% for the FLT3m, FLT3wt, and early mido groups, respectively (Table 2). The CR rates were similar for intermediate risk patients (84% and 80%, $p > 0.99$), but higher for adverse risk patients (95% and 36%, $p < 0.01$) when comparing FLT3m and FLT3wt, respectively.

3.2.2. Consolidation therapy

Post-induction consolidation therapy was observed in 74% of FLT3m, 67% of FLT3wt, and four of seven early mido patients. The median time between discharge from induction therapy and the start of consolidation therapy was 15, 14.5, and 14 days for the FLT3m, FLT3wt, and early mido groups, respectively. The median number of cycles of consolidation therapy was significantly higher in the FLT3wt cohort compared to the FLT3m cohort (3 vs. 2, $p < 0.01$). Patients in the midostaurin group also had a median of 2 consolidation cycles. A significantly higher percentage of patients maintained their complete remission in the FLT3m group compared to the FLT3wt group (83% vs. 49%, $p = 0.01$). For intermediate risk patients, the percentage of FLT3m patients that maintained their CR was higher (85% and 38%, $p < 0.01$) and similar for adverse risk patients (81% and 100%, $p > 0.99$) when comparing to FLT3wt patients, respectively. Three of four early mido patients maintained CR during consolidation therapy (Table 2).

3.2.3. Hematopoietic stem cell transplantation (HSCT)

More patients in the FLT3m group received HSCT compared to patients in the FLT3wt group (74% vs. 54%, $p = 0.04$). FLT3m patients also received HSCT earlier in their treatment course compared to the FLT3wt group (125 vs. 186 days from diagnosis, $p < 0.01$). Median time from last consolidation treatment to HSCT was also shorter for FLT3m patients compared to FLT3wt patients (55 vs. 65 days, $p = 0.05$). Five early mido patients received HSCT with a median of 53 and 23 days from diagnosis and last consolidation treatment. For the FLT3m cohort, HSCT was received after induction therapy in 7% of

Table 1
Demographic and Clinical Characteristics of AML Patients.

Patient Characteristics	FLT3m (N = 39)	FLT3wt (N = 61)	Total (N = 100)	P-value[a]	Early mido (N = 7)
Age at index					
Mean (SD)	52.5 (13.6)	47.3 (15.8)	51.6 (14.7)	0.10[b]	45.3 (11.8)
Under 60 years old, N (%)	26 (67)	46 (75)	72 (72)	0.34[c]	7 (100)
Over 60 years old, N (%)	13 (33)	15 (25)	28 (28)		0
Gender					
Female, N (%)	22 (56)	27 (44)	49 (49)	0.24[c]	1 (14)
Male, N (%)	17(44)	34(56)	51 (51)		6 (86)
Ethnicity, N (%)					
African American	1 (3)	0 (0)	1 (1)	0.39[d]	0
Asian	0 (0)	0 (0)	0 (0)		0
Caucasian/White	30 (77)	53 (87)	83 (83)		7(100)
Other	4 (10)	5 (8)	9 (9)		0
Unknown	4 (10)	3 (5)	7 (7)		0
Health Plan Type, N (%)					
Commercial	15 (38)	32 (52)	47 (47)	0.30[d]	6(86)
Medicaid	4 (10)	4 (7)	8 (8)		1(14)
Medicare	11 (28)	9 (15)	20 (20)		0
Unknown	9 (23)	16 (26)	25 (25)		0
Region, N (%)					
Utah	27 (69)	35 (57)	62 (62)	**0.04**[d]	4(57)
Non-Utah	11 (28)	14 (23)	25 (25)		3(43)
Unknown	1 (3)	12 (20)	13 (13)		0
FAB classification, N (%)					
Erythroleukemia – M6	0 (0)	4 (7)	4 (4)	0.76[d]	0 (0)
Monocytic leukemia – M5	8 (21)	14 (23)	22 (22)		0 (0)
Myeloblastic leukemia – M1	9 (23)	11 (18)	20 (20)		2 (29)
Myeloblastic leukemia – M2	12 (31)	13 (21)	25 (25)		1 (14)
Myelomonocytic leukemia – M4	5 (13)	9 (15)	14 (14)		2 (29)
Undifferentiated AML – M0	3 (8)	4 (7)	7 (7)		2 (29)
Acute megakayoblastic leukemia – M7	0 (0)	1 (2)	1 (1)		0 (0)
WHO classification, N (%)					
AML with myelodysplasia-related features	2 (5)	7 (11)	9 (9)	< **0.01**[d]	0 (0)
AML with recurrent genetic abnormalities	26 (67)	16 (26)	42 (42)		5 (71)
AML, not otherwise specified (NOS)	8 (21)	35 (57)	43 (43)		2 (29)
Myeloid proliferations related to Down syndrome	1 (3)	0 (0)	1 (1)		0 (0)
Therapy-related AML and MDS	2 (5)	3 (5)	5 (5)		0 (0)
Risk classification, N(%)					
Favorable	0 (0)	20 (33)	20 (20)	< **0.01**[d]	0 (0)
Intermediate	19 (49)	30 (49)	49 (49)		3 (43)
Adverse	20 (51)	10 (16)	30 (30)		4 (57)
Extramedullary Presentation, N (%)					
Yes	5 (13)	11 (18)	16 (16)	0.58[d]	0 (0)
CNS disease at presentation, N (%)					
Yes	2 (5)	0 (0)	2 (2)	0.15[d]	

Bold typeface indicates significance.
Favorable risk: t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-WTITD (normal karyotype) Mutated CEBPA (normal karyotype).
Intermediate-I: Mutated NPM1 and FLT3-WTITD (normal karyotype) Wild-type NPM1 and FLT3-WTITD (normal karyotype) Wild-type NPM1 without FLT3-WTITD (normal karyotype).
Intermediate-II: (9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities not classified as favorable or adverse.
Adverse: inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged -5 or del(5q); -7; abnl(17p); complex karyotype.
[a] Pre-mido FLT3-mutated vs FLT3-WT.
[b] T-test.
[c] Chi-square.
[d] Fisher's Exact test.

patients, after consolidation therapy in 79% of patients, and after salvage therapy in 14% of patients. Patients in the FLT3wt cohort, 6% received HSCT after induction therapy, 45% after consolidation, and 48% after salvage therapy. Two early mido patients received HSCT after induction, two after consolidation, and one after salvage. Response to HSCT was similar between groups, with a CRs in 90% and 77% for FLT3m and FLT3wt patients, respectively (p = 0.48). Four out of five early mido patients had a CR to HSCT (Table 2).

3.2.4. Salvage therapy

More FLT3wt patients underwent salvage therapy than FLT3m patients (56% vs. 38%, p = 0.09), and one early mido patient received salvage therapy. FLT3wt patients received salvage therapy later in therapy compared to FLT3m (343 vs. 218 days from diagnosis, p = 0.06). In addition, 33% of FLTwt patients received their first salvage therapy post-transplant compared to 21% of patients in the FLT3m cohort. The one early mido patient received salvage therapy 253 days from diagnosis prior to HSCT. FLT3wt patients were more likely to respond to salvage therapy with a CR rate of 74% compared to 40% for FLT3m patients (p = 0.05). The one early mido patient had a CR (Table 2).

3.3. Survival outcomes

Kaplan Meier survival analyses were used to estimate OS between pre-mido FLT3m and FLT3wt groups. No significant difference was

Table 2
Response rate in treatment settings.

Response criteria	FLT3m (n = 39)	FLT3wt (n = 61)	Total (n = 100)	P-value[a]	Early mido (n = 7)
Induction therapy, n (%)	**39 (100)**	**61 (100)**	**100 (100)**	**NA**	**7 (100)**
Complete remission	35 (90)	47 (77)	82 (82)	0.22[b]	6 (86)
Induction failure	4 (10)	13 (21)	17 (17)		0 (0)
Death during induction	0 (0)	1 (2)	1 (1)		0 (0)
Unknown response	0 (0)	0 (0)	0		1 (14)
Reinduction (Post-induction treatment), n (%)	**1 (3)**	**7 (11)**	**8 (8)**	0.15[b]	**0 (0)**
Complete response	1 (100)	5 (71)	6 (6)	0.90[b]	0 (0)
Induction failure (refractory/resistant disease)	0 (0)	2 (29)	2 (2)		0 (0)
Consolidation therapy (Post-induction only), n (%)	**29 (74)**	**41 (67)**	**70 (70)**	0.61[c]	**4 (57)**
Complete response maintained	24 (83)	20 (49)	44 (44)	**0.0054**[c]	3 (75)
Relapse during/following consolidation therapy	5 (17)	21 (51)	26 (26)		1 (25)
Death during consolidation	0 (0)	0 (0)	0		0 (0)
HSCT, n (%)	**29 (74)**	**33 (54)**	**62 (62)**	**0.042**[c]	**5 (71)**
Complete response	26 (90)	24 (77)	50 (50)	0.48[b]	4 (80)
HSCT Failure (relapsed/refractory disease post-transplant)	2 (7)	6 (19)	8 (8)		0 (0)
Death during HSCT	1 (3)	1 (3)	2 (2)		0 (0)
Recurrence following achieving a CR from HSCT					
Yes	6 (23)	4 (17)	10 (10)	0.73[b]	0 (0)
No	20 (77)	20 (83)	40 (40)		4 (100)
Salvage therapy (anytime during follow-up)	**15 (38)**	**34 (56)**	**49 (49)**	0.092[c]	**1 (14)**
Complete response	6 (40)	25 (74)	31 (31)	**0.045**[d]	1 (100)
Failure (refractory/resistant disease)	7 (47)	7 (21)	14 (14)		0
Death	1 (7)	1 (3)	2 (2)		0
Unknown	1 (7)	1 (3)	2 (2)		0

No complete remission included death, treatment failure or unknown response.
[a] Pre-mido FLT3-mutated vs. FLT3-WT.
[b] Fisher's Exact test.
[c] Chi-square.
[d] Complete response vs. the combination of failure and death, Fisher's Exact test, Bold typeface indicates significance.

observed between FLT3m and FLT3wt groups for overall survival (Hazard ratio = 1.56; 95% CI 0.73–3.27; p = 0.24) (Supplementary Fig. 1). A subgroup analysis of patients without HSCT showed improved OS for FLT3wt patients compared to FLT3m patients (Hazard ratio = 4.81; 95% CI 1.61–14.39; p < 0.01) (Supplementary Fig. 1a).

Cox proportional hazard models estimated the effect of demographic and clinical variables on OS and EFS between FLT3m and FLT3wt. Covariates in the OS and EFS models included age, gender, ethnicity, risk classification and presence of extramedullary disease. Covariates were included in the models dependent on model convergence and model fit. No significant difference was observed in OS between both groups (Adjusted Hazard Ratio = 0.98; 95% CI 0.41–2.34; p = 0.96). However, FLT3wt patients had lower hazard of an event compared to FLT3m patients (Adjusted Hazard ratio = 0.46, 95% CI = 0.24-0.87; p = 0.0016) (Table 3).

The median follow-up time for patients in the early mido cohort was 7.5 months (compared to 14 and 24 months for the FLT3m and FLT3wt cohorts, respectively). As a result, the survival data was immature at time of analysis. Among the seven early mido patients, all were still alive, and only one relapse had been observed at 8.3 months from index.

3.4. Health care resource utilization

The median number of inpatient visits during follow-up was five for all patients. The median duration of all inpatient visits was 63 days which can be separated into 25 days for induction, 12 days for the first consolidation, five days for the second consolidation, six days for the third consolidation, and eight days for the first cycle of salvage. Patients in the FLT3wt cohort had a higher number of health care visits compared to FLT3m during consolidation therapy (14 vs. 4 visits, p < 0.01); however, similar numbers of health care visits were observed between FLT3wt and FLT3m during induction, salvage therapy, and HSCT. The median number of outpatient visits during follow-up was 41 per patient (Table 4).

3.5. Health care charges

The majority of health care charges were attributed to the AML diagnosis (69%). Patients in the FLT3m cohort had higher mean all-cause charges compared to patients in the FLT3wt cohort by 40% (p < 0.01); similarly, FLT3m patients had a higher mean of total charges by 64% compared to the early mido cohort. Of note, the addition of midostaurin in the early mido cohort did not result in an overall increase in AML-related medication charges compared to the FLT3m cohort. For all patients, 86% of health care charges were associated with inpatient services. Total health care charges for all AML patients were distributed into facilities/technical charges (42%), physician/professional charges (35%), and pharmacy charges (23%). While the AML-related health care charges associated with facilities/technical charges and pharmacy charges were similar for FLT3m and FLT3wt patients, the physician/professional charges were higher by 137% in the FLT3m cohort compared to the FLT3wt cohort (p < 0.01) (Table 5).

4. Discussion

The prevalence of the *FLT3* mutation was 23% in this study, which is consistent with previous reports in AML patients [4,5]. A prior study analyzed treatment costs among Medicare beneficiaries newly diagnosed with AML and reported that 76% of total costs were attributable to inpatient costs [13]. We similarly estimated 82% of total median charges attributable to inpatient charges. The current study estimated HSCT as the most expensive treatment for AML, followed by induction therapy (Table 5), which is aligned with contemporary findings that allogeneic stem cell transplant is associated with higher costs than other treatments [14]. Previous research evaluated newly diagnosed AML patients from a claims database between 2006 and 2015 [15]. For induction therapy, mean costs were $145,189 for commercially insured patients with median inpatient duration at 28 days [15]. Lower induction costs were reported for Medicare beneficiaries ($85,734), and

Table 3
Overall Survival and Event-Free Survival Univariate and Multivariate Analysis.

Patient Characteristics	Number of Patients	Number of deaths	Median Survival	Unadjusted Hazard ratio (95%CI)			Adjusted Hazard ratio (95%CI)		
			OS (months)	HR	95% CI	P-value	HR	95% CI	P-value
FLT3m vs. FLT3wt	100	29	NR vs NR	1.56	0.75–3.27	0.24	0.98	0.41–2.34	0.96
Age (continuous)	100	29	NA	1.04	1.01–1.08	< **0.01**	1.05	1.02–1.09	< **0.01**
Gender (Male vs Female)	100	29	NR vs NR	1.10	0.53–2.29	0.79	1.32	0.58–2.98	0.51
Ethnicity									
Caucasian	83	20	NR	Ref			Ref		
Other	10	4	24.0	2.54	0.86–7.51	0.09	5.35	1.53–18.72	< **0.01**
Unknown	7	5	8.4	23.60	6.95–80.16	< **0.01**	31.12	8.23–117.63	< **0.01**
Risk Classification- molecular and cytogenetic data									
Favorable	20	4	NR	Ref			Ref		
Intermediate	49	14	NR	1.50	0.49–4.57	0.47	0.84	0.25–2.87	0.78
Poor	31	11	NR	2.00	0.63–6.29	0.24	1.63	0.41–6.47	0.49
Extramedullary Presentation									
Yes vs No	100	29	NR vs NR	1.13	0.43–2.97	0.80	1.72	0.59–5.00	0.32
		Number of Events	EFS (months)						
FLT3m vs. FLT3wt	99	62	10.9 vs 12.3, (p = 0.26)	0.73	0.43–1.24	0.25	0.46	0.24–0.87	**0.02**
Age (continuous per year of age)	99	62	NA	1.01	0.99–1.02	0.41	not included		
Gender (Male vs Female)	99	62	18.1 vs 8.4, (p = 0.03)	1.77	1.07–2.96	**0.03**	1.70	1.01–2.90	**0.05**
Ethnicity									
Caucasian	82	50	13.6	Ref			Ref		
Other	10	7	7.4	1.65	0.68–3.46	0.25	2.45	0.96–5.52	0.06
Unknown	7	5	6.5	3.13	1.05–7.57	**0.04**	3.06	1.01–7.60	0.48
Risk Classification- molecular and cytogenetic data									
Favorable	31	19	22.1	Ref			Ref		
Intermediate	48	32	8.7	1.69	0.88–3.52	0.12	1.70	0.85–3.63	0.13
Poor	31	19	10.2	1.56	0.75–3.41	0.23	3.07	1.28–7.56	**0.01**
Extramedullary Presentation									
Yes vs No	99	62	8.7 vs 12.3, (p = 0.31)	1.79	0.93–3.23	0.08	1.93	0.95–3.70	0.07

EFS: event-free survival, HR: Hazards ratio, NA: Not available, NR: Not reached, OS: Overall survival.

median inpatient duration was 31 days [15]. In our study, the median inpatient duration was 25 days, and health care charges were in line with previous reports for commercially insured patients. The health care charges used in our study are defined as the amount that the health care provider bills the payer and is typically higher than the actual costs incurred by the provider. The Center for Medicaid and Medicare Services has published a charge-to-cost ratio of 0.492 in 2013 [16]. However, this ratio is based solely on Medicare data and is limited in its applicability to the specific diagnosis-related groups (DRGs) used for our patients. It is expected that percent differences with charge data reported in this study will be the same as the percent differences for the actual cost data.

In our study, a comparison of OS between FLT3m and FLT3wt patients showed a non-significant difference (HR: 1.56, p = 0.24).

Table 4
Median Health Care Utilization by *FLT3* Status.

Utilization	FLT3m (N = 39) Median (Q1,Q3)	FLT3wt (N = 61) Median (Q1,Q3)	Overall (N = 100) Median (Q1,Q3)	p-value*	Early mido (N = 7) Median (Q1,Q3)
AML related					
No. of Inpatient visits	5 (4,6)	6 (4,9)	5 (3,7)	0.10	9 (3,10)
Duration of hospital stays (days)	74 (58,93)	76 (49,113)	63 (46,94)	0.91	57 (41,65)
No. of Outpatient visits	47 (31,75)	51 (24,87)	41 (7,74)	0.40	50 (27,89)
No. of Emergency room visits	0 (0,0)	0 (0,0)	0 (0,0)	0.40	0 (0,0)
Non-AML related					
No. of Inpatient visits	0 (0,1)	0 (0,1)	0 (0,1)	0.85	0 (0,1)
Duration of hospital stays (days)	15 (8,31)	15 (8,52)	15 (8,39)	0.71	14 (7,21)
No. of Outpatient visits	4 (2,12)	7.5 (3,17)	5 (2,14)	0.08	4 (0,8.5)
No. of Emergency room visits	0 (0,0)	0 (0,0)	0 (0,0)	0.84	0 (0,3)
Overall by Treatment setting (visits)					
Induction	1 (1,1)	1 (1,2)	1 (1,2)	0.54	2 (1.5,2.5)
Post-induction	2 (2,2)	1 (1,1)	1 (1,1)	0.04	0 (0,0)
Consolidation	4 (1,8)	14 (5,23)	7.5 (2,16)	< **0.01**	9.5 (6,10)
Conditioning	1 (1,1)	1 (1,1)	1 (1,1)	0.70	1 (1,1)
HSCT	1 (1,2)	1 (1,1)	1 (1,2)	0.78	1 (1,2)
Salvage	3.5 (1,12)	2 (1,5)	2 (1,7)	0.38	13 (2,74)

Q1 is the lower quartile, Q3 is upper quartile, interquartile range (IQR) is Q1-Q3.
* p-value calculated using Wilcoxon rank sum test between pre-mido FLT3-mutated and FLT-WT.

Table 5
Comparison of Mean health care charges by FLT3 Status and Initial Treatment Setting.

	FLT3m			FLT3wt			% difference[a]	P-value*
	N	Mean charges (SD)	Median charges	N	Mean charges (SD)	Median charges		
All-cause								
Overall	39	$1,371,645 (1,013,109)	$1,006,054	61	$982,279 (1,019,769)	$655,046	39.64%	< **0.01**
Induction	38	$367,656 (278,100)	$273,815	59	$190,530 (128,303)	$153,451	92.97%	< **0.01**
Consolidation	30	$26,007 (18,225)	$23,861	43	$23,482 (23,126)	$16,895	10.76%	0.17
Salvage	15	$1,311,047 (2,572,189)	$192,143	34	$311,983 (214,748)	$214,748	320.23%	0.94
HCT	26	$404,113 (212,769)	$378,680	27	$450,675 (664,402)	$274,588	−10.33%	0.12
AML-related								
Overall	39	$941,531 (523,799)	$847,795	61	$695,417 (543,449)	$565,497	35.39%	< **0.01**
Induction	38	$366,742 (278,539)	$273,815	59	$182,722 (132,984)	$151,063	100.71%	< **0.01**
Consolidation	30	$26,007 (18,225)	$23,861	43	$23,482 (23,126)	$16,895	10.76%	0.17
Salvage	15	$880,035 (2,159,763)	$109,475	34	$299,633 (389,761)	$195,376	193.68%	0.60
HCT	26	$315,445 (241,579)	$271,191	27	$290,585 (342,100)	$236,805	8.56%	0.38

N: number of patients that received each type of treatment.
* P-values calculated for mean charges using Kruskal-Wallis test.
[a] FLT3wt = reference, % difference calculated as FLT3m/FLT3wt for mean charges (A positive % represents higher cost in FLT3m group.

However, when non-transplant patients were compared, FLT3wt patients had significantly longer OS (HR: 4.81, P < 0.01). These results support the claim that stem cell transplant ameliorates the prognostic impact of the *FLT3* mutations [17]. The economic analysis demonstrated that patients in the FLT3m cohort received significantly fewer cycles of consolidation therapy and proceeded to HSCT earlier and more often compared to FLT3wt patients. Likewise, FLT3m patients were associated with higher health care charges. The increase in health care charges reflect the increased utilization of transplant and could also be attributed to FLT3m patients being billed under a diagnosis-related group (DRG) with major complications.

An international study reported mean utilizations of approximately 7 outpatient visits, 5 days of inpatient hospitalization, and less than 1 ICU or ED visit per month for patients with AML [18]. These utilization results are similar to the utilization data collected in our study. Likewise, the real-world treatment patterns of AML patients across the globe are similar to those reported in our study with the majority of both *FLT3* mutated and wild type newly diagnosed AML patients receiving standard-to-intermediate dose cytarabine as first-line therapy [18]. International rates of stem cell transplant for AML patients was approximately 22% and 17% for *FLT3* mutated and *FLT3* wild type respectively; much lower than the 74% and 54% respectively found in our study at a U.S. academic cancer center [18]. The current study provides additional evidence in utilization patterns dependent on *FLT3* mutation status. Patients in the FLT3m cohort utilized stem cell transplant more frequently and earlier in therapy compared to patients in the FLT3wt cohort [18]. As a result, the FLT3m cohort reported lower median consolidation cycles than FLT3wt cohort (2 vs. 3, respectively) and fewer median days spent during consolidation treatment (33 days for FLT3m vs. 78 days for FLT3wt). These differences in treatment patterns are likely due to the different distributions of risk classifications between the FLT3m and FLT3wt cohorts.

The results of this study should be interpreted based on the standard AML practices of HCI, a Comprehensive Cancer Center and member of the NCCN, with a HSCT service. Eligibility for 7 + 3 induction therapy is based on patient specific factors including performance status, age, co-morbid conditions, and goals of care. It is standard practice for AML patients undergoing induction therapy with 7 + 3 to remain inpatient until count recovery. Clinical trial enrollment in interventional induction studies has historically be approximately 10% of AML patients. No significant changes to institutional practice has been implemented over the course of the study besides following updates to NCCN guidelines as appropriate.

This study is the first to report the clinical and economic data on early midostaurin use. The early data at HCI suggests that patients with a *FLT3* mutation who receive midostaurin are continuing to be treated with few cycles of consolidation therapy (median two cycles) and early use of HCT during therapy (median 53 days from diagnosis). As newer *FLT3* inhibitors are approved and the utilization of first-generation *FLT3* inhibitors increases, continued follow-up is needed to assess the impact on treatment patterns and healthcare utilization. This study provides early insight into the evolving treatment landscape for AML.

4.1. Limitations

The results from this study are from a single institution and may not be generalizable to a larger population of AML patients or to a geographic area where clinical practices differ. In addition, due to the small sample size and shorter follow-up time of the midostaurin group, statistical comparisons between FLT3m group and early mido group were not possible. However, presenting early data from new medications has important health policy implications.

We did not convert health care charges to health care costs which limits direct comparison to published costs in other studies. In addition, it was not possible to determine the DRGs associated with *FLT3* mutation. As a result, it was not possible to determine the discrepancies between FLT3m and FLT3wt charges, specifically with respect to physician and facility/technical health care charges.

Lastly, FLT3m patients were not stratified based on their *FLT3*-ITD allelic ratio. This stratification was not possible due to the lack of available information due to local testing practices. As a result, this study was unable to evaluate the impact of allelic ratio on clinical and economic outcomes.

5. Conclusions

Prior to approval of midostaurin, FLT3m patients received fewer cycles of consolidation therapy and experienced a shorter time to stem cell transplant than FLT3wt patients and had similar survival outcomes as FLT3wt. While these trends were also observed post-approval of midostaurin, additional patients and longer follow-up time is needed to fully evaluate the real-world treatment strategies for *FLT3*-mutated patients in the presence of *FLT3* inhibitors and the impact of these treatment strategies on clinical and economic outcomes.

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Declaration of Competing Interest

Diana Brixner is a principal of Millcreek Outcomes Group, LLC which has provided consultation to Novartis.

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References

[1] E. Estey, H. Dohner, Acute myeloid leukaemia, Lancet 368 (9550) (2006) 1894–1907.
[2] American Cancer Society, What Are the Key Statistics of Acute Myeloid Leukemia? Accessed Feb 26, 2018 (2018) https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html.
[3] National Cancer Institute. Surveillance, Surveillance, Epidemiology, and End Results Program (SEER). Cancer Stat Facts: Acute Myeloid Leukemia, Accessed January 5, 2018 (2018) https://seer.cancer.gov/statfacts/html/amyl.html.
[4] S. Frohling, C. Scholl, R.L. Levine, M. Loriaux, T.J. Boggon, O.A. Bernard, et al., Identification of driver and passenger mutations of FLT3 by high-throughput DNA sequence analysis and functional assessment of candidate alleles, Cancer Cell 12 (6) (2007) 501–513, https://doi.org/10.1016/j.ccr.2007.11.005.
[5] D.L. Stirewalt, J.P. Radich, The role of FLT3 in haematopoietic malignancies, Nat. Rev. Cancer 3 (9) (2003) 650–665, https://doi.org/10.1038/nrc1169.
[6] J. Koreth, R. Schlenk, K.J. Kopecky, et al., Allogeneic stem cell trans- plantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials, JAMA 301 (22) (2009) 2349–2361.
[7] B. Oran, J. Cortes, A. Beitinjaneh, et al., Allogeneic transplantation in first remission improves outcomes irrespective of FLT3-ITD allelic ratio in FLT3-ITD-positive acute myelogenous leukemia, Biol. Blood Marrow Transplant. 22 (7) (2016) 1218–1226.
[8] S. Gaballa, R. Saliba, B. Oran, et al., Relapse risk and survival in patients with FLT3 mutated acute myeloid leukemia undergoing stem cell transplantation, Am. J. Hematol. 92 (4) (2017) 331–337.
[9] A.E. DeZern, A. Sung, S. Kim, et al., Role of allogeneic transplantation for FLT3/ITD acute myeloid leukemia: outcomes from 133 consecu- tive newly diagnosed patients from a single institution, Biol. Blood Marrow Transplant. 17 (9) (2011) 1404–1409.
[10] R.F. Schlenk, S. Kayser, L. Bullinger, et al., Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation, Blood 124 (23) (2014) 3441–3449.
[11] RYDAPT (Midostaurin) for Oral Use, Silver Spring, US Food and Drug Administration, MD, 2017 Accessed 16 May 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf.
[12] R.M. Stone, S.J. Mandrekar, B.L. Sanford, K. Laumann, S. Geyer, C.D. Bloomfield, et al., Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation, N. Engl. J. Med. 377 (5) (2017) 454–464, https://doi.org/10.1056/NEJMoa1614359.
[13] J. Meyers, Y. Yu, J.A. Kaye, K.L. Davis, Medicare fee-for-service enrollees with primary acute myeloid leukemia: an analysis of treatment patterns, survival, and healthcare resource utilization and costs, Appl. Health Econ. Health Policy 11 (3) (2013) 275–286, https://doi.org/10.1007/s40258-013-0032-2.
[14] A.M. Zeidan, D. Mahmoud, I.T. Kucmin-Bemelmans, C.J. Alleman, M. Hensen, B. Skikne, B.D. Smith, Economic burden associated with acute myeloid leukemia treatment, Expert Rev. Hematol. 9 (1) (2016) 79–89, https://doi.org/10.1586/17474086.2016.1112735.
[15] E.M. Stein, G. Bonifacio, D. Latremouille-Viau, A. Guerin, S. Shi, P. Gagnon-Sanschagrin, et al., Treatment patterns, healthcare resource utilization, and costs in patients with acute myeloid leukemia in commercially insured and Medicare populations, J. Med. Econ. 21 (6) (2018) 556–563, https://doi.org/10.1080/13696998.2018.1425209.
[16] Centers for Medicare & Medicaid Services, Impact File for IPPS FY 2013 Final Rule, (2019) Accessed May, 31, 2019. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Historical-Impact-File s-for-FY-1994-through-Present.html.
[17] S.O. Ciurea, Allogeneic stem cell transplantation for FLT3 mutated acute myeloid leukemia in first complete remission: does age really matter? Haematologica 103 (2) (2018) 191–193, https://doi.org/10.3324/haematol.2017.186346.
[18] J.D. Griffin, H. Yang, Y. Song, D. Kinrich, M.V. Shah, C.N. Bui, Treatment patterns and healthcare resource utilization in patients with FLT3-mutated and wild-type acute myeloid leukemia: a medical chart study, Eur. J. Haematol. 102 (4) (2019) 341–350, https://doi.org/10.1111/ejh.13205.