

Outcomes of FLT3-mutated Acute Myeloid Leukemia Patients: A Single Center Real-World Experience

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Abstract

OBJECTIVE: Real-world experience for patients with the FMS-like tyrosine kinase (FLT3) mutations in small academic institutions is scanty.

DESIGN: We reviewed retrospectively new diagnosed *FLT3*-ITD mutated acute myeloid leukemia (AML) patients from March 2015-December 2019. The median follow-up was 11.2 months [range, 1.2-48.1 months].

SETTING: All *FLT3*-ITD mutated AML patients in our institution were included irrespective of the allelic frequency.

PATIENTS OR OTHER PARTICIPANTS: Twenty-five patients with newly diagnosed *FLT3*-ITD mutated AML were identified.

INTERVENTIONS: FLT3 inhibitors (midostaurin, and gilteritinib) (FLT3is) were administered as a single agent or in combination with cytotoxic chemotherapy (CCT) or low intensity therapy (LIT) (hypomethylating agents).

MAIN OUTCOMES MEASURES: We analyzed these patients' responses to treatment, and outcomes.

RESULTS: Ten patients (40%) received CCT and 15 patients (60%) received CCT+FLT3i. The most frequently used FLT3i was midostaurin (12 patients, 48% of all patients). The complete remission rate (CR) and the overall response rate (ORR) (CR+CR with incomplete hematologic recovery [CRi]) were 32% and 84%, respectively. Among the patients who received CCT+FLT3i, CR and OOR were 46% and 93% respectively. The median duration of response in frontline *FLT3*-ITD patients who did not receive allogeneic stem cell transplantation (ASCT) was 8 months [range, 1-22 months] (87% received CCT+FLT3i). Ten patients (40%) received an ASCT (8 patients were in CR); two relapsed after ASCT (20%); one received ivosidenib and azacitidine (IDH1 mutation) after ASCT, achieved remission then received a 2nd ASCT and maintained remission after ASCT. The other one received CCT after ASCT and subsequently died of septic shock. Four patients (40%) received maintenance therapy with FLT3is after ASCT, all of them are still in remission. All patients who did not receive ASCT relapsed; 4 received gilteritinib alone (n=3) or with LIT (n=1) after relapse. CR rate was 25% and CRI 50%; two patient relapsed (50%), and two patients (50%) subsequently received ASCT. The median overall survival for all patients was 9.2 months versus 22.8 months for patients who received ASCT.

CONCLUSIONS: Combination of FLT3i based therapy with CCT is effective therapy in *FLT3*-ITD frontline patients in real-world setting. Duration of response is short in the absence of ASCT.

Background

Internal tandem duplications (ITDs) within the FMS-like tyrosine kinase 3 (*FLT3*) gene (FLT3-ITD) is a common driver mutation and confers a poor prognosis in patients with acute myeloid leukemia (AML) due to proliferative presentation, short remission durations and early relapse. The addition of midostaurin to induction therapy has become standard therapy in newly diagnosed *FLT3*-mutated AML. Next-generation FLT3 inhibitors (FLT3i) as gilteritinib and quizartinib are more specific, more potent, and may have fewer toxicities associated with off-target therapies but are only available in clinical trials or for salvage therapy. Real-world experience in smaller academic institutions is scanty.

Methods

- We reviewed newly diagnosed FLT3-ITD mutated acute myeloid leukemia (AML) patients at our institution from March 2015-December 2019. All patients received cytotoxic chemotherapy (CCT) with or without FLT3 inhibitors (FLT3i) in the frontline setting.
- DNA was subjected to polymerase chain reaction (PCR) amplification using primers targeting the juxtamembrane domain of FLT3, and products were analyzed by capillary electrophoresis.
- We analyzed the characteristics of these patients, responses to therapy, and outcomes.

Table 1: Patient characteristics

Characteristics	FLT3-ITD mu patients (N=25)
	N (%) / Median [range]
Age	48 [18-76]
Male	13 (50)
Follow up (months)	11.2 [1.2-48.1]
Bone marrow Blasts	75 [20-91]
De Novo AML	21 (84)
Secondary AML (s-AML)	4 (16)
Therapy related (t-AML)	3 (12)
AML evolving from AHD	1 (4)
Karyotype	
Intermediate	15 (60)
Adverse	10 (40)
Co-occurring mutations	
NPM1	11 (44)
NRAS	8 (32)
DNMT3	2 (8)
IDH1	2 (8)
FLT3Is	15 (60)
Midostaurin	12 (48)
Gilteritinib	3 (12)

FLT3: FMS-like tyrosine kinase 3; FLT3i: ITDs: Internal tandem duplications; mu;mutated; AML: acute myeloid leukemia; AHD; antecedent hematological disorder; FLT3Is: FLT3 inhibitors.

Results

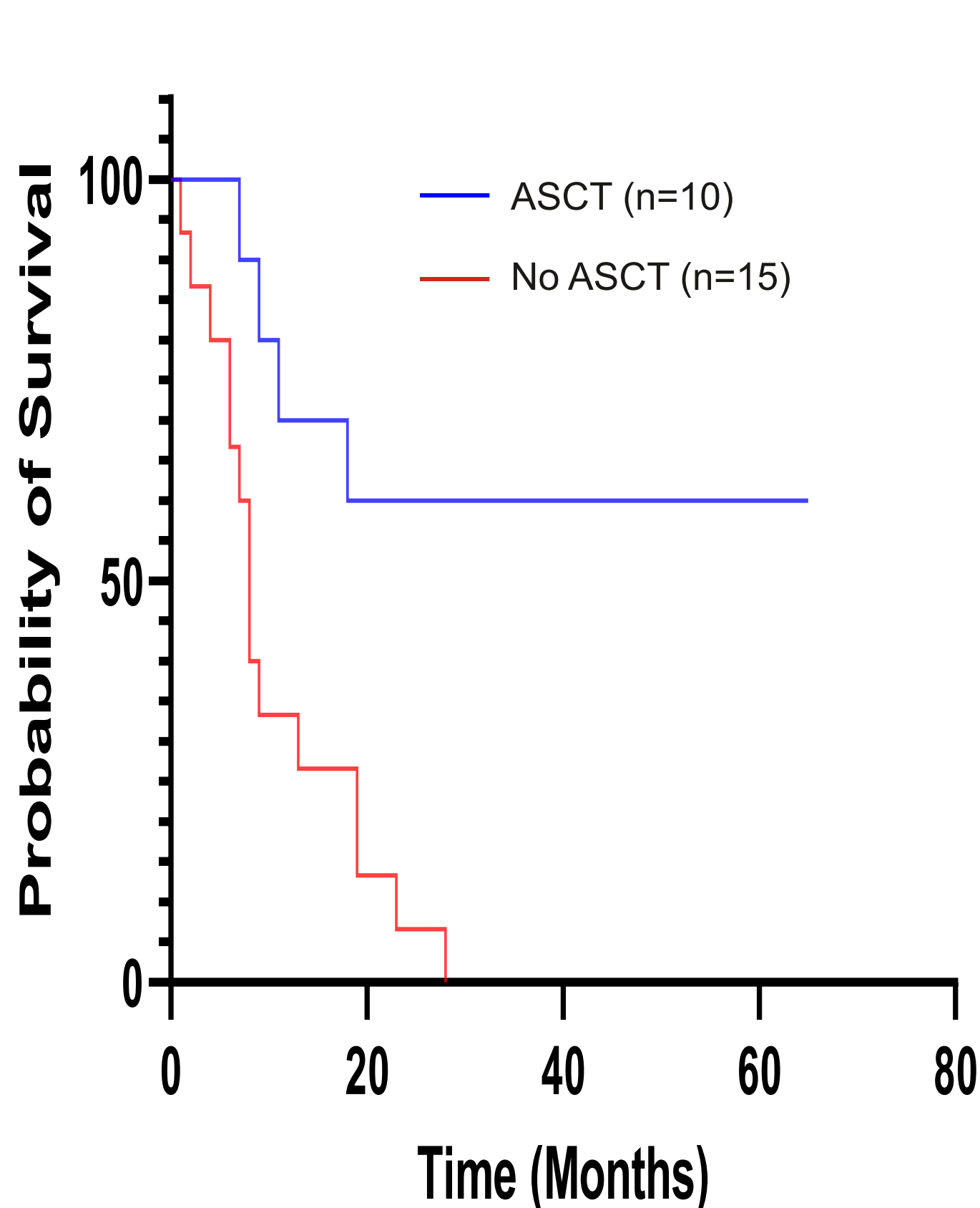
Table 2:Patient outcomes

Inhibitor/Treatment	FLT3-ITD mu patients (N=25)
	N (%)
CCT + FLT3Is	N=15
CR	7 (46)
CRi	7 (46)
CR/CRi	14 (92)
CCT	N=10
CR	1 (10)
CRi	6 (60)
CR/CRi	7 (70)
ASCT	10 (40)
MRD	4 (16)
MUD	3 (12)
HIT	2 (8)
DCT	`1 (4)

FLT3: FMS-like tyrosine kinase 3; ITD: internal tandem duplication; FLT3Is: FLT3 inhibitors; CCT: cytotoxic chemotherapy; CR: complete remission; CRi: complete remission without count recovery; ASCT: allogeneic stem cell transplantation; MRD: match related donor; MUD: match unrelated donor; HIT: Haploidentical transplant DCT: dual cord transplant.

- Time from AML diagnoses to FLT3 detection: 4 days [range, 3-5 days].
- There was no statistically significant difference in response in patients with NPM1 mutation compared with patients with NRAS mutation (P=0.6). There was no statistically significant difference in response in patients with FLT3-ITD alone compared with patients with FLT3-ITD and other concurrent mutations.
- Ten patients (40%) received an allogeneic stem cell transplantation (ASCT) (6 had only FLT3 mutation)
 - 2 relapsed after ASCT (20%); both had received FLT3 inhibitors (FLT3i) before ACST
 - One received ivosidenib and azacitidine (IDH1 mutation) after ASCT, achieved remission then received a 2nd ASCT and maintained remission after ASCT.
 - One received cytotoxic chemotherapy (CCT) after ASCT and subsequently died of septic shock.
 - Four patients (40%) received maintenance therapy with FLT3is after ASCT; all are still in remission.
- All patients who did not receive ASCT relapsed; 4 received gilteritinib alone (n=3) or with low intensity therapy (LIT) (n=1) after relapse (2 received CCT, and 2 received CCT+midostaurin in the frontline).
 - CR rate was 25% and complete remission without count recovery (CRI) 50%; two patient relapsed (50%), and two patients (50%) subsequently received ASCT (Both are still in remission).

Figure 1: Overall survival



Conclusions

- Combination of FLT3 inhibitors with cytotoxic chemotherapy is highly effective in a real-world setting with high response rates.
- Allogeneic stem cell transplantation (ASCT) after FLT3-based therapy is effective in achieving durable remissions in most patients with FLT3-mutated AML.
- Duration of response is short in the absence of ASCT.
- Coexistence of other mutations had no impact in outcome in this small sample of patients, possibly due to small numbers.
- Gilteritinib was effective in the salvage setting and allowed patients to be bridged to ASCT.

References

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Disclosures

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