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The role of FLT3 inhibitors as maintenance therapy following hematopoietic stem cell transplant

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ABSTRACT

Activating mutations in FLT3 in acute myeloid leukemia (AML) portend a poor prognosis, and targeting FLT3 with a tyrosine kinase inhibitor has been an area of intense research recently. Most FLT3 mutated AML patients undergo hematopoietic stem cell transplantation (HSCT) as standard of care but a significant proportion of patients relapse. Although the use of FLT3 inhibitors in the pre-HSCT perspective is more clearly defined, its use in the post-HSCT scenario, when most relapses occur, remains unclear. In this review, we comprehensively present the data on the recent and ongoing studies evaluating the role of various FLT3 inhibitors in AML with a particular focus in the post-HSCT setting.

1. Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults with an incidence of 3 to 4 cases per 100,000 per annum [1]. The prognosis for AML is highly dependent upon the patient's clinical and molecular characteristics, including cytogenetic aberrations, with complete remission (CR) rates ranging from 40–80% [2].

One of the most common mutations detected in AML and represents a promising target for therapy, is the "FMS"-like tyrosine kinase 3 (FLT3) [3,4]. FLT3 belongs to the class III tyrosine kinase receptor family and plays a key role in early hematopoietic development. FLT3 regulates the growth and differentiation of CD34+ hematopoietic cells *via* multiple signaling pathways, including PI3 kinase-Akt, Ras-MAPK and STAT5a, and dysregulation of these pathways leads to increased proliferation and decreased apoptosis [3,5,6].

Activating mutations in FLT3 are present in about 30% of newly diagnosed AML patients, with the internal tandem duplications (ITD) within the juxtamembrane domain of FLT3 being the most common type, representing about 20–30% of newly diagnosed patients with AML. Activating mutations in the FLT3 tyrosine kinase domain (TKD), particularly at the activation loop residue D835 (FLT3-D835), are found in about 7% of newly diagnosed AML, and has been associated with increased clinical resistance to certain FLT3 inhibitors and contribute to disease relapse with tyrosine kinase inhibitor (TKI) therapy [3,7,8]. Furthermore, the detection of FLT3 mutation in AML portends a poor prognosis, with lower rates of CR, shorter disease free survival (DFS), and shorter event free survival (EFS) compared to patients with wild type FLT3 (FLT3-WT) [7].

To date, more than 20 different small molecule TKIs of FLT3 have been reported in literature and many have advanced to phase 2 and 3 clinical trials. A number of them have also shown promising results in clinical trials involving patients with FLT3-ITD+ AML [3,9]. Midostaurin, an orally bioavailable multikinase inhibitor with activity against FLT3, is among the most studied [10–13]. Recently, Stone et al. demonstrated a significant improvement in overall survival (OS) in newly diagnosed FLT3+ AML by adding Midostaurin to standard chemotherapy and this triggered the approval of Midostaurin by U.S. Food and Drug Administration (FDA) for treatment of untreated AML in induction and consolidation phase [14].

Allogeneic hematopoietic stem cell transplant (alloHSCT) is often recommended for patients with FLT3-ITD+ AML due to poor prognosis but the presence of FLT3-ITD also portends a poor post-transplant outcome [15]. As an attempt improve post-transplant outcomes and reduce rates of relapse, clinicians include various tyrosine kinase inhibitors (TKIs) that block the constitutively active FLT3 to the pre-

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transplant treatment regimens [9]. However, it currently remains unclear whether FLT3 inhibitors in the post-alloHSCT setting would also improve outcomes in patients with FLT3 mutations. Here, we provide an overview of the current clinical data on FLT+ AML and the role of FLT3 targeted treatment with a focus on the post-transplant setting.

2. Outcomes of post-transplant patients with FLT3 mutations

Patients with FLT3-ITD AML tend to have a poor outcome despite hematopoietic stem cell transplant (HSCT) with higher rates of relapse. Through a retrospective study of 171 patients who had undergone FLT3-ITD testing, Song et al. 2016 reported a higher incidence of relapse (HR 3.63; $p < 0.001$) at 3-year follow-up with nearly twice the relapse rate (FLT3+ 63% vs. FLT3− 37%, $p < 0.001$), and a shorter DFS (HR 2.05; $p < 0.01$), which translated to a decreased OS (HR 1.92; $p < 0.05$) in patients with FLT3-ITD compared to FLT3-WT [16].

Many investigators have noticed that HSCT, both alloHSCT and autologous hematopoietic stem cell transplant (autoHSCT) compensate for the negative prognostic effect of FLT3-ITD on OS. In a retrospective analysis of 376 patients (31.5% FLT3-ITD) with intermediate-risk AML treated with two cycles of high dose cytarabine (HiDAC) for induction therapy, 103 patients underwent alloHSCT with a matched sibling donor, 141 patients underwent alloHSCT with a matched unrelated donor (if there was no matched sibling donor) and 132 patients underwent conventional consolidation chemotherapy with two cycles of HiDAC (patients with failure to identify successful donor). Investigators found that FLT3-ITD patients receiving conventional chemotherapy for consolidation therapy had a significantly inferior probability of survival (FLT3-ITD 21% vs. FLT3-WT 46%; hazard ratio [HR] = 2.2; $p = 0{,}001$) and significantly higher probability of relapse (FLT3-ITD 94% vs. FLT3-WT 59%; HR = 4.0; $p < 0.001$) when compared to their FLT3-WT counterparts, confirming the poor prognostic indicator for patients with FLT3-ITD AML. However, when FLT3-ITD patients were compared to FLT3-WT patients after having undergone autoHSCT or alloHSCT, there was no longer a significant difference in OS. The authors suggested until alternative strategies are introduced, autoHSCT or alloHSCT seem to be warranted to negate the poor prognostic impact of FLT3-ITD mutation [17]. Similar conclusions that autoHSCT and alloHSCT may overcome the poor prognostic implications of FLT3-ITD mutation, has been confirmed by multiple other retrospective studies as well [18–20].

3. Overview of FLT3 inhibitors

Although alloHSCT is recommended in FLT3-ITD AML due to its association with poor prognosis, the prognosis remains poor with high rate of early relapse and up to 50% of deaths post HSCT from primary disease relapse [21]. Therapeutic options for patients who relapse post-alloHSCT is limited, so many researchers are looking into strategies to prevent post-transplant relapse with FLT3 inhibitors as maintenance therapy [22].

The first generation FLT3 inhibitors, including Sorafenib (BAY43-9006), Midostaurin (PKC412) and Lestaurtinib (CEP-701), are relatively nonspecific for FLT3 [23]. They were initially designed to target other receptor tyrosine kinases (RTK) such as KIT, platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor (VEGF), and Janus kinase 2 (JAK2), but have been found to have activity against FLT3 [24].

Sorafenib is a first generation, orally bioavailable multikinase inhibitor that has been FDA approved for hepatocellular, thyroid and renal cell carcinomas. It has been shown to have activity against several RTKs such as FLT3, VEGF, PDGFR, and Raf family kinases, and has been studied in multiple clinical trials for FLT3+ AML. Sorafenib monotherapy produced reduction in peripheral blood and bone marrow blasts in relapsed and refractory (r/r) AML with FLT3-ITD, but not FLT3-WT, and CRs were rare [25,26,62,68]. In a phase 2 study with 37 patients with FLT3+ (93% FLT3-ITD), relapsed or refractory AML, the combination of Sorafenib with the hypomethylating agent, 5-azacitidine, produced an overall response rate (ORR) of 46% with CR in 16%, complete remission with incomplete count recovery (CRi) in 27%, and partial remission (PR) in 3% of patients. However, the responses were not durable, lasting only a median of ~2.3 months [26]. When combined with standard chemotherapy, Sorafenib was not shown to have a significant improvement in event free survival (EFS) or OS and had lower CR rates with higher toxicity in older patients (≥60 years) [27]. In younger patients (< 60 years), however, Sorafenib was found to have improved EFS and relapse free survival (RFS). A CR rate as high as 100% including patients with CR with incomplete platelet recovery (CRp) have been reported but relapse rates were also high without durable responses. The most common side effects seen with Sorafenib therapy were grade 3/4 cytopenias, infection, skin toxicity and GI upset [28–30].

Midostaurin is also an orally bioavailable multikinase inhibitor with activity against FLT3, VEGF, PDGFR and c-KIT [31]. As monotherapy, Midostaurin had high response rates of up to 70% in patients with FLT3+ AML, but a poor rate of CR (0–5%) was seen [3,11,12]. In combination with hypomethylating agents for adult patients with r/r AML, the CR rates including CRi were also low, ranging from 2 to 25% [32,33]. However, in combination with cytotoxic chemotherapy, the CR rate was as high as 92% in newly diagnosed and 50% in r/r FLT3+ AML patients [13,34]. In a multicenter, international, phase III, placebo-controlled randomized controlled trial (RCT) (RATIFY trial), Stone et al. 2017 looked at 717 patients (aged 18–59 years) with FLT3+ AML who had received Midostaurin or placebo with induction and consolidation chemotherapy and those who were in remission after consolidation received either Midostaurin ($n = 360$) or placebo ($n = 357$) as maintenance therapy. They found that there was no difference in CR between the two arms (Midostaurin 59% vs. placebo 54%; $p = 0.15$) but the median OS was significantly superior in Midostaurin arm (Midostaurin 74.7 mo vs. placebo 25.6 mo; $p = 0.009$) and the median event-free survival was also significant superior in the Midostaurin arm (Midostaurin 8.2 mo vs. placebo 3.0 mo; $p = 0.002$) [14]. On April 28, 2017, the FDA approved Midostaurin for the treatment of adult patients with newly diagnosed FLT3+ AML in combination with chemotherapy. The most common adverse events included GI upset and increased risk of infections.

Lestaurtinib is an orally bioavailable, multikinase inhibitor with activity against FLT3, JAK2 and tropomyosin receptor kinase (Trk) A, TrkB and TrkC. Lestaurtinib was one of the earliest TKI studied and has been investigated in multiple clinical trials as monotherapy, especially in older patients unsuitable for intensive chemotherapy, and in combination with chemotherapy. However, studies did not show promising results. As monotherapy, Knapper et al. looked at 29 older patients with untreated AML irrespective of FLT3 status, who were considered not fit for intensive chemotherapy, in a multicenter, open-label, prospective, phase 2 clinical trial [35]. 6.9% of the patients had FLT3-ITD mutations, 10.3% had FLT3-TKD mutations and the rest were FLT3-WT. Response was evaluable in 27 patients and clinical response was evident in 30% of patients, including hematologic response (HR) and bone marrow response (BMR), defined as reduction of more than 50% bone marrow blasts), but no patients achieved complete remission (CR) or partial remission (PR). 60% of patients harboring FLT3 mutations had a response compared to 23% of FLT3-WT patients, but the difference in response rates did not meet statistical significance. The investigators then looked at the addition of Lestaurtinib to first-line chemotherapy in 500 patients with FLT3+ AML in a multicenter, open-label, prospective, phase 3 RCT [36]. However, Lestaurtinib failed to meet its primary endpoints and no significant differences were seen in either 5-year OS (Lestaurtinib 46% vs. control 45%; hazard ratio, 0.9; $p = 0.3$) or 5-year relapse free survival (Lestaurtinib 40% vs. control 36%; hazard ratio, 0.88; $p = 0.3$). Investigators hypothesized that the lack of response with Lestaurtinib was related to its complex pharmacokinetics, making it difficult to maintain at a biologically effective level [23].

Table 1
Post-transplant trials.

Trial	Study type	# of patients +characteristics	Treatment	TKI/dosage	Outcomes	Side effects
Schlenk et al. (NCT01477606) [59]	Interventional, treatment, single arm, prospective, Phase II clinical trial	40 patients (aged 18–70yo) with newly diagnosed FLT3-ITD + AML received maintenance post alloHSCT with Midostaurin	Induction: daunorubicin (60 mg/m^2, days 1–3) and cytarabine (200 mg/m^2, continuously, days 1–7) Consolidation: alloHSCT	Induction: Midostaurin 50 mg BID starting D8 Consolidation: Midostaurin 50 mg BID starting D6 after alloHSCT Maintenance: Midostaurin 50 mg BID for 1 year starting 30–100d after alloHSCT	Low cumulative incidence of relapse Relapse Post-AlloHSCT: - 12% low ratio - 5% high ratio	Grade 3/4 AE attributed to Midostaurin included GI and infections
Maziarz et al. (NCT01883362) RADIUS trial [60]	Interventional, prevention, single arm, randomized, prospective, Phase II clinical trial - Safety trial	56 patients (aged 18–60years) with FLT3-ITD mutations randomized to receive SOC (n = 28) or Midostaurin + SOC (n = 28) after alloHSCT	Study treatment started 28–60d after alloHSCT and SOC dictated by treating physician	Midostaurin 50 mg BID in Midostaurin arm continuously for ≤12 mo	SOC arm: - 64% stopped treatment Midostaurin arm: - 68% stopped treatment	SOC arm: - Fatigue (29%) - AST elevations, headache, nausea and vomiting (all 25%) - Gr3/4 nausea, HTN - 57% GvHD Midostaurin arm: - Nausea and vomiting (both 64%) and diarrhea (43%) - Gr3/4 diarrhea, elevated ALT, neutropenia (11%/ea), and decreased platelets (18%) - 64% GvHD
Sandmaier et al. (NCT01468467) [61]	Interventional, treatment, single arm, prospective, Phase I clinical trial - Safety trial	13 patients (age ≥ 18years) with FLT3-ITD mutations, in remission, enrolled to 40 mg (n = 7) or 60 mg (n = 6) daily of Quizartinib after alloHSCT	Patients were given Quizartinib daily in 28d cycles. Toxicities were assessed after 2 cycles and patients were allowed to continue up to max 24 cycles	DL1: Quizartinib 40 mg qday in continuous 28d cycles DL2: Quizartinib 60 mg qday in continuous 28d cycles	DL1: grade 3 gastric hemorrhage which resolved and patient was allowed to continue on dose reduced 30 mg qday - 1/7 patients relapsed DL2: grade 3 anemia and was able to continue on dose reduced 30 mg qday - 0/6 patients relapsed	3 subjects discontinued due to AE - grade 4 neutropenia - grade 2 corneal epithelium defect - grade 4 autoimmune hemolysis Most common AE: - Diarrhea (38%), neutropenia (31%), nausea (23%), leukopenia (23%)
Metzelder et al. [62]	Interventional, treatment, single arm, prospective, study; compassionate-use basis, not clinical trial	6 patients with R/R FLT3-ITD + AML treated before (n = 3) or after (n = 3) alloHSCT on a compassionate-use basis in the absence of alternative therapeutic options	Patients followed up for median duration 158d post alloHSCT	Sorafenib 400 mg BID; dose-adjusted for toxicities/cytopenias or resistance	- 2/6 patients developed Sorafenib resistance (1/2 treated post-alloHSCT) - 2/6 patients obtained ongoing CMR (1/2 post-alloHSCT)	- Grade 3/4 neutropenia and thrombocytopenia - Pneumonia, hemolysis, sepsis, hand-foot syndrome, hyperkeratosis - 2/6 GvHD of skin, intestines, joints, polyserositis
Metzelder et al. [63]	Retrospective study	65 patients with FLT3-ITD + , relapsed AML (36relapse after conventional chemotherapy, 29 relapsed after alloHSCT)	CT: - 19pts standard dose Sorafenib - mean dose 486.5 mg qday Sorafenib alloHSCT: - 23pts standard dose Sorafenib - mean dose 600 mg qday Sorafenib CMR = CR + FLT-ITD negativity by qPCR	Standard dose Sorafenib: 400 mg BID - CT: mean treatment duration 74d - alloHSCT: mean treatment duration 76d	64/65 achieved HR (n = 54) or PR (n = 10) - CMR 24% alloHSCT vs CMR 8% in CT Secondary resistance to Sorafenib 24% in CT vs 8% in alloHSCT Sorafenib bridged one relapsed and 6 primary refractory patients to alloHSCT Time to treatment failure significantly shorter in CT than alloHSCT (p = 0.0305)	- Grade 3/4 cytopenias (n = 19), infection (n = 8), skin toxicity (n = 6), hand-foot syndrome (n = 3), mucositis (n = 5), neurotoxicity (n = 1), cardiac decompensation (n = 1) - GI bleed, HTN, angina, intracranial bleed - Fatal in 10 patients

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Table 1 (*continued*)

Trial	Study type	# of patients +characteristics	Treatment	TKI/dosage	Outcomes	Side effects
Metzelder et al. [54]	Observational study, retrospective	29 patients with FLT3-ITD + treated with Sorafenib at relapse post alloHSCT	Patients given Sorafenib as maintenance therapy	Standard dose Sorafenib: 400 mg BID	- 6/29 (21%) still alive at a median follow-up of 7.5years - 5/29 (17%) achieved sustained complete remissions - 4/5 patients in treatment-free remission for median 4.4years	- skin/GI toxicities, hyperkeratosis, MI
Sammons et al. [64]	Retrospective study	13 patients (age > 18) with FLT3-ITD + AML	Patients received Sorafenib for > 4wks in pre-transplant (n = 5), post-transplant setting (n = 4) or both (n = 4)	Standard dose Sorafenib: 400 mg BID	7/13 in CR at median 510d follow up since induction (3before, 3after, 1 both)	- Transaminitis, cytopenias, infections, GvHD
Sharma et al. [65]	Retrospective study	16 patients with FLT3-ITD + AML who relapsed after alloHSCT treated with Sorafenib (n = 8) vs in combination with chemotherapy (n = 8) 4/16 had second transplant prior to Sorafenib therapy	Sorafenib alone: Sorafenib given on a 3-week cycle with either 5d on therapy and 2d off weekly or 14d on and 7d off Sorafenib combo: Sorafenib given with cytarabine and idarubicin (n = 7) or azacitidine (n = 1)	Sorafenib alone: Sorafenib 400 mg BID (n = 6) or 600 mg BID (n = 2) - Median duration treatment 39d Sorafenib combo: 400 mg qday (n = 4) or 400 mg BID (n = 4) with chemo - Median duration treatment 7d	9/17 patients had pre and post Sorafenib bone marrow aspirates - 3/9 PR (2 sorafenib alone and 1 in combo) Remaining 7/16 had PD apparent from peripheral blasts Circulating blasts decreased in 80% of patients - Median absolute reduction in peripheral blasts was 50% Median OS 83d	Sorafenib alone: 4 developed grade ≥2 AE including grade 2 increase in ALT, grade 3 fatigue, grade 3 diarrhea, grade 3 hyperbilirubinemia
Liegel et al. [66]	Case series	2 patients with FLT3-ITD + AML who relapsed post-alloHSCT treated with Sorafenib	Patient 1 relapsed 180d post alloHSCT, failed IL-15 clinical trial, initially started on quizartinib then switched to Sorafenib then treated with DLI 65d after Sorafenib Patient 2 relapsed 8d post alloHSCT and started rapidly on Sorafenib	Not reported	Patient 1 achieved CMR and remains in remission 5mo post Sorafenib and 3 mo post DLI Patient 2 achieved CMR and remains in remission 6mo post Sorafenib	Not reported
Chen et al. (NCT01398501) [67]	Interventional, treatment, single arm, prospective, Phase I clinical trial	22 patients (20–67yo) with FLT3-ITD + AML in CR1 (n = 16), CR2 (n = 3) or refractory (n = 3) given Sorafenib maintenance post-alloHSCT	Sorafenib started between 45–120d post-alloHSCT, given daily in 28d cycles by continuous dosing for at least 12 cycles with median followup 16.7 mo post-alloHSCT	3 + 3 design study with 3 escalating doses of Sorafenib: - Dose level 1: 200 mg BID (n = 3) - Dose level 2: 400 mg qAM, 200 mg qPM (n = 3) - Dose level 3: 400 mg BID (n = 16)	3/22 patients relapsed (2/3 initially refractory) Entire cohort: 2-year: PFS is 72% (49%–86%); OS is 78% (51%–91%) Patients in CR1/CR2: 2-year: PFS is 86% (90% CI, 61%–96%); OS is 78% (51%–91%)	1 patient developed GvHD after starting Sorafenib and 4 patients developed prior to starting Sorafenib (but did not flare after starting Sorafenib) Nephrotic syndrome, weight loss, GI symptoms, tongue and facial swelling, rash, cytopenias, HTN, transaminitis, hand-foot syndrome, dyspnea, headache, peripheral neuropathy, pericardial effusion
Safaian et al. [68]	Case report	One 43yo patient received Sorafenib after relapse 4mo post alloHSCT	Patient was treated with Sorafenib starting 373d post-HSCT	Sorafenib 400 mg BID dose reduced to 400 mg qday 100d later	Patient remained qPCR neg for FLT3-ITD and in CMR 225d after starting Sorafenib	Localized GvHD of skin Asymptomatic tachycardia, grade II thrombocytopenia, 5 fold elevation in AST and ALT

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Table 1 (*continued*)

Trial	Study type	# of patients +characteristics	Treatment	TKI/dosage	Outcomes	Side effects
Brunner et al. [53]	Retrospective study	81 patients with FLT3-ITD AML in CR1 who underwent alloHSCT and received Sorafenib as maintenance (n = 26) or did not receive Sorafenib (control group; n = 55)	Median time to initiate Sorafenib was 68d post alloHSCT and median follow-up 27.2 mo post alloHSCT for Sorafenib and 38.4 mo for control group	Sorafenib 200 mg BID (n = 6), 400 mg qAM with 200 mg qPM (n = 3) and 400 mg BID (n = 17) for median 336.5d	Sorafenib maintenance had improved OS (HR for death 0.264, p = 0.021) and PFS (HR for death 0.25, p = 0.016) compared to control Sorafenib maintenance had improved 2-year OS (81% vs. 62%, p = 0.029) and 2-year PFS (82% vs. 53%, p = 0.0081). Sorafenib maintenance had lower 2-year cumulative incidence of relapse (8.2% vs. 37.7%, p = 0.0077).	7/26 developed acute GvHD (four grade 2, three grade 1) Rash, diarrhea, weight loss, cytopenias
Pratz et al. [64]	Prospective, off-label use, interventional, treatment	28 patients with FLT3-ITD AML in CR undergoing allo-HSCT who were started on Sorafenib in peritransplant period (8 pre-alloHSCT, 28 post-alloHSCT)	Patients followed up for median 450d post-alloHSCT; median duration of Sorafenib therapy is 252d	Pre-transplant Sorafenib dosing at physicians discretion but post-transplant Sorafenib started 200 mg BID between 30–120d post-alloHSCT. Some patients escalated to 400 mg BID once tolerated (n = 6)	6 patients died (3 from progression and 3 from alloHSCT complications) 5 patients relapsed (3/5 off therapy at time of relapse) 15/28 on therapy without relapse at median 450d post-alloHSCT followup	9 patients with grade ≥2 GvHD
Antar et al. [69]	Retrospective analysis	6 patients (32–58yo) with FLT3-ITD + AML who received Sorafenib as maintenance (n = 5) or treatment of relapsed disease with subsequent maintenance (n = 1) post-alloHSCT		Sorafenib 400 mg BID and adjusted based on AEs	6/6 patients in CMR at median 12mo followup since Sorafenib	5 patients developed grade II skin GvHD Increased liver enzymes, MI
Battipaglia et al. [52]	Retrospective study	27 patients with FLT3-ITD + (n = 25) and FLT3-TKD + (n = 2) AML who received Sorafenib post-alloHSCT	Patients were introduced Sorafenib at median 70d post-alloHSCT and treated for median duration of 8.4 mo	Sorafenib 400 mg BID (n = 13), Sorafenib 200 mg BID (n = 13), Sorafenib 200 mg qday (n = 1)	25/27 patients in CR at median 18 mo followup - 18/25 still receiving treatment at median duration 14 mo 1year OS 92% ± 6% and 1year PFS 92% ± 5%	13 patients with GVHD (9 limited, 5 extensive) resulting in dose reduction in 5 patients and withdrawal in 1 Cytopenias, GI, cardiac, cutaneous, amylase or lipase elevations
Tarlock et al. [55]	Retrospective study	15 pediatric patients (6 - 21yo) with FLT3-ITD + AML treated with Sorafenib post-alloHSCT	All patients treated within 18 mo post-alloHSCT. 6 patients were administered Sorafenib as relapse prophylaxis and 9 patients were administered Sorafenib at time of relapse	Sorafenib max tolerated dose 200 mg BID. Median initial dosing 150 mg/m^2 qday (range 75 mg–340 mg/m^2/day)	10/15 (67%) patients alive at median followup of 21 mo from start of Sorafenib 8/10 remain in CR with median survival 3.7years from HSCT - 4/8 in CR from Sorafenib prophylaxis group 7/15 PD or recurrent disease on Sorafenib	11/15 experienced medically significant toxicities including myelosuppression (n = 3), thrombocytopenia (n = 3), GI upset (n = 2), rash (n = 4), infection (n = 2), transaminitis (n = 2), cardiac dysfunction (n = 2), palmar plantar erythrodesia (n = 2)
Salem et al. [70]	Retrospective study	10 patients (30–65yo) with FLT-ITD + and NPM1 + AML treated with Sorafenib maintenance post-alloHSCT	10patients proceeded to alloHSCT (7MRD, 3HID) and received Sorafenib as post-alloHSCT maintenance therapy Sorafenib started median 55d post-alloHSCT	Sorafenib initial dose 400 mg BID and dose adjusted per side effects	At median 12.5 mo post-alloHSCT follow-up, 9/10 patients CMR, MRD neg for both FLT3 and NPM1 1/10 patient died from severe, refractory liver GvHD 7mo post alloHSCT	Rash, hematologic toxicity 3/10 patients developed acute GVHD before sorafenib

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Table 1 (*continued*)

Trial	Study type	# of patients +characteristics	Treatment	TKI/dosage	Outcomes	Side effects
Campregher et al. [71]	Case series	3 patients with FLT3-ITD + AML relapsed post-alloHSCT treated with combination chemotherapy, DLI, Sorafenib and azacitidine	Patient 1: relapsed day +54, treated with fludarabine, cytarabine followed by DLI with Sorafenib and Azacitidine beginning 1 mo post DLI Patient 2: relapse 1 year, treated with HIDAC followed by DLI with Sorafenib and Azacitidine after count recovery from HIDAC Patient 3: relapse day + 84, treated with FLAG then FLAMSA MEL followed by DLI and azacitidine. Sorafenib started 3 mo later but discontinued due to AE. Then developed granulocytic sarcoma 2 mo later treated with radiation followed by Sorafenib maintenance	Patient 1: fludarabine 30 mg/m^2 q12h x5d, cytarabine 2000 mg/m2 q12hx5d, DLI (CD3: 1×10^7/kg), Sorafenib 400 mg BID and Azacitidine 32 mg/$m^2 \times$ 5d qmonthly Patient 2: HIDAC (cytarabine 3000 mg/m^2), DLI (CD3: 4.2×10^7/kg), Sorafenib 200 mg BID and Azacitidine 32 mg/$m^2 \times$ 5d qmonthly Patient 3: DLI (CD3: 4.7×10^8/kg), Azacitidine 32 mg/$m^2 \times$ 5d qmonthly and Sorafenib 800 mg qday initially then 400 mg qday	Patient 1: CR, 100% chimerism 28 mo after Sorafenib Patient 2: CR, 100% chimerism 17mo after Sorafenib Patient 3: CR, 100% chimerism 7 mo after Sorafenib	Squamous syringometaplasia, GI upset, severe skin reaction 3/3 developed GvHD of GI and liver, skin

Abbreviations: FLT3-internal tandem duplication (FLT3-ITD+); acute myeloid leukemia (AML); allogeneic hematopoietic stem cell transplant (alloHSCT); autologous hematopoietic stem cell transplant (autoHSCT); wild type (WT); overall survival (OS); adverse event (AE); standard of care (SOC); high-dose cytarabine (HIDAC); aspartate aminotransferase (AST); graft vs. host disease(GvHD); alanine aminotransferase (ALT); complete molecular response (CMR); complete remission (CR); partial remission (PR); hematologic response (HR); conventional therapy (CT); hypertension (HTN); progression of disease (PD); donor lymphocyte infusion (DLI); fludarabine + high-dose cytarabine + granulocyte colony-stimulating factor (FLAG); fludarabine + cytarabine + granulocyte colony-stimulating factor + amsacrine (FLAMSA MEL).

Because the initial studies for the first generation FLT3 inhibitors were not impressive and were not specifically designed to target FLT3, second-generation FLT3 inhibitors, such as Quizartinib (AC220), Gilteritinib (ASP2215) and Crenolanib (CP-868596) were created as more selective and thus potent inhibitors targeted against FLT3.

Quizartinib is currently the most specific TKI for FLT3 in investigation and also has activity against PDGFR, KIT, and colony-stimulating factor 1 receptor (CSF1R). As monotherapy, Quizartinib has shown promising results with CRc (CR + CRi + CRp) rates ranging from 23 to 54% in patients with R/R, FLT3-ITD AML in multiple phase I and phase II clinical trials [37,38]. Researchers also showed that about 35% of FLT3+ AML patients treated with Quizartinib was able to proceed to alloHSCT, many of whom had previously been refractory to other treatments [37,38]. In a phase I/II safety/efficacy trial, 26 patients with FLT3-ITD AML were given Quizartinib in combination with azacitidine (n = 18) or with low dose cytarabine (n = 8). The results were promising with 82% of patients responding to treatment and 27% in CRc [39]. Quizartinib was generally well tolerated with most common side effects being nausea, diarrhea, neutropenia and leukopenia

Gilteritinib is a selective inhibitor of FLT3 and AXL that has shown activity in FLT3+ AML. A phase I/II dose escalation trial looked at Gilteritinib as monotherapy in 182 patients with FLT3+ r/r AML. Investigators found that Gilteritinib had an ORR of 55% with a higher ORR of 60% in patients with FLT3-ITD+ AML, and a median OS of 29weeks. Gilteritinib was generally well tolerated and the main side effects were diarrhea, fatigue, increased AST, and QT prolongation [40].

Crenolanib is a TKI with activity against PDGFR and both FLT3-ITD and FLT3-TKD and is currently under investigation in phase II and III clinical trials for patients with FLT3+ AML. Collins et al. showed clinical activity of Crenolanib in 19 patients with r/r AML, including to other TKIs and alloHSCT [41]. 1/19 patient achieved rapid molecular response and clinical CR with full count recover. Moreover, 2/19 patients achieved CRi, 4 patients PR and 4 patients bridged to transplant. Most common adverse events included GI upset and transaminitis.

4. FLT3-targeted treatment in Post-transplant patients

Despite recent advances in treatment, the incidence of relapse after alloHSCT is around 30–40% at 3 years with 40–50% of deaths post-transplant due to primary disease relapse [21]. Available therapies for relapse post-transplant are limited and investigators are looking into new strategies to prevent relapse [22] and for salvage therapy after relapse.

The use of donor lymphocyte infusion (DLI) was one of the earliest reported method to induce a graft vs. leukemia effect to achieve CR in patients who relapsed post alloHSCT. The response rate is as high as 40% in patients with ALL [42] but with a high rate of fatal graft vs. host disease. Another strategy for patients who are on immune suppression is tapering the immune suppression to induce a graft vs. leukemia response. Kekre et al. found that 34 out of 123 patients responded to only the tapering of immunosuppressant's medicaitons in a median of 82 days, but 97.1% developed or had progression of their acute or chronic graft vs. host disease as a consequence [43]. The median OS for responders was 5.1 years but 6 patients subsequently relapsed at a median time of 2 years. Use of hypomethylating agents is another commonly studied approach. 5-Azacitidine [44] was generally well tolerated in the post transplant setting and had a 2 year OS of 12.4%. It has been shown to significantly increase the number of T regulatory cells and thus augmenting a graft vs. leukemia effect without increasing graft vs. host disease [45]. Several other new strategies, including the deacetylase inhibitor, panobinostat [46], the use of donor-derived NK cells [47,48] and the use of immunotherapy such as Nivolumab [49,50] and Ipilumimab [51], are currently under development to prevent relapse and as salvage therapy.

Table 2
Ongoing trials.

Drug	Trial; # of patients (*n*); status	NCT ID	Patients/Treatment	Outcome measures
Sorafenib	A pilot study of Sorafenib as peri-transplant remission maintenance; *n* = 45; active, not recruiting	NCT01578109	Patients ≥19 years with FLT3-ITD+ AML in CR/PR who plan on undergoing HSCT are given Sorafenib ≥30 days after completion of induction until 4 days before conditioning and within 120 days after HSCT for up to 2 years until progression or unacceptable toxicity	Primary: toxicity Secondary: change in FLT3 suppression and MRD, incidence of NRM and relapse, DFS, OS and pharmacodynamics parameters of Sorafenib
	Phase I/II study of sorafenib added to busulfan and fludarabine conditioning in patients with relapsed/refractory AML undergoing transplantation; *n* = 74; recruiting	NCT03247088	Patients 18–65 years with relapsed/refractory FLT3+/− AML (excluding t(8:21) or inv (16)) who are undergoing HLA-matched HSCT are given Sorafenib on D-24 through D-5 with Busulfan/Fludarabine conditioning and then Sorafenib starting between D + 30 and D + 120 for up to 1 year	Primary: MTD and efficacy of Sorafenib when combined with Busulfan/Fludarabine conditioning Secondary: toxicity, neutrophil engraftment, NRM and OS
	Phase II/III Sorafenib for prophylaxis of leukemia relapse in allogeneic HSCT recipients with FLT3-ITD positive AML; *n* = 196; recruiting	NCT02474290	Patients 18–60 years with FLT3-ITD + AML who have received alloHSCT will be given Sorafenib vs. control between D + 30 and D + 180 post-transplant	Primary: incidence of relapse Secondary: OS, leukemia-free survival, incidence of toxicity
Midostaurin	RADIUS Trial (phase II); *n* = 60; recruiting	NCT01883362	Patients 18–60 years with FLT3-ITD + AML (excluding M3) who underwent alloHSCT with match related or unrelated donor are randomized to SOC ± Midostaurin for 12 mos in the post-transplant setting	Primary: relapse free survival Secondary: disease free survival, NRM, OS, toxicity, PK of Midostaurin and its metabolites, FLT-ITD mutation status (e.g. mutant:WT)
	Phase-II study evaluating midostaurin in induction, consolidation and maintenance therapy also after AlloHSCT in patients with newly diagnosed FLT3-ITD + AML; *n* = 440; recruiting	NCT01477606	Patients 18–70 years with newly diagnosed FLT3-ITD+ AML (excluding M3, CBFB-MYH11, RUNX1-RUNX1T1 and t(8;21)(q22;q22)) are given Midostaurin during induction, consolidation, and as maintenance (post HSCT or post consolidation) for 1 year	Primary: EFS Secondary: CR rate, relapse free survival, OS, cumulative incidence of relapse, cumulative incidence of death in CR, FLT3 inhibitory activity, QOL, rates of early deaths, death in CR, toxicity, impact of alloHSCT
Quizartinib	QuANTUM-First trial (Phase III); *n* = 536; recruiting	NCT02668653	Patients 18–75 years with newly diagnosed FLT3-ITD+ AML (excluding M3 and pH+) are randomized to standard induction, consolidation ± HSCT and maintenance chemotherapy with Quizartinib or placebo	Primary: EFS Secondary: OS, CR and composite rate at end of first induction, and % of patients achieving CR with no evidence of MRD
	QuANTUM-R (Phase III); *n* = 367; active, not recruiting	NCT02039726	Patients ≥18 years with FLT3-ITD+ AML (excluding M3) in first relapse within 6 mos or refractory to prior therapy ± HSCT are randomized to Quizartinib monotherapy or salvage chemotherapy (LoDAC, MEC, or FLAG-IDA)	Primary: OS Secondary: EFS
Gilteritinib	A Multi-center, randomized, double-blind, placebo-controlled Phase III trial of the FLT3 inhibitor Gilteritinib administered as maintenance therapy following AlloHSCT with FLT3-ITD AML; *n* = 346; recruiting	NCT02997202	Patients ≥ 18years with FLT3-ITD+ AML in CR1 undergoing alloHSCT will be randomized to receive Gilteritinib or placebo between D + 30 and D + 90 after alloHSCT for 2 years.	Primary: relapse-free survival Secondary: toxicity, OS, NRM, EFS at 12 and 24 mos, cumulative incidence of acute GvHD and cumulative incidence of chronic GvHD at 12 and 24 mos, cumulative incidence of detection of FLT3-ITD MRD, incidence of severity of infection
	Phase 3 open-label, multicenter, randomized study of ASP2215 vs. salvage chemotherapy in patients with relapsed or refractory FLT3-ITD AML; *n* = 318; recruiting	NCT03182244	Patients ≥18 years with relapsed or refractory (including after HSCF) FLT3+ AML (excluding M3 and pH+) are randomized to receive Quizartinib or standard salvage chemotherapy (LoDAC, MEC or FLAG-IDA)	Primary: OS Secondary: EFS, CR, leukemia free survival, duration of CR, CRc, CRi, and CRp, composite CR rate, transplantation rate, brief fatigue inventory, toxicity, effect on laboratory testing (chemistry, hematology, coagulation, urinalysis), vital sign abnormalities, safety assessed by EKG, PK of Quizartinib through max concentration and trough, time after dosing when max concentration occurs, concentration of Quizartinib in blood, effect on ECOG status
	Phase 3 Open-label, Multicenter, Randomized Study of ASP2215 Vs. Salvage Chemotherapy in Patients With Relapsed or Refractory FLT3-ITD AML; *n* = 369; recruiting	NCT02421939	Patients ≥18 years with relapsed or refractory FLT3+ AML (excluding M3 and pH+; including after HSCT) are randomized to receive Quizartinib or standard salvage chemotherapy (LoDAC, Azacitidine, MEC or FLAG-IDA)	Primary: OS and CR and CR with partial hematologic (CRh) rate Secondary: EFS, CR rate, leukemia free survival, duration of remission, CRc rate, transplantation rate, brief fatigue inventory, CRh rate, transfusion conversion rate, transfusion maintenance rate

(*continued on next page*)

Table 2 (*continued*)

Drug	Trial; # of patients (*n*); status	NCT ID	Patients/Treatment	Outcome measures
Crenolanib	A Phase II Study of Crenolanib Besylate maintenance following AlloHSCT in patients with FLT3+ AML; $n = 48$; recruiting	NCT02400255	Patients ≥18 years with FLT3+ AML who had undergone alloHSCT are split into two cohorts (in CR at time of transplant and not in CR at time of transplant) and given Crenolanib between D + 30 to D + 90 after alloHSCT for up to 728 days	Primary: PFS Secondary: disease free survival, OS, GvHD, 100-day transplant related mortality
	Dose-finding run-in Phase I followed by a Phase III, multicenter, randomized, double-blind, placebo-controlled study of Crenolanib with chemotherapy in patients with relapsed or refractory FLT3+ AML; $n = 276$; recruiting	NCT02298166	Patients ≥18 years with relapsed or refractory (including after HSCT) FLT3+ AML are randomized to standard induction, consolidation and maintenance chemotherapy with Crenolanib or placebo.	Primary: EFS, OS Secondary: CR and CRi rates, cumulative incidence of relapse and death, QOL, rates of early deaths, toxicity

Abbreviations: Minimal residual disease (MRD); non-relapse mortality (NRM); maximum tolerated dose (MTD); event-free survival (EFS); plasma pharmacokinetics (PK); quality of life (QOL).

In patients with FLT3+ AML, TKIs are currently under investigation in the post transplant setting to prevent relapse. Table 1 summarizes the various published clinical trials and Table 2 summarizes the current, ongoing clinical trials for FLT3-targeted treatment in post-transplant patients.

Sorafenib, the TKI most studied through multiple retrospective and early clinical trials, has shown promising results for patients with FLT3-AML in the post-transplant setting. As maintenance therapy, Sorafenib was well-tolerated and showed sustained complete remissions and lower incidence of relapse in both the adult and pediatric population. Battipaglia et al. introduced Sorafenib as maintenance therapy post alloHSCT and found a 1-year OS 92% ± 6% and 1 year PFS 92% ± 5% with 93% of patients in CR at a median follow up of 18 months [52]. When Brunner et al. 2016 compared adult FLT3 mutated patients who had received Sorafenib as maintenance therapy post alloHSCT to patients who had not, they found a significant improvement in 2-year OS and PFS (OS HR for death 0.264, $p = 0.021$, and PFS HR 0.25, $p = 0.016$) [53]. They also noticed a significantly lower 2-year cumulative incidence of relapse in patients who had received Sorafenib as maintenance therapy (8.2% vs. 37.7%, $p = 0.0077$). Metzelder et al. showed that Sorafenib was even able to have a sustained response as rescue therapy in FLT3 mutated patients who had relapsed post alloHSCT with 21% patients still alive and 83% of those patients in CR at a median follow up of 7.5 years. Sorafenib was generally well tolerated and most common grade 3/4 adverse effects included skin, GI, infections and cytopenias [54]. Tarlock et al., through a retrospective study of 15 patients (≤21 years), confirmed the efficacy of Sorafenib as relapse prophylaxis and as salvage therapy at time of relapse, in the pediatric population [55]. Several other smaller, retrospective, prospective and case studies also support the use of Sorafenib as post-transplant maintenance therapy and as salvage therapy in relapsed or refractory FLT3-ITD+ AML.

The early promising data inspired larger clinical trials for Sorafenib in the post-transplant setting. A Phase II/III trial (NCT02474290) is currently underway, investigating the use of Sorafenib maintenance as relapse prophylaxis after alloHSCT in patients with FLT3-ITD+ AML. The endpoints for this trial include the incidence of relapse, OS, leukemia free survival and toxicity. The trial is expected to complete in late 2018. Sorafenib is also currently studied as a part of bulsufan/fludarabine conditioning regimen for patients with relapsed/refractory FLT3-ITD + AML undergoing alloHSCT in a phase I/II clinical trial (NCT03247088). Patients are expected to receive Sorafenib between D-24 through D-5 prior to alloHSCT and continue Sorafenib as maintenance therapy starting between D + 30 to D + 120 after alloHSCT for up to 1-year. The trial will look at the maximum tolerated dose of Sorafenib with bulsufan/fludarabine conditioning and efficacy of Sorafenib as its primary endpoint, as well as toxicity, OS, non-relapse mortality and neutrophil engraftment.

Midostaurin is another TKI that is currently under investigation in the post-transplant setting. Schlenk et al. [59] (NCT01477606) treated 40 patients with newly diagnosed FLT3-ITD AML with Midostaurin during the induction, consolidation and for 1-year as maintenance therapy post alloHSCT. They noted a low incidence of relapse in patients with both high and low FLT3-ITD mutant to wild type (WT) ratio (5% and 12%, respectively), suggesting Midostaurin is an effective maintenance therapy post-transplant, particularly in patients with high FLT3-ITD mutant to WT ratio.

The ongoing, phase 2 RADIUS trial (NCT01883362) is comparing patients with FLT3-ITD+ AML who underwent alloHSCT who received standard of care chemotherapy with or without Midostaurin for up to 1-year in the post-transplant setting. The trial's endpoints include relapse free survival, DFS and OS. Preliminary safety data from the RADIUS trial showed that Midostaurin was generally well tolerated compared to standard of care with only higher rates of grade 1/2 GI upset in the Midostaurin arm [60].

Quizartinib is also currently studied in the post-transplant setting.

Sandmaier et al. 2014 enrolled 13 patients in a phase I safety trial, looking at Quizartinib as maintenance therapy following alloHSCT. 77% of patients had received Quizartinib for over 1-year and preliminary data indicated a lower rate of relapse with only one relapse out of 13 patients. A couple of other ongoing clinical trials are evaluating the use of Quizartinib in the post-transplant setting as well. The QuANTUM-First is a phase III randomized, placebo-controlled, clinical trial (NCT02668653) looking at Quizartinib compared to placebo in patients with FLT3-ITD+ AML receiving standard induction, consolidation with or without alloHSCT, and maintenance therapy. The QuANTUM-R is a phase III RCT (NCT02039726) looking at Quizartinib monotherapy compared to standard salvage chemotherapy in patients with relapsed or refractory, including to alloHSCT, FLT3-ITD+ AML. Both trials endpoints include OS and EFS.

Gilteritinib has limited published data on its efficacy in the post-transplant setting but multiple clinical trials are currently in progress. In a phase III, double-blind, placebo-controlled clinical trial (NCT02997202) looking at Gilteritinib in the post-transplant setting, patients with FLT3-ITD+ AML in CR1 undergoing alloHSCT will be randomized to receive Gilteritinib or placebo after alloHSCT for up to 2-years. Relapse free survival, OS, non-relapse mortality, and incidence of GvHD will be examined. Two phase III, multicenter studies are also underway (NCT02421939 and NCT02400255), investigating Gilteritinib vs. standard salvage chemotherapy in patients with relapsed and refractory, including to alloHSCT, FLT3-ITD+ AML.

Finally, **Crenolanib** also has multiple clinical trials ongoing evaluating its use in the post-transplant setting. Through a phase II study (NCT02400255), investigators will give Crenolanib between D + 30 and D + 90 after alloHSCT in patients with FLT3-ITD+ AML, for up to 728 days and look at PFS, OS, disease free survival and rates of GvHD. In patients with r/r FLT3-ITD+ AML, including after alloHSCT, Crenolanib is under investigation in a dose-finding phase I followed by a randomized, double blind, placebo-controlled phase III clinical trial (NCT02298166). Patients are randomized to standard induction, consolidation and maintenance chemotherapy with Crenolanib or placebo and endpoints include EFS, OS, CR rates, cumulative incidence of relapse and death, and toxicity.

5. Drug resistance of FLT3 inhibitors

Despite new advances in therapy and improvements in survival for patients with FLT3+ AML, the overall outcomes are still poor and patients are at a high risk of relapse even after alloHSCT. The use of FLT3 TKIs has shown promising data in the prevention of relapse in the post-transplant setting but for many patients, the effect is only transient.

Multiple mechanisms have been proposed for the temporary responses to current FLT3 TKIs. Williams et al. [33] described new mutations in the FLT3-ITD domain, including F621L, A627P and Y842C mutations, which result in ineffective inhibition by certain TKIs of FLT3 autophosphorylation and signaling through MAPK, STAT5 and Akt signaling pathways [33]. Clinical and preclinical trials suggest that FLT3-TKD mutations on the D835 residue confer inherent resistance to certain FLT3 inhibitors such as Quizartinib and Sorafenib. Breitenbuecher et al. proposed that the upregulating the anti-apoptotic protein myeloid cell leukemia 1 (MCL-1) seen in patients with FLT3-ITD627E mutations, as a mechanism of resistance [56]. Many trials have also described resistant secondary mutations arise during the treatment course. For example, Alvarado et al. 2011 saw that 21% of patients progressed from a single FLT3-ITD mutation to combined FLT3-ITD and D835/I836 mutations on the TKD domain after the treatment with various TKIs [57]. Man et al. also noticed that the emergence of a new D835Y/H mutation in the TKD domain in 67% of patients treated with Sorafenib who had lost response to Sorafenib, suggesting the loss of response was from the secondary mutations [58]. The identification of FLT3 resistant mutations is still at an early phase and more research is needed to optimize therapy. These data suggest that combinations therapies that include FLT3 inhibitor along with another agent targeting resistance-conferring mechanisms may need to be explored.

6. Conclusion

Emerging data suggests that FLT3 TKIs may be effective as both maintenance therapy to prevent relapse and salvage therapy at time of relapse in the post-transplant setting, and is generally well-tolerated, for the treatment of FLT3-ITD+ AML. Multiple prospective, randomized, placebo-controlled clinical trials are currently underway and data from those trials will be crucial to further evaluate the clinical benefits of TKIs post-HSCT and incorporate their user into the standard of care. Further trials are also needed to investigate the mechanism of resistance to certain TKI therapies in order to improve results of therapy. Future goals and considerations include the development of more potent and/or specific FLT3 inhibitors and the incorporation of TKI therapy as post-transplant maintenance therapy as monotherapy or in combination with hypomethylating agents or other molecules.

Authors' contributions

Grace Xiuqing Li and Lan Wang prepared the manuscript. George Yaghmour Bassam Yaghmour and Giridharan Ramsingh reviewed and edited the manuscript.

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