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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].

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