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Will FLT3 Inhibitors Fulfill Their Promise in AML?

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Abstract

Purpose of Review—FLT-3 mutations in Acute Myeloid Leukemia (AML) have been brought from discovery in the early 1990's to clinical targeting in the last ten years. Despite several promising leads in pre-clinical models, no agent has yet been approved for clinical use. Here we will review the development of novel therapies for AML with FLT3 mutations.

Recent findings—Initial clinical development focused on broad kinase inhibitors which were found to have limited clinical activity due to insufficient kinase inhibitory activity and high toxicity. Subsequent development has brought forth narrow spectrum inhibitors with potent in-vivo activity and reasonable clinical tolerance but many patients still progress with prolonged use.

Summary—The optimal role for targeting FLT3 may depend on multi-modality therapy and will likely require hematopoietic transplant. The incorporation of ABL kinase inhibitors into acute lymphoblastic leukemia management should serve as a model for incorporation of FLT3 targeted agents into clinical care. Strategies incorporating FLT3 targeted agents into AML therapy are ongoing, but challenges in trial design, clinical heterogeneity and need for long term follow up make these investigations complicated in design and implementation.

Keywords

Acute myeloid leukemia; FLT3 mutations; tyrosine kinase inhibitors

Introduction

Following the success of small molecule inhibition of BCR/ABL in chronic myeloid leukemia (CML)[1] a large effort has been underway to identify and target activated kinases in other malignancies with the goal of improving clinical outcomes. One promising target in AML is the receptor tyrosine kinase FLT3 (“FMS”-Like Tyrosine kinase 3). FLT3 was first described in humans in 1994,[2] and is thought to play a role in early hematologic differentiation and early B and T cell development.[3] Activating mutations of the receptor tyrosine kinase FLT3 are some of the most common molecular abnormalities in acute myeloid leukemia (AML), present in about 30% of newly diagnosed patients.[4] Internal

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tandem duplications (ITD) within the juxtamembrane domain of FLT3 are found in about 23% of *de novo* AML, and represent the most common activating mutation. The presence of a FLT3 ITD mutation in AML patient portends a poor prognosis, with only 22% of younger adult patients maintaining a remission for two years in a recent phase III cooperative group study.[5] FLT3 kinase domain mutations(FLT3 TKDmut), which are found in about 7% of newly diagnosed AML, seem to have limited impact on clinical outcomes; therefore attention has been primarily focused on developing improved therapies for FLT3-ITD AML. [6] More than 20 different small molecule inhibitors of FLT3 kinase activity have been described in the literature, several of which have advanced to phase 2 and phase 3 clinical trials.[7] This review will discuss the results of these studies, the issues encountered and the ongoing direction for clinical development.

FLT 3 ITD AML

Clinical outcomes of patients with FLT3-ITD mutant leukemias are influenced by several leukemia specific factors. High ratio of the mutant FLT3-ITD allele compared to FLT3 wild type (WT) allele (allelic burden) has been associated with inferior survival and decreased complete remission (CR) in response to conventional chemotherapy in newly diagnosed AML patients[8]. The presence of a concurrent Nucleophosmin (NPM1) mutation in the setting of a FLT3 ITD mutation, may abrogate the adverse effects of FLT3 ITD, particularly in patients with low FLT3 ITD allelic burden[9]. This ratio can change during the course of disease;patients with relapsed disease having a higher allelic burden. [10] The allelic burden is also predictive for in vitro response to FLT3 inhibitors with patients homozygous for the ITD allele being the most responsive to more selective FLT3 inhibitors.[10] Lastly, the length of the ITD is variable and a longer ITD length has been associated with worse clinical prognosis in some[11] but not all reports[9].

FLT3 inhibitors as monotherapy

Several small molecule inhibitors of tyrosine kinases were studied in early phase clinical studies. (Table 1) One of the most studied early agents in development is lestaurtinib (CEP701) with a phase 1/2 trial of lestaurtinib in relapsed or refractory AML patients with FLT3 mutations in 2003.[13] Correlative assays in this and a subsequent phase 2 study demonstrated that clinical response was more likely in patients who had in vitro leukemic blast sensitivity to CEP-701, and if, in vivo, CEP-701 in plasma level was sufficient to significantly inhibit FLT3 autophosphorylation in a sustained fashion. Partial response was achieved in 8 of 27 patients (3 of 5 FLT3 ITD. 5 of 22 WT) All 8 responders had drug plasma levels sufficient to inhibit FLT3 phosphorylation to below 15% of baseline activity.

Midostaurin, an indolocarbazole derivative like lestaurtinib was evaluated in a phase II trial for relapsed or refractory FLT3 mutated AML patients.[27] At a dose of 75 mg three times daily, 14/20 patients displayed at least hematologic improvement, with 1 CR. Midostaurin is tightly bound to Alpha-1 Acid Glycoprotein (AAG) and responses correlated very well with the degree of FLT3 inhibition determined by the pharmacodynamic assessment of FLT3 inhibitory activity in the patient's plasma (PIA). [28]

The multi-kinase inhibitor sorafenib (bi-aryl urea), approved for use in renal cell carcinoma, has been evaluated in early phase clinical trials. As a single agent, sorafenib has been studied on an intermittent schedule in refractory AML with or without a FLT3 mutation.[29] A clinical response was observed in 9/16 patients (56%) including all 6 patients with FLT3-ITD as a solitary. In a separate Phase I dose escalation trial of sorafenib in relapsed/refractory acute leukemias, PIA of kinase targets ERK and FLT3-ITD demonstrated excellent target inhibition, with FLT3-ITD silencing occurring below the MTD.[20] Despite encouraging correlatives studies, no patients met criteria for complete or partial response in this monotherapy study. Several case reports of compassionate use of sorafenib off protocol, with CRs, have however been reported in the literature.[30, 31]

Quizartinib (AC220) a novel bis-aryl urea, may well be the most potent and specific inhibitor of FLT3 currently in development.[23, 32] A phase I study has recently been completed, studying activity in both FLT3 wild type(WT) and ITD relapsed and refractory AML.[33] Seventy-six patients were treated on one of two schedules: intermittent (day 1-14) or continuous (day1-28) dosing. Pharmacokinetic studies revealed a prolonged plasma half-life of ∼36hrs and excellent ex-vivo target inhibition at dose levels above 12mg per day. Additionally an active metabolite was found, which likely contributes significantly to the biologic activity of AC220. The dose limiting toxicity was QTc prolongation at 300mg continuous dosing. The Phase II study of quizartinib was preliminarily reported, evaluating 90mg per day in females and 135mg per day in males in a continuous dosing strategy.[24] Of 99 FLT3-ITD mutated patients, the rate of CR with or without count recovery (CRc) was 44%. Thirty four of the 44 responding patients were able to proceed to allogeneic transplant. The median duration of CRc was 11.3 weeks.

Ponatinib, which was clinically approved in the United States for refractory CML, has also been found to have activity in FLT3 mutant AML.[26] In a phase I study of relapsed and refractory AML patients with or without FTL3 mutations, ponatinib was found to induce CRi in two of the 10 patients with documented FLT3-ITD mutations. Preclinically, ponatinib is suggested to have activity against several of the common kinase domain mutations excluding the most common acquired resistance clone with D835Y mutation. [34] Concerns regarding arterial thrombus risk in post marketing study of CML and Ph+ ALL has led the FDA to remove ponatinib from the market as of October 31st, 2013 (FDA press release October 31th 2013).

The use of these agents as monotherapy supports the concept of targeted therapy but has not resulted in prolonged disease free survival. These results however support the study of these agents in combination with chemotherapy or in the maintenance of remission setting.

Combinational Studies

With limited clinical activity of early phase agents targeting FLT3 ITD, combinational studies for newly diagnosed and relapsed refractory AML were begun.

Lestaurtinib in combination with chemotherapy

Drawing on the results of pre-clinical studies combining lestaurtinib with chemotherapy demonstrating sequential synergy[35], the Cephalon 204 trial began accruing patients in

2003. AML patients were eligible for this trial if they were in first relapse and they harbored a FLT3 mutation. The trial was stratified according to the duration of first remission: Patients whose first remission lasted less than 6 months received mitoxantrone, etoposide and cytarabine (MEC)[36], while those whose first remission lasted greater than 6 months were treated with high dose cytarabine (HiDAc).[37] (Table 2) Patients were randomized to receive lestaurtinib at a dose of 80 mg twice daily beginning with the completion of chemotherapy and continuing for up to 16 weeks. The efficacy of target inhibition was determined through the use of a PIA for FLT3.[28] The results failed to demonstrate clinical benefit to the addition of lestaurtinib to standard salvage therapy.[38] Correlative assays demonstrated incomplete target inhibition in 42% of patients at day 15 of therapy. Those patients who were found to have sustained inhibition (>85% inhibition) were more likely to have CR suggesting some association of clinical response with target activity.

Midostaurin combined with chemotherapy

In a pilot trial of newly diagnosed AML with or without FLT3 mutations, midostaurin was evaluated in different schedules in combination with induction therapy using a conventional cytarabine and daunorubicin (“7+3”) regimen followed by high dose cytarabine consolidation. One arm was given midostaurin on day 1-7 & 15-21 and a second arm received midostaurin on day 8-21 of chemotherapy. In general, midostaurin doses that were well-tolerated when used as monotherapy (100 mg orally twice daily) were intolerable (due to nausea) when given concomitantly or following chemotherapy. This study was amended due to the high level of grade 3 nausea and vomiting with 100mg of midostaurin.[40, 44] In the amended study, midostaurin, was started at a dose of 50 mg twice daily. Maintenance midostaurin was allowed on this protocol per the initial dosing randomization. At the MTD of 50mg twice a day, CRs were achieved in 20 of 27 patients with WT-FLT3 and 12-13 patients with FLT3-ITD. Based on these results a Phase III randomized trial of midostaurin combined with chemotherapy for newly diagnosed FLT3-ITD and FLT3-TKDmut AML patients under age 60 (RATIFY) was performed.[45] No results are yet available, but a presentation of enrollment data at ASCO in 2011 illustrated the complexity of performing such a study with a need to screen 2470 patients centrally to enroll 564 patients on protocol.

Sorafenib combined with chemotherapy

In a phase II single institution study of newly diagnosed AML with or without FLT3 mutations, sorafenib was administered for seven days at 400mg twice a day with cytarabine and idarubicin in induction and consolidation, followed by a year of maintenance sorafenib. [46, 47] The combination was tolerable, and the investigators reported a high CR rate in FLT3 mutated patients (14/15). Despite this high initial CR rate 9/14 patients have gone on to relapse, with the other five in ongoing CR with median follow up of 62 weeks.

In an elderly patient population, a randomized trial of chemotherapy +/- sorafenib was studied in FLT3-ITD and FLT3 WT. In the investigational arm, sorafenib was given at a dose of 400mg twice daily continuously from day 3 until 3 days before next cycle.[41] There were more adverse events associated with inclusion of sorafenib into chemotherapy and there was no significant improvement in event free survival(EFS) or overall survival(OS). In the 29 FLT3-ITD patients CR was lower than in WT FLT3(40% vs 77%

respectively) and sorafenib did not impact on CR rate in this small group(57% vs 64% without).

Quizartinib combined with Chemotherapy

Quizartinib is being incorporated into conventional cytarabine/daunorubicin induction in an ongoing phase I study in newly diagnosed AML. Preliminary reports from this study suggest quizartinib is tolerated well at 40mg twice daily when given for 14 days in induction and consolidation (Altman et al ASH 2013 abstract). Plans are in development for a cooperative group Phase III study to examine the efficacy of quizartinib in FLT3 mutated patients.

Post-transplant and other maintenance strategies

Allogeneic transplant carried out in first remission appears to be the most effective conventional strategy for curing FLT3-ITD AML.[48] Even after CR with induction therapy, there is high likelihood to relapse, a short duration of remission, with relapse before a donor can be found. Therefore challenges with these patients include maintaining remission long enough to undergo transplant, and suppression of the growth of any leukemia clone still present after a transplant. Several case reports have documented somewhat durable remissions to sorafenib when given to patients relapsing post-transplant.[49, 50] Clinical trials are ongoing investigating the utility and safety of quizartinib, sorafenib and midostaurin post allogeneic transplant.[50]

Factors affecting clinical FLT3 targeting efficacy and associated resistance mechanisms

Preclinical studies evaluating small molecule inhibitors of FLT3 were described shortly after the discovery of FLT3 mutations in AML.[12] Through these studies it was revealed that the timing of incorporation of FLT3 inhibitors into therapy is predicted to influence clinical efficacy due to the cell cycle arresting characteristics of FLT3 inhibition.[35] The ligand of the FLT3 receptor, FL, is found at peak levels 15 days after chemotherapy.[51] This ligand surge during aplasia renders the FLT3 ITD receptors more resistant to all FLT3 inhibitors and the surge appears to increase in levels with each subsequent cycle of cytotoxic chemotherapy.[51] The surge of FL with each successive cycle as a potential resistance factor is an important consideration regarding the early incorporation of transplantation in FLT3-ITD leukemia.[51] It is unclear if ITD length is associated with sensitivity to FLT inhibitor therapy but there appear to be biologic changes that occur with long ITD insertions.[52]

Resistance to agents targeting FLT3 ITD has been well described and can develop rapidly. The most common change associated with resistance is the acquisition of a point mutation in the kinase domain (D835Y)[53, 54] or others.[55, 56] Other mechanisms have been described including up-regulation of anti-apoptotic pathways such as MCL-1[57] or stromal response signaling cascades such as CXCR4[58]. A retrospective study of patients receiving off label sorafenib upon relapse, however, revealed that only few developed resistance to sorafenib when given in the post-transplant setting (47v38% p=0.03).[50]

Summary and Future Directions

Clinical development of novel therapeutics in AML has been a challenging endeavor for many years. Cytarabine and anthracycline based regimens have been the standard for more than two decades. Despite numerous novel genetic lesions discovered over the last two decades, individualized therapy for AML has yet to be realized for most AML patients. While clinical activity of FLT3 inhibitors has now been well described in FLT3 ITD AML, statistical evidence of improved outcomes has yet to be documented. There are several potential explanations for this. 1) We have yet to develop an effective inhibitor of FLT3 2) FLT3 inhibitory therapy begets increased FLT3 dependency and signaling thus leading to failure of therapy due to further up-regulation or resistant mutation development 3) FLT3-ITD is not a founding lesion and therefore its inhibition as a sole modality is not expected to result in durable responses.

As demonstrated by several correlative studies of lestaurtinib, poor bioavailability and tolerability of early FLT3 inhibitor studies likely led to clinical failure. This does not appear to be the case with more recent studies of quizartinib and sorafenib. Clinical resistance appears to be mediated through development of point mutations in the kinase domain.[25, 53] Further development of agents to specifically inhibit both point mutations and ITD mutations is ongoing. Crenolanib is a novel agent in phase I studies with data to suggest activity against kinase domain mutations in vitro. [25]

The promise of targeted therapy in oncology is to deliver high potency therapy to specific subsets of patients to improve outcomes and lessen toxicity. Kinase inhibitor therapy alone for malignancies with more than one driving lesion is unfortunately unlikely to be successful in large numbers of patients. Despite the dramatic outcome improvements in CML with single agent Abl kinase inhibitors, in Philadelphia Chromosome positive ALL clinical outcomes are only dramatically improved when inhibitor therapy is incorporated into multi-modality therapy such as chemotherapy with allogeneic transplant.[59, 60] Clinical trials incorporating novel therapeutics into multi-modality therapy are complex to design, difficult to execute, and require large numbers of patients to obtain results which are statistically significant makes the uniform study of these patients extremely challenging, but it remains critical to their development and to progress in these diseases.

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Bullet Points

- Successful incorporation of novel therapeutics for FLT3-ITD Acute Myeloid Leukemia will require multimodality therapies.
- Potent and well tolerated inhibitors of FLT3-ITD such as quizartinib are in late stage development and show promising results.
- Strategies for management of resistance to FLT3-ITD inhibitors are needed

Table I

Agent	Phase	Patient population	DLT	ORR at MTD
Lestaurtanib(CEP-701) [12, 13]	1	Relapsed or refractory AML w FLT3 mutation	Nausea vomiting, fatigue	5/14 (1CRi)
Midostaurin(PKC412) [14, 15]	IIb	Relapsed or refractory AML w or w/o FLT3 mutation	Nausea vomiting	32/57(1PR)
Sunitinib (SU11248) [16, 17]	I	Relapsed refractory AML w or w/o FLT3 mutation	Fatigue, hypertension, heart failure	7/16(1CRi)
Tandutinib (MLN518) [18, 19]	I	Relapsed refractory AML w or w/o FLT3 mutation	Muscle weakness, fatigue	2/8(2 blast reductions)
Sorafenib(Bay 43-9006) [20]	I	Relapsed refractory AML w or w/o FLT3 mutation	Elevated transaminases, Musculoskeletal pain	11/15(11 SD)
KW-2449 [21, 22]	I	Relapsed refractory AML w or w/o FLT3 mutation	Nausea, vomiting fatigue	1/6(1blast reduction)
Quizartinib(AC220) [23, 24]	II	Relapsed or refractory AML with FLT3 ITD mut	QTc prolongation	44/99(44CRc)
Crenolanib[25]	I	Relapsed refractory AML w or w/o FLT3 mutation	TBD	Ongoing
Ponatinib[26]	I	Relapsed refractory AML w or w/o FLT3 mutation	Pancreatitis	3/12(2CRi)

Table 2

Agent (author)	Phase	Patient population (n)	Combination agents	ORR	Median EFS
Lestaurtinib (Levis) [38]	II	Relapsed or refractory AML with FLT3 mutation(224)	MEC or HiDAC	21% vs 26%(with Lestaurtinib)	
Sorafenib (Ravandi) [39]	I/II	Newly diagnosed AML +/- FLT3 mutation(51)	Ida+ Ara-C	75%(all AML), 93% (FLT3mut)	9.9mo
Midostaurin(Stone) [40]	Ib	Newly diagnosed AML +/- FLT3 mutation(40)	DNR + Ara-C	74%(all AML), 92% (FLT3mut)	
Sorafenib (Serve) [41]	II	Over age 60 with newly diagnosed AML +/-FLT3 mutation(201)	DNR + Ara-C	64 vs 57(%with sorafenib)	7mo vs 5mo(with sorafenib)
Sorafenib (Rollig) [42]	III	Under age 60 with newly diagnosed AML under age 60 +/- FLT3 mutation(264)	DNR+ Ara-C	56% vs 60%(with sorafenib)	12.2 vs Not yet reached in sorafenib arm
AC220 (ongoing)	I	Under age 60 with newly diagnosed AML +/- FLT3 mutation	DNR+ Ara-C	Too early to assess	
AC220 (Cooper) [43]	I	Relapsed or refractory AML or ALL in children up to age +/- FLT3 mutation (12)	VP16+ HiDAC	8/12(1CR 3CRi)	

MEC= mitoxantrone, etoposide, cytarabine; Ida=idarubicin; Ara=cytarabine, VP16=etoposide, HiDAC=high dose cytarabine; mo=month, ORR =Overall response rate, EFS=event free survival, CR=complete remission, CRi=complete remission with incomplete recovery of counts