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Advances in the Treatment of FLT3-Mutated AML

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Abstract

AML is a heterogeneous disease and is the most common acute leukemia in adults. It has an annual US incidence over 20,000 and death rate of over 10,000 per year. The 5-year remission rates after conventional induction therapy is 40% below 60 years and 10%-20% in older patients. *FLT3*-ITD mutation has been added to the WHO risk stratification as a predictor of poor prognosis. On April 28, 2017 FDA approved midostaurinin combination with standard cytarabine and daunorubicin induction and cytarabine consolidation for treating adult newly diagnosed AML patients who are FLT3 mutation positive as detected by an FDA approved test.

Abbreviations: AML: Acute Myeloid Leukemia; CR: Complete Remission; DFS: Disease -Free Survival; OS: Overall Survival; ITD: Internal Tandem Duplication; FLT3: Fms-Like Tyrosine kinase 3; RTK: Receptor Tyrosine Kinase; TKI: Tyrosine Kinase Inhibitors; FL: FLT3 Ligand; PIM: Proviral Integration site; MDS: Myelodysplastic Syndrome; DLI: Donor Lymphocyte Infusion; ATP: Adenosine Triphosphate; PDGFR: Platelet Derived Growth Factor Receptor; VEGFR: Vascular Endothelial Growth Factor receptor; AEs: Adverse Events

Introduction

The FLT3 gene is located on chromosome 13q12, and the resultant protein is a member of the class III RTK family. The FLT3 RTK expression is normally limited to early myeloid progenitors and it appears to play a key role in the differentiation and maturation of hematopoietic precursors. FL binding to the receptor activates downstream signaling cascades, which mediate differentiation and growth. These pathways include the key intermediary proteins RAS, MEK, PI3K, AKT, and STAT-5 [1]. Over expression of FLT3 in cell lines results in increased proliferation and decreased apoptosis [2].

FLT3-ITD AML

FLT3 mutations occur as secondary events during AML clonal evolution [3] in approximately 30% of AMLs. In 23%, the mutations occur via ITD in the juxtamembrane domain and in 7% via point mutation usually in the Asp835 residue within the activation loop. Both mutations result in constitutive activation of the kinase [2]. FLT3/ITD AML frequently presents with leukocytosis and normal cytogenetics and is more likely to arise de novo rather than out of an antecedent disorder such as MDS or a myeloproliferative neoplasm. FLT3 mutations frequently co-occurred with NPM1 and DNMT3A mutations (39%) and chromatin or RNA splicing gene mutations (15%), and were also associated with t(15;17) and t(6;9) translocations (35% and 80%, respectively).Patients with FLT3-ITD mutation are usually not cured with conventional chemotherapy [4]. They have higher induction death rate, a lower CR rate, increased risk of relapse, and adverse DFS, event-free survival, and OS [5].

Relapse of FLT3-ITD-positive AML

Is frequently observed within 1 year after completion of conventional chemotherapy with or without allogeneic SCT [5]. Because of its poor outcomes, FLT3-ITD mutation in any newly diagnosed AML is classified as one of the most frequent bad-prognostic mutations, at least in younger or relapsed patients [6].

The putative impact of FLT3 mutation on AML prognosis

Is related to the localization of the genomic duplication with a worse prognosis in a more C-terminally located FLT3-ITD. The allelic ratio of FLT3-ITD to wild-type FLT3 has also been shown to correlate with AML prognosis [5]. A ratio >0.5 between the mutated and the wild-type allele is associated with an adverse prognosis after conventional therapy [3]. The impact of FLT3 mutation on transplantation may depend upon the length of the ITD as well as the allelic burden of the FLT3-ITD sub clone for a given patient [7].

The current guidelines

Support the use of allogeneic stem cell transplantation in FLT3-ITD AML in first remission to decrease relapse risk [3]. The risk of *FLT3/ITD* AML relapse with HSCT in CR1 remains unacceptably high and is frequently associated with an unfavorable outcome [1]. No guidelines are available for refractory/relapse patients which generally have very short survival regardless of the therapeutic intervention used [3]. Palliative concepts include immunotherapeutic approaches using DLI, hypomethylating agents (e.g., 5-azacytidine, decitabine) or TKI-based therapy [5]. Intensive chemotherapy may be considered for young AML patients relapsed

more than 12 month following allogeneic SCT in order to achieve a second or third CR prior to a second allogeneic SCT [5].

Tyrosine kinase/Fms-like tyrosine kinase 3 inhibitors

FLT3 inhibitors are tyrosine kinase inhibitors. They compete for the ATP binding site in the active domain of the kinase, which inhibits protein phosphorylation, and subsequently decreases its activity [8]. Inhibiting the FLT3 pathway is an attractive target therapy [9]. Preclinical studies showed that inhibiting FLT3 phosphorylation and downstream signaling could induce leukemia cells apoptosis [8]. In addition, preclinical evidence suggests that FLT3 is present on dendritic cells and their stimulation leads to regulatory T cells expansion [1]. This has led to the evaluation of multikinase or more specific kinase inhibitors in this AML subset [6].

Using FLT3 TKIs as a potential maintenance therapy after HSCT may decrease the risk of disease relapse and improve long-term survival [1]. The immunomodulatory effect of FLT3 inhibitors may contribute partly to its observed efficacy after HSCT [1]. Clinical trials showed promising results for 5-azacytidine and sorafenib combination. Also, the schedule of sorafenib in the presence of chronic GvHD seems to facilitate graft versus- leukemia reaction [5].

FLT3 inhibitors are currently classified into three generations: the first generation such as sorafenib, sunitinib, midostaurin, and lestaurtinib are relatively nonspecific for FLT3 [9]. They have diminished efficacy in mutated FLT3 with high allelic burden [8]; the second generation includes selective inhibitors, such as quizartinib; and [9] the third generation such as crenolanib and gilteritinib tackles the problem of drug resistance. Third generation agents are currently in phase I/II clinical trials, and their therapeutic values in pediatric patients are not yet clear [9].

Midostaurin (PKC412A, CGP41251)

N-benzoyl-staurosporine, [10] is a type III receptor. Midostaurin is a multi-targeted indolocarbazole with activity against PKC-alpha, VEGFR, KIT, PDGFR, and FLT3. It is equally active against ITD mutated and TKD-mutated FLT3 [4]. *In vitro*, midostaurin slows tumor cell growth, in G2/M phase, induces polyploidy, apoptosis and radiosensitivity, with inhibition of the PI3K/Akt pathway. In vivo midostaurin inhibits growth of several murine tumors, potentiates paclitaxel, doxorubicin and radiation, and may affect multidrug resistance. Angiogenesis is also inhibited by midostaurin [10].

As a single agent, midostaurin was able to confer a robust antiblast response [9] and induces responses in relapsed/refractory AML. When administered in combination with standard induction chemotherapy, midostaurin has the potential to deepen and/or prolong response. Whether midostaurin improves relapse-free survival after transplant remains under active investigation [2]. On April 28, 2017 FDA approved midostaurinin combination with standard cytarabine and daunorubicin induction and cytarabine consolidation for treating adult newly diagnosed AML who are FLT3 mutation positive as detected by an FDA approved test [11].

Midostaurin as a single agent is generally well tolerated [2]. Common adverse reactions occur in at least 20% of patients [11]. Nausea and vomiting were the most commonly reported AEs, and rarely cause drug discontinuation, especially at lower doses [2]. Other adverse reactions included febrile neutropenia, mucositis, headache, petechiae, musculoskeletal pain, epistaxis, device related infection, hyperglycemia and upper respiratory infection [11]. `Midostaurin AEs and drug discontinuation increased when midostaurin particularly higher doses was combined with conventional cytarabine and daunorubicin [2]. Sequential midostaurin administration is better tolerated than concomitant midostaurin and standard induction therapy administration [2]. Gastrointestinal toxicity increased when midostaurin is administered with cytarabine/daunorubicin combination or azacitidine, and hematologic toxicity increased with all combinations. The increase in AEs with drug combinations is due to inherent toxicities of the additional agents or due to pharmacokinetic interactions between these drugs and midostaurin. A possible interaction has been suggested between daunorubicin and midostaurin, but no apparent interactions between midostaurin and decitabine or azacitidine [2].

Overview of the resistance mechanisms to FLT3 TKI in AML

Resistance to FLT3 TKIs arise either from the outset ''primary resistance'', or during the course of treatment ''secondary resistance'' [4]. It can be due to extrinsic (pharmacokinetics), receptor-intrinsic (mutated FLT3 or wild-type) and cell-intrinsic factors (persistent activation of pathways downstream of the FLT3 receptor) [4]. The suggested mechanisms are:

I. The activation of bypass signaling oncogenic pathways such as tyrosine kinases (SYK or AXL) or serine/threonine kinases (PIM) in response to FLT3-ITD receptors inhibition.

II. Significant FLT3-L overproduction from bone marrow stromal cells and T lymphocytes after chemotherapy impaired the ability of FLT3 TKI to inhibit FLT3-ITD activity.

III. Soluble molecule secretion as well as cellular interactions between AML and stromal cells was reported as cytoprotective factors against TKI.

IV. Amino acid substitutions within the FLT3-TKD (generally at position D835) decrease the affinity of TKI for their target receptors [3].

These mechanisms activate intracellular signaling pathways such as ERK or STAT5 even in the presence of TKI, and consequently AML cells escape from their cytotoxic effects [3].

A. The modest, transient responses to midostaurin in single-agent trials could be explained by

I. The midostaurin concentration may be sub therapeutic at the bone marrow.

II. Recovery of *FLT3* activity during treatment breaks of cyclic drug administration.

III. Presence of driver mutations in addition to FLT3 could

offset the inhibition conferred by midostaurin treatment, through clonal evolution [2].

B. Transient responses to midostaurin in previously treated patients with FLT3 inhibitors: Could reflect development of resistance from point mutations to global alterations in gene expression [2].

C. How to target the mutations arising after TKI therapy?

i. Other TKI, such as AUZ454 or the third-generation multi-kinase Bcr-Abl inhibitor ponatinib can challenge *FLT3-TKD* mutations [3]. Ponatinib can also inhibit constitutively activated FLT3. Ponatinib is able to overcome resistance to other TKI (e.g., sorafenib) conferred by additional FLT3-ITD point mutations. Ponatinib represents a promising compound in FLT3-ITD positive AML [5].

ii. Dual therapy with a FLT3 TKI and another inhibitor may circumvent signaling pathways activated in *TKD*-mutated AML cells. These include combination of FLT3 inhibitors with mTOR, NFkB, MEK, or PI3K inhibitors and also new compounds with dual activity against FLT3 and PIM, JAK, or aurora kinases [3].

Conclusion

Dual targeting therapy of a FLT3 TKI and any pathway involved in TKI resistance may be considered a potential target for a rigorous preclinical evaluation [3].

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