Midostaurin approved for FLT3-mutated AML

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Abstract

Midostaurin was recently approved by the U.S. Food and Drug Administration for the treatment of FLT3-mutant acute myeloid leukemia (AML). This is the first drug to receive regulatory approval for AML in the U.S. since the year 2000. Midostaurin is a small molecule kinase inhibitor with activity against the receptor tyrosine kinase FLT3, and its approval will hopefully mark the beginning of an era of targeted agents for the treatment of molecularly-defined subtypes of AML.
On April 28, 2017, the U.S. Food & Drug Administration (FDA) approved midostaurin (Rydapt®; Novartis Pharmaceuticals, Inc.) for the treatment of adult patients with newly diagnosed FLT3-mutated acute myeloid leukemia (AML). A companion diagnostic test for the detection of FLT3 mutations (“LeukoStrat CDx FLT3 Mutation Assay”; Invivoscribe Technologies Inc.) was also approved. According to the FDA label, the recommended dose of midostaurin (available in 25 mg capsules) is 50 mg twice daily on days 8-21 of each cycle of induction with cytarabine and daunorubicin and days 8-21 of each cycle of consolidation with high-dose cytarabine. The label notes that the drug is not indicated for single agent treatment of AML. Midostaurin, as an inhibitor of both wild type and D816V-mutated KIT, was simultaneously approved for the treatment of aggressive systemic mastocytosis, although as a single agent, and at a higher dose (100 mg twice daily).

Activating mutations of the receptor tyrosine kinase FLT3 are among the most common genetic lesions found in AML and represent an often difficult-to-treat subtype. The most common mutation (~23% of AML cases), an internal tandem duplication (FLT3-ITD), is associated with leukocytosis (often life-threatening) and a high relapse rate, all leading to reduced overall survival. The less common mutations (7% of cases) are those found in the tyrosine kinase domain (FLT3-TKD). Most published reports suggest they confer a negative prognosis, although to a lesser degree than the FLT3-ITD mutations, and there are some reports suggesting that FLT3-TKD mutations have no prognostic impact or even have a favorable impact. Regardless, FLT3 mutations are a common feature of AML, as anyone who treats the disease will readily attest. There is a general consensus that allogeneic transplant, when feasible, is the preferred consolidation treatment for patients with FLT3-ITD mutations, although there is
ongoing debate regarding the impact of *NPM1* mutations and *FLT3-ITD* allelic burden on the benefit of transplant.  

Midostaurin (N-benzoyl staurosporine, previously referred to as CGP41251 and PKC412) is an indolocarbazole and a direct derivative of staurosporine, the original “pan-kinase” inhibitor. While by no means a pan-kinase inhibitor, midostaurin can certainly be referred to as a multi-targeted kinase inhibitor, at least in comparison with some other compounds (Figure 1). The drug has quite literally been under investigation for decades, originally as an inhibitor of protein kinase C. Around the same time that *FLT3* mutations were being recognized as important prognostic factors in AML, midostaurin was characterized as a FLT3 inhibitor using in vitro and animal models. In a study of 20 relapsed/refractory patients with *FLT3*-mutated AML treated with 75 mg midostaurin three times daily, no patient achieved a complete remission (CR), but peripheral blood blasts were reduced in 70% (14/20), and 6 patients achieved a greater reduction in bone marrow blasts of at least 50%. A larger study examined the effects of 50 mg or 100 mg twice daily in both *FLT3*-mutated and non-mutated AML patients and noted blast reductions in about half of the *FLT3*-mutated patients and, interestingly, blast reductions in about a third of the non-mutated patients- but still no CRs. Next, a phase 1B study examined the safety and tolerability of combining midostaurin with induction chemotherapy in newly diagnosed AML patients, using different doses and schedules. Gastrointestinal adverse events were common, as was the withdrawal rate from this trial, and there were concerns that midostaurin administered concomitantly with daunorubicin resulted in elevated mean levels of the anthracycline. Out of 6 cohorts of patients, the most tolerable regimen to emerge was midostaurin 50 mg twice daily.
on days 8-21 following a conventional induction with cytarabine and daunorubicin, which was the regimen carried forward into the phase 3 study.

From these pre-clinical and early phase clinical studies, we can draw the following conclusions about midostaurin: 1) The drug is a multi-targeted kinase inhibitor with inhibitory activity against both the \textit{FLT3-ITD} and \textit{FLT3-TKD} mutants; 2) As a single agent, it has little or no clinical utility in AML (i.e., it is unlikely to induce remissions or allow for a bridge to transplant), but clearly has biologic activity as manifest by reductions in blood and marrow blasts; 3) It probably has activity in non-mutated \textit{FLT3} AML, although the specific sub-types will hopefully be better defined using molecular techniques; 4) Midostaurin is associated with an increase in gastrointestinal side effects (nausea, vomiting, diarrhea) both as monotherapy and when the drug is incorporated into chemotherapy regimens. This may limit our ability to incorporate it into different AML treatment scenarios; 5) The pharmacokinetics are complex,\textsuperscript{29,30,32} with two active metabolites, and the highest levels of active drug are seen during the first few weeks of treatment (either as monotherapy or when given sequentially following chemotherapy); and 6) It can be safely combined with induction and consolidation chemotherapy.

CALGB10603 (“\textit{RATIFY}”) was a global, randomized, placebo-controlled phase 3 trial carried out in 225 sites across 17 countries to determine if the addition of midostaurin to induction and consolidation, followed by one year of maintenance, would improve the overall survival (OS) of patients with \textit{FLT3}-mutated AML aged 18-59.\textsuperscript{33} Patients were screened for the presence of
FLT3 mutations at the start of the trial. As noted above, this trial implemented the regimen deemed to be most tolerable of the ones tested in the Phase 1B study. After the mutation status was confirmed, patients were randomized to receive either placebo or 50 mg midostaurin twice daily, administered on days 8-21 following a 7+3 regimen (cytarabine 200 mg/meter-square/day on days 1-7 by continuous intravenous infusion and daunorubicin 60 mg/meter-square/day on days 1-3) and on days 8-21 of consolidation with high dose cytarabine (cytarabine 3000 mg/meter-square intravenously over 3 hours twice daily on days 1, 3, and 5). On completion of consolidation, patients were treated with midostaurin as a single agent 50 mg twice daily for 12 months. There were three strata: FLT3-TKD alone, FLT3-ITD allelic ratio < 0.7, and FLT3-ITD allelic ratio ≥ 0.7. Enrollment started in May 2008 and was completed in October 2011. The original design was to conduct the final analysis after 509 OS events had occurred. However, as of April 2015 there were still only 357 events, and the event rate appeared to have reached a plateau. The reason for this was likely because of a higher than expected transplant rate and a higher than expected incidence of FLT3-TKD mutations (23%). Given that there was sufficient follow up to assess OS, the trial was amended to conduct the primary analysis in May of 2015. The results (Figure 2; presented at the 2015 Annual Meeting of the American Society of Hematology in Orlando, FL) indicated that patients randomized to receive midostaurin had a higher median OS, with a hazard ratio (HR) of 0.78 compared to those receiving placebo. The 4 year OS rates were 51.4% in the midostaurin arm versus 44.3% in the placebo arm, and the rate of protocol-defined CR (CR within 60 days of initiation of protocol therapy) was 59% versus 53%, respectively.
While we are awaiting the final peer-reviewed publication, a closer look at the data from the FDA label and from the meeting abstract reveals a number of interesting findings. First, patients in all three strata (FLT3-TKD, FLT3-ITD low, or FLT3-ITD high ratio) benefitted from midostaurin, and those in the TKD strata actually had the lowest HR (0.648) compared to placebo. The fact that these three groups behave very differently with respect to their clinical outcomes in response to standard therapy, coupled with the biologic activity of midostaurin against non-mutant FLT3 AML, may indicate that a significant component of midostaurin’s efficacy is derived from its multi-targeted nature. Second, there was a higher than expected incidence of FLT3-TKD patients (23% versus the expected rate of 7%). We can speculate that this is because patients were required to undergo molecular screening for FLT3 mutations prior to enrollment. Patients with FLT3-TKD-mutated AML have lower white blood cell counts and generally less proliferative disease than FLT3-ITD patients, and this likely biased the enrollment. FLT3-TKD patients are more likely than FLT3-ITD patients to be stable enough to allow for treatment delay until the results of molecular testing were known. Third, the survival curves separate quickly and remain roughly parallel thereafter (Figure 1), suggesting that the primary benefit from midostaurin occurs early on. This would be consistent with the drug’s pharmacokinetic profile, in which plasma levels are highest during the first few weeks of treatment. A two-week course of treatment following chemotherapy, therefore, may be the best way to adapt this drug into a standard regimen. A fourth interesting finding is the remarkable difference in survival of midostaurin-treated patients who underwent allogeneic transplant in first CR compared to those on the placebo arm. Given the well-described impact of minimal residual disease (MRD) on outcomes after allogeneic transplant for AML, this finding may represent evidence that midostaurin truly augments induction chemotherapy and
leads to deeper remissions. To address this issue, future comparative studies could focus on MRD levels following midostaurin treatment.

Now that midostaurin is approved, how shall we use it to treat FLT3-mutated AML? Of course, we are awaiting the final publication, and any ancillary studies, and therefore important additional details may emerge to guide us. However, to start with, we should use it exactly as the label states. During the roughly ten years that elapsed from trial conception to drug approval, two important concepts regarding FLT3-mutated AML emerged from studies around the globe. First, allogeneic transplant is an effective consolidation treatment for FLT3-ITD AML. Second, the disease is genetically polyclonal at diagnosis, with sub-clones defined by different mixtures of driver mutations. Midostaurin, as a multi-targeted kinase inhibitor, can fit very neatly into that paradigm, particularly in light of the impressive survival results achieved in the midostaurin patients who underwent transplant in CR1. The data we have before us suggests that a newly-diagnosed patient with FLT3-ITD AML should be given chemotherapy in combination with midostaurin, and, once remission is achieved, proceed as soon as possible to an allogeneic transplant. Transplant in first CR may, of course, not be necessary for those patients with FLT3-TKD AML, as the role of allogeneic transplant for these patients is less obvious.

What about maintenance therapy? Even though CALGB10603 included a maintenance phase of treatment, from what has been presented thus far, there is little to support the use of midostaurin as a maintenance drug. More than half (59%) of midostaurin-treated patients underwent
allogeneic transplant, and per protocol therefore did not receive maintenance therapy. The lack of further separation of the survival curves after the first few months of therapy attests to either the fact that midostaurin doesn’t work as maintenance or that few patients were taking midostaurin- either because they had been transplanted, or because of some other reason. Regardless, midostaurin seems better suited to use during induction and consolidation, given that drug levels are highest early on, and given that its side effect profile (mainly gastrointestinal) doesn’t lend itself readily to patient compliance. Midostaurin administered as maintenance therapy after allogeneic transplant is currently under active study, although it is too early to draw any conclusions about tolerability or efficacy in this setting.39,40

There are, of course, several other kinase inhibitors under investigation for the treatment of FLT3-mutated AML.41 Midostaurin is the “oldest”, and so it’s not surprising that it is the first across the finish line. The inhibitors vary in their selectivity (Figure 1), and it is interesting to note that lestaurtinib, a drug even less selective than midostaurin, failed to lead to improvement in survival in a trial relatively similar in design to CALGB10603.42 Certainly it makes sense to move in the direction of more selective, more potent FLT3 inhibitors, and to this end there are several interesting drug candidates,43-45 and a number of phase 3 trials of these newer FLT3 inhibitors underway. QuANTUM-First (NCT02668653), for example, will test quizartinib in combination with chemotherapy administered during induction, consolidation, and maintenance (including post-transplant) against placebo for newly-diagnosed FLT3-ITD AML patients, and the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) 1506/Morpho trial (NCT02997202) will examine the effect of gilteritinib versus placebo as post-transplant maintenance therapy. Crenolanib, another new FLT3 inhibitor,44 is being tested in combination
with salvage chemotherapy in a phase 3 trial for relapsed or refractory FLT3-mutated AML patients (NCT02298166).

Finally, we must be grateful to the patients who participated in this study, and we must congratulate the investigators, the leadership of the international cooperative groups, and the industry sponsor for having the foresight to design the trial and the resolve to open it globally and to see it through to the end. Their efforts have brought us the first major breakthrough in AML therapy in many years.

Looking back on the years it took to accomplish this breakthrough, we should also take this opportunity to join others in questioning the wisdom of a rigid insistence on OS as the only acceptable endpoint in AML trials. Indeed, this rigidity resulted in the withdrawal from the market of gemtuzumab ozogomycin in 2010, a drug that we subsequently learned is probably quite useful in the treatment of select subsets of AML patients. As we learn more about this disease, and as we sub-divide it into smaller and smaller molecularly-defined groups, we may find that in using OS as our only definitive endpoint we have truly made the perfect the enemy of the good.

**Authorship**

Contribution: M.L. wrote the manuscript.

**Conflict-of-interest**
M.L. receives research funding from Novartis and Astellas. M.L. serves as a consultant for Novartis, Daiichi-Sankyo, Astellas, and Arog.
References


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Figure Legends

Figure 1. Kinase interaction maps. Shown here are the maps for five small molecule kinase inhibitors ranging from very non-selective (staurosporine) to highly selective (quizartinib). The black arrow on each dendrogram denotes the approximate location for the FLT3 receptor. Lestaurtinib, midostaurin, sorafenib, and quizartinib have all been studied as FLT3 inhibitors. Adapted by permission from Macmillan Publishers Ltd: Nature Biotechnology; Davis MI, Hunt JP, Herrgard S, et al. Comprehensive analysis of kinase inhibitor selectivity. Nat Biotechnol. 2011;29(11):1046-1051,26 copyright 2011.

Figure 2. Kaplan-Meier curve for overall survival for patients on CALGB10603. This was presented at the 2015 annual meeting of the American Society of Hematology.
Staurosporine  Lestaurtinib  Midostaurin  Sorafenib  Quizartinib

Adapted from Davis et al; *Nat Biotechnology* 2011; 29(11):1046-1051
Overall Survival
With Number of Subjects at Risk

Survival Probability

0.0
0.2
0.4
0.6
0.8
1.0

Midostaurin 1
Placebo 2

360
221
178
77
0
357
172
143
71
0

survival time (months)

Arm
1: Midostaurin
2: Placebo

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