Blood Spotlight

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Midostaurin approved for FLT3-mutated AML

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Midostaurin was recently approved by the US 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 United States 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. (*Blood*. 2017;129(26):3403-3406)

Introduction

On April 28, 2017, the US Food and Drug Administration (FDA) approved midostaurin (Rydapt; Novartis Pharmaceuticals, Inc) for the treatment of adult patients with newly diagnosed *FLT3*-mutated acute myeloid leukemia (AML).[1] 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 to 21 of each cycle of induction with cytarabine and daunorubicin and days 8 to 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,[2] 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.[3] The most common mutation (~23% of AML cases), an internal tandem duplication (ITD; *FLT3-ITD*), is associated with leukocytosis (often life-threatening) and a high relapse rate, all leading to reduced overall survival (OS).[4-9] The less common mutations (7% of cases) are those found in the tyrosine kinase domain (TKD; *FLT3-TKD*).[9] Most published reports suggest that 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.[7,10-13] 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 of 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.[14-24]

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.[25] By no means a pan-kinase inhibitor, midostaurin can certainly be referred to as a multitargeted kinase inhibitor, at least in comparison with some other compounds (Figure 1).[26] The drug has quite literally been under investigation for decades, originally as an inhibitor of protein kinase C.[27] 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.[28] In a study of 20 relapsed/refractory patients with *FLT3*-mutated AML treated with 75 mg of midostaurin 3 times daily, no patient achieved a complete remission (CR), but peripheral blood blasts were reduced in 70% (14 of 20), and 6 patients achieved a greater reduction in bone marrow blasts of at least 50%.[29] A larger study examined the effects of 50 mg or 100 mg twice daily in both *FLT3*-mutated and nonmutated AML patients and noted blast reductions in about half of the *FLT3*-mutated patients and, interestingly, blast reductions in about a third of the nonmutated patients, but still no CRs.[30] 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.[31] 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.[31] Of 6 cohorts of patients, the most tolerable regimen to emerge was midostaurin 50 mg twice daily on days 8 to 21 following a conventional induction with cytarabine and daunorubicin, which was the regimen carried forward into the phase 3 study.

From these preclinical and early-phase clinical studies, we can draw the following conclusions about midostaurin: (1) the drug is a multitargeted kinase inhibitor with inhibitory activity against both the *FLT3-ITD* and *FLT3-TKD* mutants; (2) as a single agent, it has little or no clinical utility in AML (ie, 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 nonmutated *FLT3* AML, although the specific subtypes 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, which may limit our ability to incorporate it into different AML treatment scenarios; (5) the pharmacokinetics are complex,[29,30,32] with 2 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 ("RATIFY") was a global, randomized, placebo-controlled phase 3 trial carried out in 225 sites across 17 countries to determine whether the addition of midostaurin to induction and

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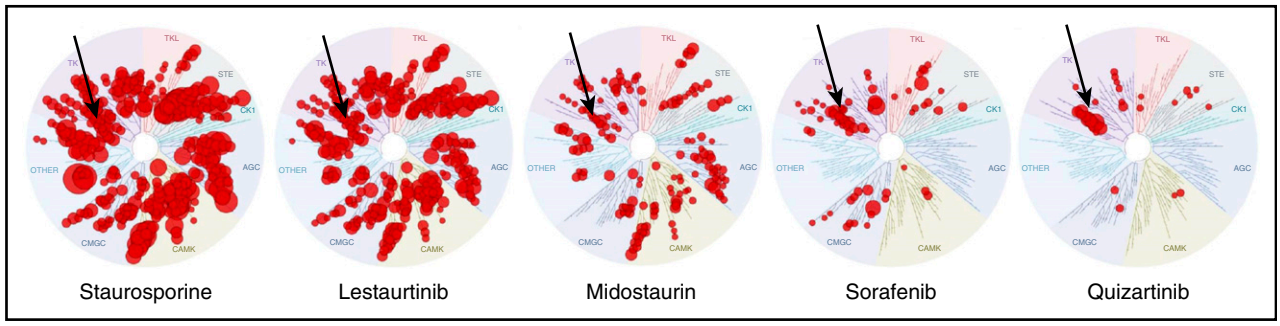

Figure 1. Kinase interaction maps. Shown here are the maps for 5 small-molecule kinase inhibitors ranging from very nonselective (staurosporine) to highly selective (quizartinib). The black arrow on each dendrogram denotes the approximate location for the FLT3 receptor. Lestaurtinib, midostaurin, sorafenib, and quizartinib have all been studied as FLT3 inhibitors. Adapted from Davis et al[26] with permission.

consolidation, followed by 1 year of maintenance, would improve the OS of patients with *FLT3*-mutated AML aged 18 to 59 years.[33] Patients were screened for the presence of FLT3 mutations at the start of the trial. As noted, this trial implemented the regimen deemed to be most tolerable of the ones tested in the phase 1B study. After mutation status was confirmed, patients were randomized to receive either placebo or 50 mg of midostaurin twice daily, administered on days 8 to 21 following a 7+3 regimen (cytarabine 200 mg per meter-square per day on days 1-7 by continuous IV infusion and daunorubicin 60 mg per meter-square per day on days 1-3) and on days 8 to 21 of consolidation with high-dose cytarabine (cytarabine 3000 mg per meter-square IV 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 3 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) indicated that patients randomized to receive midostaurin had a higher median OS, with a hazard ratio of 0.78 compared with those receiving placebo. The 4-year OS rates were 51.4% in the midostaurin arm vs 44.3% in the placebo arm, and the rate of protocol-defined CR (CR within 60 days of initiation of protocol therapy) was 59% vs 53%, respectively.

While we await 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.[1,33] First, patients in all 3 strata (*FLT3-TKD*, *FLT3-ITD* low, or *FLT3-ITD* high ratio) benefitted from midostaurin, and those in the TKD strata actually had the lowest hazard ratio (0.648) compared with placebo. The fact that these 3 groups behave very differently with respect to their clinical outcomes in response to standard therapy, coupled with the biologic activity of midostaurin against nonmutant *FLT3* AML, may indicate that a significant component of midostaurin's efficacy is derived from its multitargeted nature. Second, there was a higher than expected incidence of *FLT3-TKD* patients (23% vs the expected rate of 7%). We can speculate that this is because patients were required to undergo

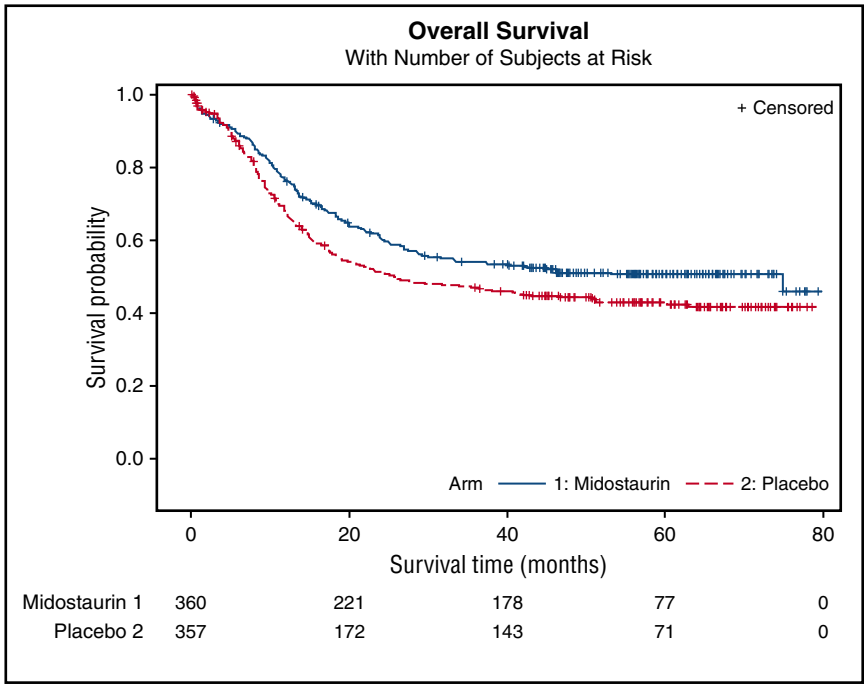

Figure 2. Kaplan-Meier curve for OS for patients on CALGB10603. This was presented at the 2015 annual meeting of the American Society of Hematology, Orlando, FL, 5-8 December 2015. Reprinted from Stone et al.[33]

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 were 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.[27,30,32] A 2-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 with those on the placebo arm. Given the well-described impact of minimal residual disease on outcomes after allogeneic transplant for AML,[34,35] 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 minimal residual disease 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 10 years that elapsed from trial conception to drug approval, 2 important concepts regarding *FLT3*-mutated AML emerged from studies around the globe. First, allogeneic transplant is an effective consolidation treatment of *FLT3-ITD* AML.[14-16,19,21,23,24,36] Second, the disease is genetically polyclonal at diagnosis, with subclones defined by different mixtures of driver mutations.[37,38] Midostaurin, as a multitargeted 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 suggest 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 of midostaurin-treated patients (59%) 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 the fact that either midostaurin does not 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) does not 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 is 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]; a number of phase 3 trials of these newer FLT3 inhibitors are under way. QuANTUM-First (NCT02668653), for example, will test quizartinib in combination with chemotherapy administered during induction, consolidation, and maintenance (including posttransplant) against placebo for newly diagnosed *FLT3-ITD* AML patients; the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) 1506/Morpho trial (NCT02997202) will examine the effect of gilteritinib vs placebo as posttransplant 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 end point in AML trials.[46] Indeed, this rigidity resulted in the withdrawal from the market of gemtuzumab ozogamicin in 2010, a drug that we subsequently learned is probably quite useful in the treatment of select subsets of AML patients.[47] As we learn more about this disease and as we subdivide it into smaller and smaller molecularly defined groups, we may find that, in using OS as our only definitive end point, we have truly made the perfect enemy of the good.

Authorship

Contribution: M.L. wrote the manuscript.

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