Comment on Knapper et al, page 1143

**3 + 7 + FLT3 inhibitors: 1 + 1 ≠ 2**

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In this issue of *Blood*, Knapper et al analyzed 2 consecutive randomized Medical Research Council (MRC) trials in newly diagnosed patients with mutant FMS-like tyrosine kinase-3 (FLT3) acute myeloid leukemia (AML) and suggested no benefit for the addition of the kinase inhibitor lestaurtinib to chemotherapy.1

The path from the original promise of FLT3 inhibition in mutant FLT3 AML to potential approval of a putative FLT3 inhibitor has been long and winding. The relatively disappointing results of early phase trials with the so-called first-generation FLT3 inhibitors in advanced AML were ascribed in part to their nonspecificity for FLT3. Indeed, results from trials in which the more specific quizzartinib2 or gilteritinib3 were used in advanced cases suggested overall response rates in the 50% range, but complete remissions with full hematopoietic recovery were relatively uncommon. However, some degree of response might be good enough to get a patient with relapsed AML to an allogeneic transplant that could promote long-term survival. There are 2 important ongoing trials comparing 1 of these 2 specific single-agent FLT3 inhibitors to standard-of-care salvage therapy in relapsed/refractory mutant FLT3 AML (NCT02039726 and NCT02421939). Of note, quizzartinib is active only against FLT3 internal tandem duplication (ITD) mutations and resistance has emerged in the form of mutant FLT3 tyrosine kinase domain (TKD) AML,4 whereas gilteritinib is active against both types of FLT3 mutations.

While the development of potent single agents was ongoing, investigators hypothesized, in part based on preclinical data, that effective antileukemic therapy in the form of standard chemotherapy in combination with a FLT3 inhibitor might provide increased efficacy compared with chemotherapy alone in newly diagnosed or relapsed patients with mutant FLT3 AML. A nonrandomized study designed to determine a safe dose of midostaurin that might be good enough to get a patient with relapsed AML to an allogeneic transplant that could promote long-term survival. There are 2 important ongoing trials comparing 1 of these 2 specific single-agent FLT3 inhibitors to standard-of-care salvage therapy in relapsed/refractory mutant FLT3 AML (NCT02039726 and NCT02421939). Of note, quizzartinib is active only against FLT3 internal tandem duplication (ITD) mutations and resistance has emerged in the form of mutant FLT3 tyrosine kinase domain (TKD) AML,4 whereas gilteritinib is active against both types of FLT3 mutations.

While the development of potent single agents was ongoing, investigators hypothesized, in part based on preclinical data, that effective antileukemic therapy in the form of standard chemotherapy in combination with a FLT3 inhibitor might provide increased efficacy compared with chemotherapy alone in newly diagnosed or relapsed patients with mutant FLT3 AML. A nonrandomized study designed to determine a safe dose of midostaurin that could be given with induction and consolidation chemotherapy showed that the outcome of those with mutant FLT3 disease was similar to that of wild-type patients.5

Five randomized trials that evaluated the addition of an agent with FLT3-inhibiting activity to chemotherapy in AML have been reported. Two of the trials compared chemotherapy alone to chemotherapy plus the multikinase-targeted agent sorafenib and were not restricted to patients with mutant FLT3 disease. Sorafenib provided no added benefit and caused increased toxicity in previously untreated adults older than 60 years of age.6 However, a trial conducted by the Study Alliance Leukemia Group in Germany in younger adults showed an event-free survival (EFS) benefit when sorafenib was added to chemotherapy, but there was no overall survival (OS) benefit.7 Although not relapsing probably has intrinsic benefit to patients, EFS does not clearly correlate with OS in all cases, especially in AML where therapies after an event, notably allogeneic transplant, provide major survival effects. Neither trial showed a clear benefit for the addition of sorafenib in the subsets with mutant FLT3 AML.

Adding lestaurtinib to standard salvage chemotherapy in relapsed mutant FLT3 AML seemed to offer no benefit.8 However, only about half of the patients on this trial had a sufficient level of FLT3 inhibitory activity in their plasma to inhibit the target. Moreover, using a relatively nonspecific FLT3 inhibitor in relapsed AML where blasts might be particularly addicted to activated FLT3 is not ideal.

The “best” place to use one of the nonspecific multitargeted FLT3 inhibitors

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**Table: Comparison of trials of chemotherapy ± FLT3 multikinase inhibitor in previously untreated mutant FLT3 AML**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ref.</th>
<th>Median age (range), y</th>
<th>N (FLT3 ITD %)</th>
<th>Agent</th>
<th>OS Agent % vs control % (y)</th>
<th>DFS Agent % vs control % (y)</th>
<th>Transplant rate overall CR1 %</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10603/Ratify</td>
<td>9</td>
<td>49 (18-59)</td>
<td>714 (77)</td>
<td>Midostaurin</td>
<td>51 vs 43 (5)</td>
<td>46 vs 36 (5)</td>
<td>57</td>
<td>Benefit seen in all FLT3 mutant subgroups</td>
</tr>
<tr>
<td>AML 15/17</td>
<td>1</td>
<td>49 (5-68)</td>
<td>500 (74)</td>
<td>Lestaurtinib</td>
<td>46 vs 45 (5)</td>
<td>40 vs 36 (5)</td>
<td>45</td>
<td>OS benefit in patients with significant FLT3 inhibition by PIA or on GO + azole</td>
</tr>
</tbody>
</table>

CR1, first complete remission; DFS, disease-free survival; GO, gemtuzumab ozogamicin; PIA, plasma inhibitory assay; Ref., reference.

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should be in newly diagnosed AML which is a relatively chemoresponsive disease but one composed of a variety of subclones, making a pleiotropic inhibitor more useful. There were 2 large randomized trials conducted in younger adults with mutant FLT3 AML (both FLT3 mutant subtypes were included) (see table). The trials seemingly used similar patient populations and chemotherapy. In the C10603 trial, largely conducted in North America and continental Europe, patients received standard daunorubicin/cytarabine ("7 + 3") induction therapy, 4 cycles of intensification with high-dose cytosine arabinoside, with 14 days of placebo or midostaurin (50 mg twice daily on days 8 through 21 of each cycle), and either placebo or midostaurin according to their original randomization for a year of “maintenance.” OS was the primary end point; allogeneic stem cell transplantation was not mandated but was conducted in ~25% of patients in first remission and 57% of patients overall. This study met its primary end point of reducing mortality in the midostaurin arm by 23% (P = .007).9 There was no significantly increased toxicity in patients randomized to midostaurin. EFS and OS benefits were seen in all subgroups of FLT3 mutations (high or allelic burden FLT3 ITD or TKD mutants) in analyses both censored and uncensored for allogeneic transplantation. Midostaurin seemed to be particularly beneficial in those patients who were transplanted in first remission. Thus, results from this trial likely will lead to the approval of a “targeted agent” in this genetically defined subgroup of AML.

The United Kingdom MRC randomized mutant FLT3 AML patients to chemotherapy plus or minus lestaurtinib in 2 successive trials in younger adults. Lestaurtinib was given at the end of chemotherapy administration in each cycle for a maximum of 28 days. Transplantation occurred in 45% of the patients on this trial. In this issue, Knapper et al report that the addition of lestaurtinib was not beneficial. However, post hoc analyses suggested that if more of the patients had a sufficient level of plasma FLT3 inhibitory activity, positive results might have been obtained. Further suggesting that better bioavailability may have improved the results, those patients who received an azole with gemtuzumab ozogamicin and/or those with sufficiently high plasma inhibitory activity against FLT3 had significant benefit from being randomized to lestaurtinib. Though “negative,” the MRC trials offered hope that FLT3/multikinase inhibition in newly diagnosed AML could be useful.

Midostaurin should be approved for use along with chemotherapy in younger FLT3 mutant AML patients, with the suggestion that transplant is an important part of the therapy. An important question that hopefully will be answered with subsequent clinical research will be a comparison of chemotherapy plus midostaurin “vs” a specific inhibitor in patients with mutant FLT3 AML. The negative results in a similar setting with lestaurtinib should not deter further clinical research in this distinctive genetic subgroup of AML.

Conflict-of-interest disclosure: R.M.S. provided ad hoc consultancy services for AbbVie, Amgen, Agios, Celgene, Jazz Pharmaceuticals, Novartis, and Pfizer.

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9. Stone RM, Mandrekar S, Sanford BL, et al. The mid-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (mi), high-dose C consolidation (conso), and as maintenance (maint) therapy in newly diagnosed acute myeloid leukemia (AML) patients (pts) age 18-60 with FLT3 mutations (muts): an international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]) [abstract]. Blood. 2015;126(23). Abstract 6.

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Comment on Kim et al, page 1155

Targeting precursor BCR signaling in ALL
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In this issue of Blood, Kim et al1 investigated the preclinical therapeutic potential of targeting precursor B-cell receptor (pre-BCR) signaling and its mechanism of action in acute lymphoblastic leukemia (ALL). Ibrutinib, a US Food and Drug Administration (FDA)–approved inhibitor of Bruton tyrosine kinase (BTK), was demonstrated to interfere with pre-BCR signaling and specifically suppress in vitro and in vivo cell proliferation of B-ALL cells that express a functional pre-BCR. The synergistic activity with conventional chemotherapeutic agents corroborates ibrutinib as a new therapeutic opportunity for pre-BCR1 ALL.

Pre-B-cell ALL is a hematological malignancy that arises from an oncogenic transformation of an early B-lymphocyte progenitor. It comprises multiple subtypes with distinct constellations of somatic genetic alterations. Despite cure rates exceeding 80% in children, disease-specific and treatment-related toxicity remain important causes of morbidity and mortality in children and adults.2 Therefore, development of targeted therapies that focus on specific oncogenic mechanisms of ALL cells are of great interest to improve outcomes. In this issue of Blood, the investigators explored the activity and...
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