FLT3 Inhibitor Maintenance After Allogeneic Transplantation: Is a Placebo-Controlled, Randomized Trial Ethical?

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Patients with *FLT3* internal tandem duplication (FLT3-ITD) acute myeloid leukemia (AML) are relatively common on any adult leukemia service. These patients tend to be younger and to have high white blood cell counts at presentation, and they are at high risk of relapse if they achieve a remission.[1] Prognosis has improved substantially for these patients in the current era, and cure is now a reasonable expectation that is achieved by more than half of patients. The first major advance was general acceptance of allogeneic hematopoietic cell transplantation (allo-HCT) as the standard of care in first remission when feasible (although European LeukemiaNet guidelines suggest,[2] with some controversy,[3,4] that HCT is not indicated for patients with low-mutant allelic ratio).[1]

FMS-like tyrosine kinase 3 (FLT3) tyrosine kinase inhibitors (TKIs) represent the second major advance. Sorafenib is a multitargeted TKI approved for hepatic and renal cell carcinoma,[5] and has been used off label for FLT3-ITD AML for several years.[6,7] More recently, the US Food and Drug Administration (FDA) approved midostaurin (in 2017) and gilteritinib (in 2018) for clinical use in *FLT3*-mutated AML.[8-11] Appropriately, there are numerous ongoing and planned clinical trials throughout the world designed to determine which of these inhibitors to use in whom and when. On the basis of the results of the RATIFY trial, patients with FLT3-ITD AML now routinely receive induction and consolidation chemotherapy with midostaurin in addition to conventional chemotherapy.[8] Data from that trial suggest that the outcomes in patients receiving midostaurin before transplantation are particularly favorable after allo-HCT in first remission. In addition, several small (single-arm or retrospective) studies suggest that post-HCT maintenance with FLT3 TKIs may improve outcomes even more.[7,12,13] As a result, post-HCT maintenance is being incorporated into the larger prospective, randomized trials of different FLT3 TKIs. The largest of these studies is Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1506—a multi-center, randomized, double-blind, placebo-controlled phase III trial of the FLT3 inhibitor gilteritinib administered as maintenance therapy after allogeneic transplantation for patients with FLT3-ITD AML (ClinicalTrials.gov identifier: NCT02997202)—which opened to accrual in 2017. Although these ongoing trials are actively accruing and address important questions, data presented at the 2018 American Society of Hematology (ASH) Annual Meeting are being interpreted by some as confirming the benefit of post-HCT maintenance therapy with FLT3 TKIs. The concern, therefore, is that a trial that randomly assigns patients to placebo after HCT may be unethical now that maintenance FLT3 inhibition is supposedly proven to prolong survival.

A new question now confronts clinicians. A patient with FLT3-ITD AML who has successfully run the gauntlet of induction and consolidation chemotherapy (with or without midostaurin) followed by allo-HCT has a relatively favorable prognosis, at least compared with 20 years ago. Should such patients receive post-HCT maintenance therapy with one of the multiple FLT3 TKIs available as standard of care to possibly improve outcomes more, or should enrollment in a randomized trial, such as BMT CTN 1506, be offered to determine whether there is indeed an added benefit? This is not a debate between academics about an abstract issue. Patients' lives depend on our treatment decisions, which makes it all the more important for us to understand the data and determine whether we do indeed have equipoise in this matter.

Maintenance Therapy in AML

To date, no randomized trial has demonstrated a survival advantage for maintenance therapy in AML.[14] In *BCR-ABL*–driven diseases, particularly in Philadelphia chromosome–positive acute lymphoblastic leukemia, BCR-ABL inhibitors are routinely used after allo-HCT without any randomized data to support such practice. However, any similarity between BCR-ABL TKIs and FLT3 TKIs is superficial. Unlike FLT3-ITD mutations, the presence of a *BCR-ABL* fusion alone can result in leukemia.[15,16] FLT3-ITD mutations, though important as a final step in

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leukemogenesis, are only one of several sequential mutations that result in AML.[17] BCR-ABL inhibition as monotherapy routinely results in complete responses, whereas that is seldom the case with an FLT3 inhibitor. Thus, the experience with maintenance BCR-ABL inhibition should not be the rationale for a maintenance treatment in AML. Even in acute promyelocytic leukemia, in which maintenance therapy was considered standard, recent data suggest that maintenance therapy may not be necessary with modern inductions.[18]

Data presented at the 2018 ASH Annual Meeting[19,20] might be interpreted as indicative of benefit of post-transplantation TKI maintenance therapy in FLT3-ITD AML, but some issues may compromise the generalizability of these findings.

SORMAIN trial. The randomized, phase II SORMAIN study opened in 15 sites in Austria and Germany and recruited patients from October 2010 until May 2016.[19] Patients with FLT3-ITD AML, who had undergone HCT and were stably engrafted without grades 2 or higher acute graft-versus-host disease, were randomly assigned to receive sorafenib for up to 24 months versus placebo. Assessment of minimal residual disease (MRD) status before HCT was not required. The majority of patients did not receive any FLT3 TKI during induction chemotherapy. Over the more than 5 years of accrual period, only 83 patients were randomly assigned, and the study was terminated because of low accrual. At 30 months, overall survival favored the sorafenib arm, with a hazard ratio of 0.447 ($P = .03$).

Radius trial. The Radius study opened in 19 sites in the United States and accrued 60 patients with FLT3-ITD AML who had undergone HCT and had stable engraftment.[20] Patients were randomly assigned to receive or not receive midostaurin for 12 4-week cycles. The study was purposely not powered to detect a statistical difference between the two arms; thus,, not surprisingly, the study did not detect a difference ($P = .34$); median relapse-free survival was not reached for either arm.

Post-HCT Maintenance As Current Standard of Care for FLT3-ITD AML

Standard of care for any patient is appropriately determined, whenever possible, through randomized trials that include a sufficient sample size reflective of current practice such that the results can be generalizable to the majority of patients. Should we use the results of the above studies, presented at the 2018 ASH meeting, as the basis for a new standard of care for patients with FLT3-ITD AML?

The majority, if not all, of the patients in the SORMAIN or Radius trials did not receive FLT3 TKIs with AML induction, so these patients represent a population no longer relevant to current clinical practice. A remarkable finding in the RATIFY trial is the difference in survival of midostaurin-treated patients who underwent HCT in first remission compared with those in the placebo arm.[8] Given the well-described impact of MRD on outcomes after allo-HCT for AML,[21] this finding may represent evidence that midostaurin truly augments induction chemotherapy and leads to deeper remissions. Even if FLT3 TKIs are effective as post-HCT maintenance therapy in patients who did not receive FLT3 TKI as part of induction, the question remains whether they remain effective in those patients who did. In addition, neither of the two prospective studies presented at ASH[19,20] stratified random assignment of patients on the basis of MRD status. Hence, these studies will not provide data about whether patients with MRD-negative FLT3-ITD AML derive any additional benefit from post-HCT maintenance therapy. With the availability of a commercially available, next-generation sequencing–based MRD test for such patients, demonstration of a benefit of TKI maintenance therapy (or lack thereof) is obviously important to develop and incorporate into risk-based maintenance approaches for our patients. Understanding the impact of MRD on outcomes with post-HCT maintenance is a critical objective of BMT CTN 1506.

As multitargeted inhibitors that were originally developed for inhibiting entirely different kinases than FLT3,[22,23] sorafenib and midostaurin not surprisingly have multiple off-target effects when used to treat FLT3-ITD AML. Although post-HCT maintenance with sorafenib is described as well tolerated, such a label is highly subjective. The common toxicities of sorafenib include hand-foot syndrome, rash, and diarrhea; cardiovascular toxicities, such as hypertension and cardiac ischemia, can occur. The health effects of long-term FLT3 inhibition also are unknown, but they should not be assumed to be harmless. Inhibition of FLT3 affects dendritic cell function, which in turn may affect graft-versus-host disease and/or infection risk.[24] Even if the results of the SORMAIN study[19] hold up, giving sorafenib to all patients after HCT means that seven of 10 patients would be overtreated with relatively toxic therapy from which would they derive no benefit. If the duration of maintenance is set at 24 months for everyone (on the basis of the SORMAIN trial), there currently is no indication that this approach will result in more cures; the relapse curves in the abstract-presented results suggest that many will experience relapse when the therapy is stopped.

Midostaurin seems to lack the necessary characteristics of an ideal maintenance drug, because patients either refuse or are unable to continue taking it for very long. In a recent study (German-Austrian AML Study Group 16-10),[25] just more than half of enrolled patients who had received midostaurin pre-HCT were willing or able to continue the drug post-HCT; of those, most discontinued maintenance earlier than planned. The most common reason for early termination was midostaurin toxicity. Moreover, the drug's pharmacokinetic profile is complex, and adequate high-level FLT3 inhibition may not be achieved clinically.[26,27]

Most of our patients ask us "How long do I have to stay on this therapy?" Drugs like sorafenib and midostaurin clearly

diminish quality of life because of inherent toxicities. With current data, we have no way of knowing which patients should be subjected to this treatment and for how long. In fact, none of the FLT3 TKIs in clinical practice are FDA approved for use as maintenance after allo-HCT, which makes it possible for third-party payers to refuse payment. Sorafenib is not approved anywhere specifically for AML, but it is routinely used off label throughout the world in various stages of FLT3-ITD AML, including post-transplantation maintenance. Midostaurin is approved for newly diagnosed *FLT3*-mutated AML when given with induction and consolidation chemotherapy in both the United States and Europe; in Europe, it is also approved as maintenance therapy after remission is achieved. Gilteritinib was recently approved only for relapsed/refractory *FLT3*-positive AML.

BMT-CTN 1506

The goals of this international, randomized, double-blind, placebo-controlled, phase III trial are to establish whether there is a benefit of FLT3 inhibition in the post-HCT setting and, if so, in which patients. The target accrual is 346 patients with FLT3-ITD AML who will be randomly assigned in a double-blinded fashion to placebo or gilteritinib, a clinically effective and tolerable FLT3 inhibitor.[9] Patients are screened and registered before transplantation to better understand the proportion of patients who are able to proceed to maintenance, and a highly sensitive and specific assay for MRD[28] will be used throughout the trial to potentially provide information about which patients may or may not benefit from maintenance therapy. It is expected that a total of 532 patients will be registered to achieve the random assignment target of 346. At the completion of this trial (which is currently enrolling briskly in 14 countries throughout the world), we should finally have a proven standard of care—one that applies to patients treated with today's therapies (ie, midostaurin with induction chemotherapy). It will also provide critical information about which patients may not need maintenance, important for considerations of both quality of life and health care costs.

Gilteritinib recently received regulatory approval in both Japan and the United States for relapsed or refractory *FLT3*-mutated AML. Both of these countries have numerous centers participating in BMT-CTN 1506, and so with the approval comes a new dilemma. Clinicians who care for patients in the study who experience relapse will want to know immediately if their patient was being treated with gilteritinib or placebo before launching into efforts to obtain the drug on label. Although unblinding of patient data in this type of trial carries a risk of introducing bias, most investigators (as well as the FDA) agree that it is the correct thing to do, so the trial protocol is being amended accordingly.

To relieve the crisis of confidence in the ethics of clinical trials, Benjamin Freedman coined the concept of "clinical equipoise, where the requirement is satisfied if there is genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment."[29] Using this definition of clinical equipoise, we believe the conundrum with FLT3 TKIs as post-HCT maintenance therapy becomes conceptually rather simple. Patients with FLT3-ITD disease are prone to experiencing relapse after HCT, and most investigators agree that drugs like sorafenib or midostaurin may benefit some patients.[12,30] The appearance of the relapse-free survival curves in both ASH studies suggests that this approach may not cure anyone but rather may just delay relapse. However, even if maintenance therapy can benefit some patients by delaying relapse, we are unable to accurately identify those patients. Treatment of all to benefit a minority would be reasonable if the available agents had much less toxicity than that seen with either sorafenib or midostaurin.

Is a placebo-controlled trial of a FLT3 inhibitor as post-HCT maintenance unethical? On the contrary, settling for an expensive, potentially less-than-optimal treatment on the basis of data developed in underpowered studies that involved patients who did not receive current standard of care seems not to be in the best interests of our patients. We believe that we can do better. Our position is that clinical equipoise as defined by Dr Freedman[29] clearly still exists for this important issue, and prospective, randomized trials such as BMT CTN 1506 remain critical to determine the ultimate role for post-HCT maintenance in FLT3-ITD AML.

Finally, we must all recognize that this topic is broadly applicable to the field of oncology as a whole. More and more, we are defining cancers by their genetics, so, perforce, each type of cancer is divided into smaller and smaller subsets. Whether it be FLT3-ITD AML or *BRAF*-mutated gliomas,[31] successful and responsible translation of the findings of small, nonrandomized trials into therapeutic strategies that truly benefit our patients requires randomized trials. Implementation of those trials against the headwinds generated by the excitement about transformative new therapies requires an innovative trial infrastructure, one fleet enough to open and accrue even as the field changes beneath its feet. Our patients' lives—as well as the quality of those lives—depend on our ability to accomplish this.

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