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# Maintenance therapy after allogeneic hematopoietic cell transplantation for acute myeloid leukemia

Frederick R. Appelbaum

*Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, WA, USA*

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ABSTRACT

With improvements in the safety of allogeneic hematopoietic cell transplantation, disease recurrence following the procedure is now the most frequent reason for treatment failure. Administration of maintenance therapy after transplantation is one way to try and prevent recurrence. This paper provides a brief review of the topic.

## Introduction

There are several reasons why administration of maintenance therapy after allogeneic hematopoietic cell transplantation (HCT) for acute myeloid leukemia (AML) might work. First, disease burden is usually small early after transplant. Second, the setting provides an opportunity to select drugs that mechanistically work with the allogeneic graft-versus-leukemia (GVL) effect. Third, and perhaps most importantly, maintenance needn't cure the disease; all that is needed is to prevent relapse until the GVL effect has sufficient time to accomplish its task. In the setting of chronic myeloid leukemia (CML) where polymerase chain reaction (PCR) detection of *BCR-ABL* provides a sensitive and specific measure of disease, we previously found that persistence of disease at 3 months after transplant was as common in patients who were ultimately cured of their disease as in those who weren't, whereas detection at 6–12 months was highly predictive of subsequent relapse, demonstrating that it took up to 6 months for the GVL effect to eradicate disease (Fig. 1) [1]. The requirement for a significant amount of time for the GVL effect to have its full impact likely reflects both the gradual recovery of immune function after transplant as well as the result of removal of graft-versus-host disease (GVHD) immune prophylaxis.

There are also reasons to be skeptical about the prospects for successful maintenance therapy. The leukemic cells remaining after

*E-mail address:* fappelba@fredhutch.org.

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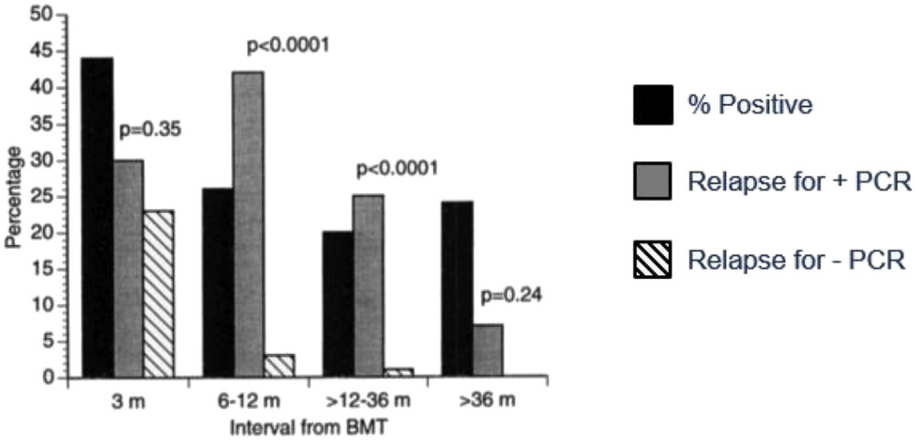


**Fig. 1.** Shown are the percentages of patients testing PCR-positive and the Kaplan-Meier estimate of relapse associated with a PCR-positive and negative test. At 3 months post-transplant, 44% tested PCR-positive, with a subsequent relapse rate of 30% in those who were PCR-positive and 23% in those who were PCR-negative [1].

induction, consolidation, and transplantation, no matter if few in number, are likely to be highly resistant to all possible therapies. Further, it is difficult to administer maintenance early after transplantation because of the fragility of the newly transplanted marrow, the existence of other transplant-related complications, and because patients are typically on multiple medications making undetected drug-drug interactions almost a certainty.

Despite many attempts, no clear role for maintenance after allogeneic HCT for AML has yet emerged.

## Hypomethylating agents

Hypomethylating agents have attracted considerable attention as maintenance therapy because they have direct antileukemic effects and a well-established toxicity profile that should allow for their safe administration in the post-transplant setting. Further, hypomethylating agents have been shown to upregulate silenced leukemia antigens and to promote re-expression of endogenous retroviral elements, suggesting that they might possibly enhance a GVL effect. Enthusiasm for their use grew with reports of occasional patients who had relapsed post-transplant treated back to remission using hypomethylating agents alone, and by the publication of small but seemingly promising phase 1/2 studies. Recently, however, the MD Anderson group reported the outcome of a prospective randomized phase 3 trial of 5-azacytidine (AZA) for AML maintenance therapy following allogeneic HCT [2]. In their study, 187 post-transplant patients were randomized to AZA (n = 93) or control (n = 94). AZA was given as 32 mg/m$^2$/day subcutaneously for 5 days each month, with a plan to give 12 cycles. Although AZA was generally well tolerated, there was no evidence that administration of AZA improved relapse-free or overall survival (Fig. 2).

A considerable number of other preliminary studies have recently been reported or are underway that are testing alternative, but related approaches. These include the use of oral AZA, AZA plus gemtuzumab ozogamicin, AZA plus donor lymphocyte infusions, decitabine, and guadecitabine [3,4]. However, the definitively negative results of the MD Anderson randomized trial diminish the likelihood that any of these alternatives will be remarkably successful.

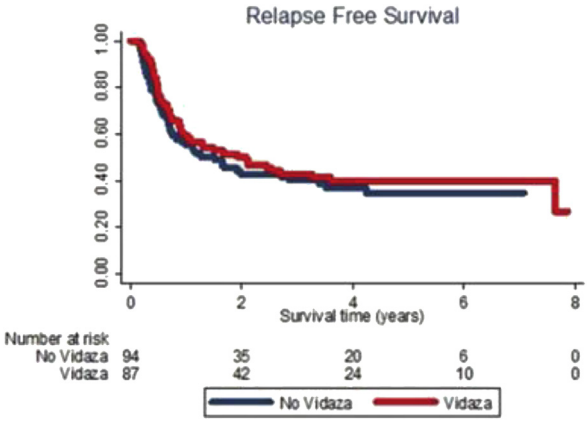


**Fig. 2.** The two curves represent the probability of relapse-free survival in 87 patients randomized to receive post-transplant maintenance with 5-azacytidine compared to the 94 patients randomized to standard of care [2].

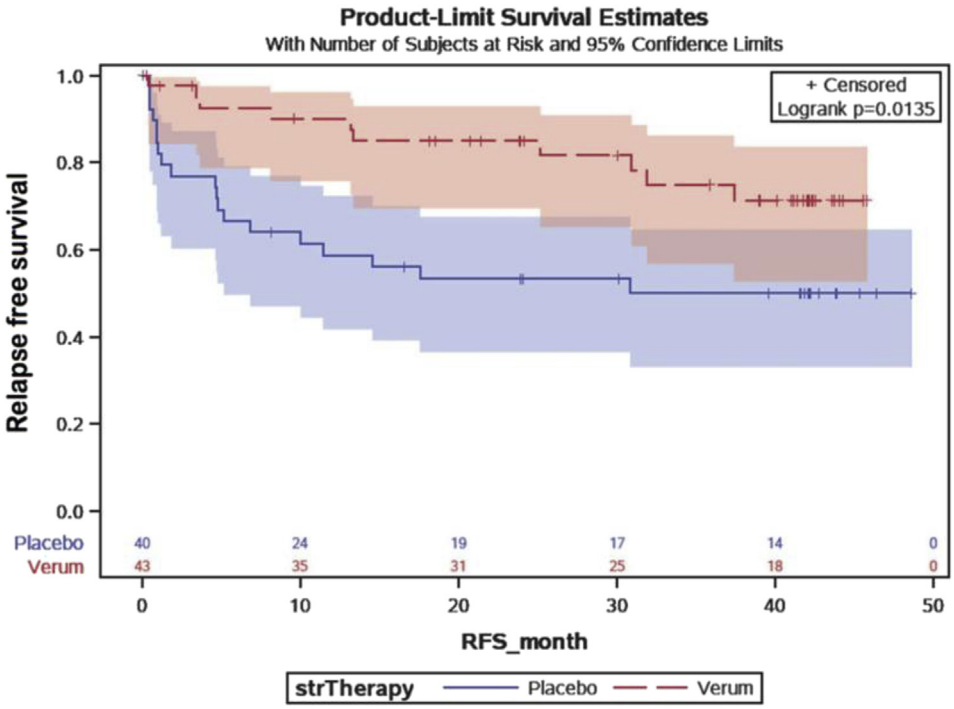


**Fig. 3.** The figure shows the relapse-free survival estimates of 43 patients who received sorafenib post-transplant versus 40 who served as controls [3].

### *FLT3* inhibitors

In the one-third or so of patients with AML whose disease includes a *FLT3* mutation, inclusion of the *FLT3* inhibitor midostaurin is now standard of care. The randomized trial demonstrating the benefit of midostaurin administered the drug during induction, consolidation, and maintenance, but if patients went on to transplant (which 57% did), midostaurin was then discontinued [5]. Patients who went on to transplant benefitted from having received midostaurin during induction and consolidation, and likewise, patients who received midostaurin during induction and consolidation benefitted from subsequent transplantation. The study thus demonstrated a benefit for both midostaurin and transplantation in patients with *FLT3*-mutated AML but leaves unanswered the question of whether such patients would benefit further by receiving a *FLT3* inhibitor post-transplant. A phase 2 study recently approached this question by randomizing 60 *FLT3*+ post-transplant patients between midostaurin 50 mg twice daily for 12 months or standard of care [6]. The estimated 18-month relapse-free survival was 76% in the standard of care arm versus 89% in the midostaurin arm, with an estimated relapse rate of 24% versus 11% respectively. Eight of the 30 midostaurin patients discontinued the drug due to intolerable nausea. While this study suggests a possible benefit for midostaurin, note the small size of the study, the limited follow-up and the fact that many of these patients did not receive midostaurin during induction and consolidation.

Sorafenib has also been studied as post-transplant maintenance for patients with *FLT3*+ AML. A report from Brunner et al. suggested a potential benefit, but this study was small, retrospective and uncontrolled [7]. More recently, the German group attempted to perform a prospective randomized trial of sorafenib maintenance post-transplant. Over a 6-year period, 83 patients were randomized to receive post-transplant sorafenib or placebo. Unfortunately, the study was terminated prior to full recruitment due to slow accrual. Results presented at the American Society of Hematology meeting in 2018 showed that sorafenib was generally well tolerated at a dose of 400 mg per day, and its use was associated with improved relapse-free survival (Fig. 3) [8]. But like the post-transplant midostaurin trial, the study was small, and in this case, none of the patients received standard *FLT3* inhibition during induction and consolidation prior to transplant.

At this point, the question of the utility of the use of a *FLT3* inhibitor as post-transplant maintenance in patients with AML who have already received effective *FLT3* inhibition as part of induction and consolidation remains open. The trial BMT-CTN 1506 will hopefully help provide an answer. This prospective trial will randomize 346 patients between placebo and gilteritinib, a potent, relatively non-toxic oral *FLT3* inhibitor. Unlike previous studies, this one is being conducted in an era where most patients will have received a *FLT3* inhibitor as part of induction and consolidation. In addition, all patients will be studied for presence of minimal residual disease at the beginning of the transplant procedure.

### Adoptive immunotherapy

A long-sought goal of the transplant community has been to harness the power of the observed GVL effect. Therapies that non-

specifically enhance immune reactivity, such as reducing the amount of GVHD prophylaxis, adding donor leukocyte infusion (DLI), or administering check-point inhibitors, can increase the GVL effect, but at the expense of increased GVHD, and none of these approaches has advanced to a standard therapy. Recently, Chapuis et al. from the Fred Hutchinson Cancer Research Center described a method for the generation of gene-modified T cells that specifically target an HLA-A2 specific WT1 epitope. In their small preliminary trial, they were able to show they could generate such cells for every patient approached, that the T cells could be given without toxicity, and that they persisted for months to years after infusion. Among the 12 high-risk patients given these cells as post-transplant maintenance (high risk by virtue of presence of minimal residual disease or high-risk cytogenetic/molecular features), none has relapsed [9]. While obviously very preliminary, this study and others like it provide a foreglimpse of what is possible.

## Summary

We are witnessing major advances in several areas of science that have the potential to transform the concept of maintenance therapy for AML. First, studies of the mutational landscape of AML are allowing us to identify the driver mutations in individual cases of AML. Second, we have invented techniques that enable the detection of miniscule quantities of residual disease. Third, an increasing number of specific inhibitors of mutated or activated genes or gene pathways are becoming available. And fourth, the new synthetic biology is providing the means to create engineered immune cells of great potency and specificity. Combining these advances should allow us to evaluate and monitor patients post-transplant, and to intervene with specific therapies at the appropriate moment. But AML is a relatively rare and variable disease. To get from where we are today to the goal of effective post-transplant interventions will require continued investment in each of these areas of science, as well as the continued cooperative studies of the community of clinical scientists who devote themselves to the care of patients with AML.

## Declaration of competing interest

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