

# inside **blood** commentary

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Comment on Dreger et al, page 3841

## Transplant for CLL: still an option?

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In this issue of *Blood*, Dreger et al present a statement from the European Research Initiative on CLL (ERIC), providing a framework for discussing the role of allogeneic hematopoietic stem cell transplantation (HSCT) in the era of novel targeted agents for chronic lymphocytic leukemia (CLL).<sup>1</sup>

**H**SCT remains the only potentially curative therapy for CLL. Sustained minimal residual disease (MRD) negativity in patients with high-risk disease has only been seen following HSCT, with up to 50% of patients achieving permanent MRD negativity.<sup>2</sup> Often, this only occurs following immunologic manipulation, such as withdrawal of immunosuppression or donor lymphocyte infusion, or following the development of chronic graft-versus-host disease (GVHD), illustrating the importance of the graft-versus-leukemia (GVL) effect.<sup>2</sup> Long-term event-free and overall survivals (OSs) are good following HSCT, up to 45% and 60%, respectively, at 5 years, and a 5-year OS of nearly 80% has been reported for patients with chemosensitive and nonbulky disease. Unlike with other therapies, the presence of known poor-risk features, including the presence of unfavorable genetic abnormalities (17p-, TP53 mutation) or refractoriness to purine analogs, does not negatively impact those outcomes.<sup>3</sup> In 2007, the European Blood and Marrow Transplant group identified patients who relapsed within 12 months of exposure to purine analogs, within 24 months of treatment with purine analog-based combination therapy, or patients with p53 abnormalities as appropriate candidates for HSCT.<sup>4</sup>

The widespread application of HSCT has been limited by its toxicity, particularly in a patient population where the median age is 72. The introduction of reduced-intensity conditioning regimens has led to improved early mortality, where <5% of patients die within the first 100 days, and the hematopoietic cell transplant comorbidity index has allowed for better patient selection, further improving mortality. Despite significant improvements, nonrelapse mortality (NRM) remains at 15% to 30% during the first 2 years after transplant,<sup>1</sup> typically owing to complications of acute and chronic GVHD, which can affect up to 70% of patients.

Continued efforts to improve outcomes for patients with CLL have led to the development of novel targeted agents. Both ibrutinib and idelalisib, B-cell receptor (BCR) signal inhibitors (BCRi), have been approved by the Food and Drug Administration for use in patients with relapsed or refractory CLL, and ABT-199, a selective B-cell lymphoma (BCL)-2 antagonist (BCL2a), has shown impressive efficacy in early clinical work. In the phase 3 study comparing idelalisib plus rituximab with rituximab plus placebo, the rates of progression-free survival (PFS) and OS were significantly superior in the idelalisib group, and overall response was 81% in the idelalisib

group compared with 13% in the placebo group (odds ratio, 29.92;  $P < .001$ ).<sup>5</sup> Similarly, in the phase 3 study comparing ibrutinib to ofatumumab, PFS and OS were significantly better for patients treated with ibrutinib, with 90% OS at 12 months.<sup>6</sup> In both studies, high-risk prognostic features did not impact response rates. Rates of adverse events were similar between the investigational agent and the antibody in both studies, and most were grade 2. Notably, relatively few patients achieved complete remissions, let alone MRD negative disease. The importance of this has been questioned, but nevertheless, patients are left with a population of CLL cells that can acquire resistance mutations.<sup>7</sup> Although progressions on ibrutinib are uncommon thus far, they often lead to dismal outcomes.<sup>8</sup> This highlights a need not only to continue the search for better agents, but also to better delineate how to incorporate HSCT into the current treatment paradigm.

Although it is difficult to define the role of HSCT with the data that are currently available, Dreger et al summarize what we know and what we do not know about both HSCT and novel agents to inform decision making. It has been well established that HSCT is an effective treatment, even in the presence of poor prognostic features. BCRi produce high response rates and prolong PFS, and remissions thus far appear to be durable, but complete remissions are rare, and patients with 17p- still have inferior outcomes with BCRi compared patients who do not harbor this mutation.<sup>9</sup> In contrast, HSCT appears to abrogate the poor prognostic effect of 17p-. Although early mortality is low with reduced-intensity conditioning, the risk of GVHD and later NRM is still considerable. The novel agents, in comparison, have a favorable safety profile. It is important to note, however, that although survival plateaus after HSCT and morbidity decrease with time, the prognosis of patients treated with BCRi/BCL2a longer than 2 to

3 years is unknown, as is the effect of long-term treatment with these agents.

The authors recommend that all high-risk patients be considered for treatment with BCRi/BCL2a, preferably in a clinical trial. HSCT should be considered for patients who fail to respond, as well as for certain responders. Younger patients with no comorbidities, a good donor, and high-risk disease are still appropriate candidates for HSCT, whereas older patients with significant comorbidities, poor donor options, and lower risk disease may be more appropriately continued on the novel agent. The question of which is a superior strategy is unlikely to be answered definitively without a prospective study, and the premature closure of Alliance 100701 indicates that a transplant study in CLL may be difficult to complete. However, HSCT and BCRi may have complementary roles. Ibrutinib has evidence of efficacy in murine GVHD models,<sup>10</sup> and a clinical trial evaluating its effect against steroid-refractory chronic GVHD is ongoing (#NCT02195869). It is interesting to think about how BCRi could be used earlier after HSCT to augment disease control while GVL is being established, particularly if it can attenuate chronic GVHD. As we learn more about the long-term effects of BCRi/BCL2a, we will be able to make more clear recommendations with respect to the role of HSCT, but until more is known, HSCT remains an important treatment modality for patients with high-risk CLL. Along with experts in CLL, HSCT experts should continue to have a role in ensuring patients are fully informed with respect to all of their therapeutic options as we enter a new era in CLL management.

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## CLINICAL TRIALS & OBSERVATIONS

Comment on Collins et al, page 3880

# GlycoPEGylated factor IX: a new step forward

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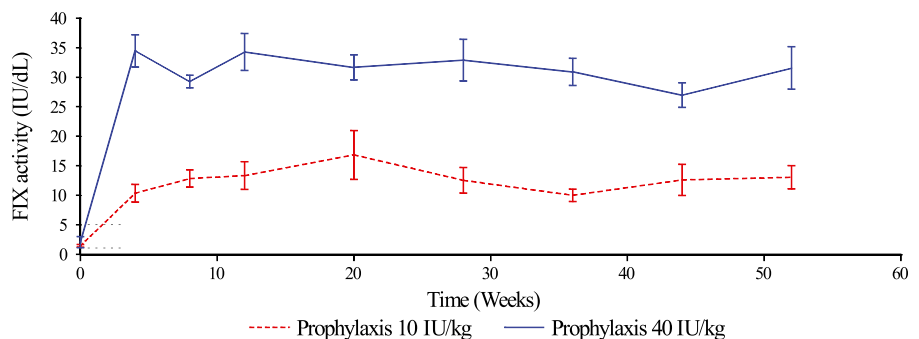
In this issue of *Blood*, Collins et al provide the results of a prospective, randomized, single-blind, phase 3 trial on the use of nonacog beta pegol, a new long-acting glycoPEGylated factor IX (FIX) molecule for the treatment and prevention of bleeding episodes in 74 patients with hemophilia B.<sup>1</sup>

It was 50 years ago that Dr Judith Pool published a paper about cryoprecipitate, the first form of replacement therapy for patients with hemophilia.<sup>2</sup> There have been many steps forward in hemophilia therapy since that seminal discovery. Clotting factor VIII (FVIII) and FIX concentrates were first derived from human plasma, and in the 1990s, they were manufactured using the recombinant technology.<sup>3,4</sup>

During the last 2 decades, the availability of safe and effective replacement therapy has changed the natural history of the disease, thanks to rapid bleeding control and the

widespread use of prophylaxis, which is the standard of care aimed at avoiding crippling joint damage.

In addition to its undeniable benefits, replacement therapy still has drawbacks mainly related to the intravenous route of administration and the relatively short half-life of clotting factors. Recently, bioengineered molecules have been developed to overcome some of these limits. In particular, long-acting FIX molecules, although still delivered intravenously, will have a profound effect on prophylaxis feasibility and adherence to treatment in patients with hemophilia B.



FIX trough levels attained and maintained with nonacog beta pegol used on prophylaxis at 10 IU/kg/week (broken line) and 40 IU/kg/week (continuous line). See Figure 2 in the article by Collins et al that begins on page 3880.