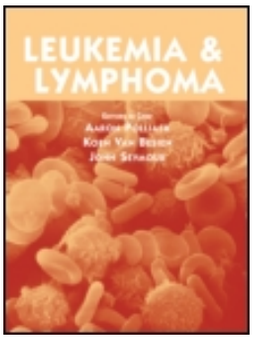

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COMMENTARY

To the end of chronic lymphocytic leukemia: what should be the role of allogeneic transplant?

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In this issue of ***Leukemia and Lymphoma***, Hebenstreit *et al*. report on the outcome of reduced intensity allogeneic transplant in 50 patients with CLL [1]. For patients transplanted early, or in or near complete remission (first partial remission [PR1] or complete remission [CR]), the relapse rate was low, and progression-free survival (PFS) was 71% at 4 years (albeit with shorter median follow-up). Some patients transplanted with active disease were also cured, but if lymphadenopathy > 5 cm was present, the PFS was only 22%; if there was a lymphocytosis $> 5 \times 10^9$/L, PFS was 18%. Thus, this publication confirms other studies that point to an important role for allogeneic transplant as a potentially curative modality for the correct patients. Most important to glean from trials such as this are the characteristics of patients who are potentially curable with allogeneic transplant. A second and equally important question is: what are those disease characteristics that would indicate a patient should be subjected to the morbidity and mortality of allogeneic transplant in order to enjoy long-term survival?

But does transplant still matter at all in the novel era of targeted therapies? Obinutuzumab has demonstrated the ability to achieve minimal residual disease (MRD) negativity in previously untreated patients with chronic lymphocytic leukemia (CLL) when used in combination with chlorambucil, and demonstrates clear improved efficacy over rituximab [2]. It is likely also superior to ofatumumab, in the pivotal study of which MRD negativity was not reported. Even more impressive are the data with the B-cell pathway inhibitors, including the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib and the phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib. Both demonstrate remarkable response rates in chemotherapy-refractory disease and excellent PFS in untreated patients with CLL [3,4]. And just over the horizon is the bcl2 inhibitor, ABT-999, with impressive activity. Targeted cellular therapies utilizing chimeric antigen receptor (CAR) T cells also show great promise, but are more difficult to implement, more toxic and require a much better understanding before they approach routine clinical use [5]. Some are talking about the end of CLL [6]. Does allogeneic transplant still play a role? We believe it might.

First, although response rates are high to the novel agents, few of the responses are complete, and ongoing treatment seems necessary to assure ongoing response. It is important to remember that since these agents cause preferential circulation of the CLL cells, CR and MRD negativity are a "higher bar" than they are with chemotherapy. But, these agents do work slowly, and partial suppression of tumors has been associated with escape and tumor evolution. This is confirmed by the reports of resistance developing to ibrutinib due to single base pair mutations in BTK and phosphoinositide phospholipase C (PLCγ) [7]. Additionally, the B cell receptor (BCR) antagonists do not control Richter transformations. There are characteristics that predict which patients are at risk for developing resistance and transformations. When examining the data reported on ibrutinib resistance, all of the patients (six reported thus far) had evidence of genomic instability, with either del17p, del11q or complex karyotypes, suggestive of a mutator phenotype. These same characteristics help predict for development of Richter transformation. When examining the ibrutinib data for treatment-naive patients aged 65 years or older, only one out of 31 patients has progressed at 2 years. This patient developed a Richter transformation at 6 weeks, likely present before going on study. By contrast, the del17p relapsed/refractory population demonstrates a median PFS of approximately 2 years [8]. As seen here, the B cell receptor (BCR) antagonists are excellent agents, but they do have limits. Understanding these limits enables us to choose which patients need to go for allogeneic transplant. Through the likely use of graft versus leukemia, allogeneic transplant offers these patients a chance at long-term survival. Data presented in the article by Hebenstreit *et al*. suggest how we can improve the likelihood of a transplant having a good outcome. Performing the transplant with the disease under excellent control, and early in its course, are the two most significant factors predicting for a good outcome. As luck would have it, the BCR antagonists demonstrate remarkably high response rates and excellent disease debulking in these patients with adverse interphase florescence *in situ* hybridization (FISH) abnormalities. Obtaining excellent

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disease control with BCR antagonists, followed by an allogeneic transplant in order to provide durable PFS, seems a logical combination. Because of the toxicity profile of these agents, they can also be used right up to the transplant.

Future areas of investigation will be the use of the BCR antagonists during the transplant to provide continued disease control and their use post-transplant to improve the graft versus leukemia effect. It is interesting to hypothesize that since both BTK and PI3K inhibitors are associated with decreased numbers of infections over time, the immune system itself is able to restore functionality [8]. Additionally, *in vitro* studies (and some *in vivo* observations) suggest that these agents may have an impact upon enhancing graft versus leukemia.

That being said, which patients with CLL should be directed toward transplant in 2014? For us, the recommendation should be based mostly on disease characteristics and response to treatment. Both idelalisib and ibrutinib will soon be approved for the treatment of CLL. Initially they will be used in patients with recurrent disease, and their use should be prioritized over allogeneic transplant. Only patients failing ibrutinib or patients with 17p abnormalities responding to ibrutinib should in our opinion be offered allogeneic transplant. It will be important, though, to proceed to transplant at the optimal time. For the patients with deleted 17p, that would be at the time of CR. But for those progressing on ibrutinib, there may be a short window between progression and the development of bulky disease, making the transplant less successful. In the future we may identify other categories of patients who will not enjoy long-term remissions with BCR antagonists and who may benefit from allogeneic transplant. Donor source or age should play little role in the decision to proceed with transplant [9]. Comorbidities, functional level, degree of frailty and possibly mental health are more important determinants of outcome than patient age *per se* [10]. Since CLL is often a familial disease, special attention should be directed to sibling donors of patients with CLL [11].

Once we succeed in identifying the patient population that requires an allogeneic transplant, combined with the necessary characteristics to enable a successful transplant, we will be able to make allogeneic transplant a non-experimental therapy for CLL.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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