Transplantation in Chronic Lymphocytic Leukemia

Does It Still Matter in the Era of Novel Targeted Therapies?

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KEYWORDS

• Chronic lymphocytic leukemia • Allogeneic hematopoietic stem cell transplantation
• Novel substances • High-risk patients • GvL • GvHD

KEY POINTS

- Hematopoietic stem cell transplantation (HSCT) offers the only potentially curative approach to the treatment of chronic lymphocytic leukemia (CLL) but is suitable only for a minority of patients and is associated with significant treatment-related mortality and morbidity.
- Guidelines suggest that HSCT is indicated in fit CLL patients with a suitable matched donor, del17p-/TP53 mutations, or who have relapsed shortly after chemo-immunotherapy (high-risk patients).
- HSCT must always be considered in view of other, potentially less toxic therapies.
- Several new agents demonstrate impressive and durable responses in high-risk patients who might be candidates for transplant.
- The choice of HSCT versus a novel agent is one that must be gauged on a patient-by-patient basis.

INTRODUCTION: HOW THE AVAILABILITY OF IMMUNOCHEMOTHERAPY AND NOVEL SUBSTANCES ARE CHANGING CHRONIC LYMPHOCYTIC LEUKEMIA TREATMENT

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in the Western world and is characterized by the progressive accumulation of mature typically CD5-positive B lymphocytes within the blood, bone marrow, and secondary

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Hematol Oncol Clin N Am 28 (2014) 1055–1071
http://dx.doi.org/10.1016/j.hoc.2014.08.005 **hemonc.theclinics.com**
0889-8588/14/$ – see front matter

lymphoid organs.[1–3] Although CLL is mostly an indolent disease, there are subgroups of patients that die within a few years from diagnosis despite intensive therapy. Over the past decade, significant advances in the understanding of the pathogenesis of CLL have led to the development of a range of novel treatment options for patients requiring therapy. In young patients without significant comorbidities, immunochemotherapy with fludarabine, cyclophosphamide, and the anti-CD20 monoclonal antibody (mAb) rituximab (FCR) has been established as the first-line standard-of-care treatment.[4,5] Although this regimen leads to high overall response rates (ORR) and a long progression-free survival (PFS), it is unsuitable for certain subgroups of patients: these include patients with p53 abnormalities who respond poorly to purine-analogue-based immunochemotherapy and relapse often and early,[6–8] and elderly patients with comorbidities unable to tolerate FCR-associated toxicities.[9]

In the latter, chlorambucil is a widely accepted therapeutic option, and the combination with rituximab is generally well tolerated and improves PFS.[10,11] A recently published pivotal phase 3 trial by the German CLL Study Group showed that the type 2 anti-CD20 antibody obinutuzumab was superior to rituximab when each was combined with chlorambucil.[12] Ofatumumab is another fully humanized anti-CD20 mAb that has revealed high efficacy in untreated and relapsed/refractory patients, and even in patients pretreated with rituximab.[13–15] Several recent clinical studies indicate that novel agents interfering with B-cell receptor (BCR) signaling, such as the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib, the PI3kp110δ inhibitor idelalisib, or the BCL2 inhibitor navitoclax, are well tolerated and very active, even for the treatment of relapsed and fludarabine-refractory CLL, and various combinations with immunochemotherapy are currently being tested in registration studies or are under clinical development.[16–22] Although these early results appear very encouraging, it is yet to be seen how they will translate into long-lasting remissions and disease control. In addition, a recent report indicates that patients can become resistant to ibrutinib therapy because of mutations of drug binding sites within the BCR pathway, and similar resistance mechanisms to other substances are likely.[23]

The only curative treatment option in CLL so far is allogeneic hematopoietic stem cell transplantation (HSCT).[24] HSCT takes advantage of the graft-versus-leukemia (GvL) effect mediated by differentiated transplanted effector cells, which are capable of mounting an antitumor immune response and inducing long-lasting clinical remission.[25] However, HSCT is only suitable for a selected group of patients, and the challenges that HSCT has to face in 2014 are the following:

- To identify and predict which patients and specific subgroups of patients benefit most from HSCT, and in which novel substances are unlikely to alter the biological course of their disease
- To recognize the appropriate time point when HSCT should be offered
- To determine if and how HSCT should be best combined with novel therapeutic options.

This review summarizes the current knowledge on HSCT in CLL and critically discusses its role in the era of novel treatment strategies.

THE UNMET NEED OF POOR-RISK CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS BEFORE THE AVAILABILITY OF NOVEL SUBSTANCES

Although immunochemotherapy has significantly improved the outcome for most CLL patients, there are subgroups of patients who have repeatedly been identified as having a poor response to therapy. The pivotal report by Döhner and colleagues[6]