New Insights Into Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia: A 2015 Perspective

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Keywords
Allogeneic hematopoietic stem cell transplantation, chronic lymphocytic leukemia, high-risk patients, immunochemotherapy, novel substances

Abstract: A considerable body of evidence demonstrates that allogeneic hematopoietic stem cell transplantation (HSCT) offers the only potentially curative treatment option for patients with chronic lymphocytic leukemia (CLL). However, this approach is suitable for only a minority of CLL patients, owing to its significant treatment-related mortality and morbidity. Until recently, internationally accepted guidelines suggested that HSCT should be considered in physically fit CLL patients who carry poor-risk features, such as *TP53* abnormalities, or who had a short response to previous immunochemotherapy. However, several new agents and alternative treatment strategies are available that demonstrate impressive and durable responses, even in CLL patients who previously might have been candidates for transplant. The decision about which patients merit HSCT therefore remains important, and HSCT must now be considered in light of other less toxic therapies. Until data on the long-term efficacy of novel treatment approaches mature, the choice of HSCT vs alternative strategies must be assessed on a patient-by-patient basis, and treatment in the setting of randomized clinical trials should be pursued whenever possible.

Introduction: HSCT in CLL Before, During, and After the Era of Novel Treatment Approaches

Chronic lymphocytic leukemia (CLL), the most common adult leukemia in the Western world, is generally an indolent disease characterized by the accumulation of mature B lymphocytes within blood, secondary lymphoid organs, and bone marrow.[1,2] In most patients, first-line immunochemotherapy with the current gold-standard treatment, FCR (fludarabine, cyclophosphamide, and rituximab [Rituxan, Genentech/Biogen Idec]), results in high overall response rates (ORR) and long progression-free survival (PFS).[3,4]

Nevertheless, FCR is unsuitable or unsuccessful for select groups of patients, including patients with *TP53* abnormalities, and some patients respond poorly or relapse shortly after initial therapy.[5,6] Until recently, allogeneic hematopoietic stem cell transplantation (HSCT) has been a promising option for poor-risk CLL patients and the only treatment approach with curative potential.[7] HSCT takes advantage of the graft-vs-leukemia (GvL) effect, which is mediated by transplanted immune effector cells that mount long-lasting antitumor immune responses. However, HSCT can only be used for a minority of CLL patients, given the generally advanced age at presentation or the existence of severe comorbidities. In addition, HSCT is associated with significant treatment-related mortality and morbidity, largely due to chronic graft-vs-host disease (cGvHD).[8-11]

The role of HSCT in CLL has recently been further challenged by the success of several well-tolerated and highly active novel treatment options. These primarily consist of kinase inhibitors that interfere with B-cell receptor (BCR) signaling[12] and BCL-2 inhibitors, but also include alternative adoptive cell therapy strategies such as CD19 chimeric antigen receptor (CAR) T cells.[13] Although the early results appear very encouraging, it is unknown whether these therapies will translate into long-lasting remissions and disease control, especially in poor-risk CLL patients. Concerns regarding the long-term efficacy of kinase inhibitors also have been raised; resistance to therapy can occur[14] and a considerable number of patients must discontinue therapy.[15] Thus, HSCT in CLL is facing 3 main challenges: (1) identifying which patients will benefit the most from HSCT and which are unlikely to respond to kinase inhibitors, (2) recognizing when during the course of the disease HSCT should be offered, and (3) determining the potential of combination approaches. The aim of this review article is to summarize the current knowledge on HSCT in CLL and to critically discuss its role in the era of novel treatment strategies.

The Clinical Challenges Associated With Poor-Risk CLL Patients

TP53 *Abnormalities Are Negative Predictors for Response to Standard Immunochemotherapy and Survival*

Although combinations of chemotherapy and monoclonal antibodies have improved outcomes in the majority of CLL patients, some subgroups with a poor response to standard immunochemotherapy have been identified repeatedly. Prospectively validated poor prognostic markers include immunoglobulin heavy chain variable region (IGHV) gene mutations,[16,17] CD38 expression,[16] ZAP-70 expression,[18] and cytogenetic abnormalities determined by fluorescence in situ hybridization (FISH).[19] Among the latter, deletion of the chromosome region 17p13.1, known as del(17p), which is observed in 5% of untreated CLL cases but in up to 30% of relapsed and refractory cases, is of high prognostic importance. In a pivotal study by Doehner and colleagues, patients with del(17p) required therapy within 1 year of diagnosis and had a median overall survival (OS) of just 32 months.[19] Within the clinical trial that demonstrated the superiority of first-line FCR over fludarabine and cyclophosphamide alone, del(17p) was the strongest negative predictive factor for response to therapy and survival, and the clinical responses that these patients achieved were not durable.[4] Although retrospective data indicate that some patients with del(17p) might experience an indolent course despite the mutation,[20] unfavorable outcomes have been observed in other prospective trials using combinations of rituximab with bendamustine (Treanda, Teva)[21] or fludarabine.[22] This lack of chemosensitivity is caused by the malfunction of the tumor suppressor protein p53; the *TP53* gene locus is located on the short arm of chromosome 17, and deletion of 17p leads to the inactivation of the *TP53* gene.[23] This is often accompanied by inactivating mutations in the second *TP53* allele, which result in a complete loss of function. Even in the absence of del(17p), *TP53* mutations are associated with an equally poor prognosis.[24,25] Several recent retrospective studies indicate that patient cohorts with *TP53* abnormalities and those with poor response to conventional immunochemotherapy also are enriched for recurrent mutations in *SF3B1*, *BIRC3*, and *MYD88*.[10,26,27] Several research groups are focusing on how to integrate such mutations into existing prognostic models and how they are affected by different treatments.

Alternative Immunochemotherapy-Based Treatment Options for Patients With TP53 *Abnormalities Have High Toxicities*

The only immunochemotherapy-based treatment option that appears to overcome the negative prognosis of *TP53* abnormalities is the anti-CD52 monoclonal antibody alemtuzumab and its combination with chlorambucil, high-dose corticosteroids, rituximab, and FCR.[28-33] Although effective, these regimens are associated with a high rate of hematologic and nonhematologic toxicity, as well as severe infectious complications. Because alemtuzumab is no longer licensed for CLL in the European and United States markets, identifying new strategies for del(17p) and *TP53*-mutated CLL remains especially urgent. The therapies for relapsed patients (with and without *TP53* abnormalities) include FCR; combinations with high-dose corticosteroids or alemtuzumab; and alternative regimens of rituximab, oxaliplatin, cytarabine, and fludarabine. These therapies have limited, short-term efficacy and are associated with high toxicity rates.[33-39]

Table 1. Summary of Transplant Characteristics and Survival in the Largest Reported Prospective Studies of RIC HSCT in CLL

	Fred Hutchinson Cancer Center[8]	German CLL Study Group[10,48]	MD Anderson Cancer Center[9]	Dana-Farber Cancer Institute[11]
Number of patients	82	90	86	76
Conditioning regimen	Flu/low-dose TBI	Flu/Cy ± ATG	Flu/Cy ± R	Flu/Bu
Donors, % sibling/% MUR	63/37	41/59	50/50	37/63
Median follow-up, months	60	72	37	61
Median PFS, %	39 (at 5 y)	38 (at 6 y)	36 (at 6 y)	43 (at 6 y)
Median OS, %	50 (at 5 y)	58 (at 6 y)	51 (at 6 y)	63 (at 6 y)

ATG, antithymocyte globulin; Bu, busulfan; CLL, chronic lymphocytic leukemia; Cy, cyclophosphamide; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; MUR, matched unrelated donor; OS, overall survival; PFS, progression-free survival; R, rituximab; RIC, reduced-intensity conditioning; TBI, total body irradiation; y, years.

Internationally Accepted Guidelines Suggest That Poor-Risk CLL Patients Are Candidates for HSCT

The European Society for Blood and Marrow Transplantation (EBMT) has addressed the needs of these high-risk patients in a transplant consensus from 2007. This group recommended HSCT as a reasonable treatment option for eligible patients with *TP53* abnormalities or relapsed/fludarabine-refractory disease (ie, nonresponse or relapse within 12 months after purine analogue–based therapy).[5] This is also reflected in the 2008 International Workshop on CLL (iwCLL) guidelines, which state that patients with resistant disease (ie, who do not achieve a complete or partial remission), who relapse within 6 months of last treatment, or with del(17p) should be offered investigative clinical protocols, including HSCT.[40] Some patients can be categorized as "highest risk" based on the predicted effectiveness of conventional immunochemotherapy; these patients are prime candidates for HSCT.[6] Features of highest risk include *TP53* loss or mutation, purine analogue–refractory disease, relapse within 24 months after FCR (or FCR-like) treatment, and failure to achieve complete response after FCR.

Another difficult-to-manage population includes those who have undergone Richter's transformation. These patients have poor response rates and survival. HSCT has been explored in these patients,[41] but most do not achieve an adequate response to induction to proceed to transplant. One potential solution is considering HSCT earlier in the disease course of highest-risk patients in order to prevent transformation.

Evidence for the Efficacy of HSCT in CLL

HSCT Provides Long-Term Disease Control in a Considerable Proportion of Patients, Including Those With Adverse Prognostic Markers

The first myeloablative treatment–based transplantation strategies in CLL were developed more than 20 years ago. Although demonstrating potent disease control, these strategies were found unsuitable for the majority of patients because of substantial morbidity and mortality.[42-44] However, later studies recognized that the toxicities could be reduced using nonmyeloablative reduced-intensity conditioning (RIC) strategies without compromising engraftment and antitumor activity.[45-47] This has made HSCT accessible to a larger cohort of CLL patients, including more elderly and fragile patients. Several large prospective studies, some of which have reached a median follow-up of up to 6 years, have indicated that RIC HSCT provides long-term disease control in approximately 40% of patients, and also overcomes the negative prognostic effect of *TP53* abnormalities, fludarabine-refractory disease, and *SF3B1* and *NOTCH1* mutations.[8-11,48-52] The results from the largest reported prospective studies are summarized in Table 1. The efficacy of HSCT in CLL is largely due to the GvL effect, which is exerted by transplanted donor hematopoietic stem cells that differentiate into immune effector cells. These cells are able to continuously mount an antitumor immune response, which likely is directed against minor host antigenic variations.[7]

Remission Status at Transplantation and Pretransplant Characteristics Are Predictive of HSCT Outcome

HSCT seems particularly active in patients with complete or partial disease remission at the time of transplantation; both prospective and retrospective studies indicate that the 5-year OS could be increased to up to 80% in patients with chemotherapy-sensitive disease.[11,48,53] However, to achieve a good remission state is challenging, especially in patients with *TP53* abnormalities. Dose-intensified immunochemotherapy and alemtuzumab-based regimens may help prepare patients for successful HSCT by improving pretransplant remission stage, but these treatments have high toxicities.[34,54-56] Other pretransplant characteristics predictive of OS include age, time from diagnosis to transplant, donor type (ie, matched unrelated donors vs human leukocyte antigen [HLA]–matched sibling donors), and donor-recipient gender combination.[53,57]

Table 2. Summary of Key Adverse Events Reported in the Largest Prospective Studies of RIC HSCT in CLL

	Fred Hutchinson Cancer Center[8]	German CLL Study Group[10,48]	MD Anderson Cancer Center[9]	Dana-Farber Cancer Institute[11]
Early mortality, % (<100 d)	<10	<3	<3	<3
NRM, %	23	23	17	16
Acute grade 3/4 GvHD, %	20	14	7	17
Severe chronic GvHD, %	53	55	56	48

CLL, chronic lymphocytic leukemia; d, days; GvHD, graft vs host disease; HSCT, hematopoietic stem cell transplantation; NRM, nonrelapse mortality RIC, reduced-intensity conditioning. .

Adverse Events and Risks Associated With HSCT in CLL

Chronic GvHD Contributes Significantly to Treatment-Related Mortality and Morbidity

GvL activity in CLL seems to be closely correlated with GvHD, because patients with cGvHD have a reduced risk of relapse.[11,58] Accordingly, an increased relapse rate was observed when donor T cells were depleted.[49,51,53] Despite these clear biological advantages, cGvHD remains a significant clinical problem. Results from large prospective studies have shown that cGvHD affects almost 60% of patients and is the major cause of increased nonrelapse mortality rates. In addition, cGvHD is the major determinant of quality of life after HSCT.[59,60] Owing to substantial improvements in supportive and anti-infective treatments and the availability of dedicated transplant units, acute side effects such as nausea, mucositis, and infections are considerably easier to manage than in the era of myeloablative HSCT. This also is reflected in the very low early mortality rates seen in the first 100 days after HSCT. A summary of key adverse events reported in the largest prospective studies of RIC HSCT in CLL is contained in Table 2.

Relapse After HSCT Is Challenging but Seems to Be Sensitive to Immunochemotherapy Treatment

To date, no standard treatments or guidelines exist for patients who do not respond to HSCT and are unresponsive to post-HSCT immunomodulation by immune suppression or donor lymphocyte infusions. Regardless, patients progressing after HSCT can be rescued by a variety of treatment approaches. In a recently published retrospective analysis of 52 patients from the MD Anderson Cancer Center, the median time to HSCT failure was 7 months.[61] The most commonly used salvage treatment regimens were anti-CD20 monoclonal antibody–based and alemtuzumab-based immunochemotherapy. Novel agents such as thalidomide (Thalomid, Celgene), lenalidomide (Revlimid, Celgene), and ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech) also were used. These salvage treatments led to 2- and 5-year PFS rates of 67% and 38%, respectively, indicating that post-HSCT relapses are sensitive to salvage therapy.

Interestingly, in multivariate analyses, cGvHD was a strong predictor of prolonged overall survival. Relapsed disease therefore appears to be susceptible to modification by immune responses, which potentially could be further exploited by the use of selected immune-modulatory agents. Attractive targets in this context include immune checkpoint proteins such as programmed death 1/programmed death ligand 1 (PD-1/PD-L1). Although their physiologic role is to guarantee immune-cell homeostasis and prevent autoimmunity, they often are used by tumor cells to provide a protumor microenvironment by suppressing immune cell effector functions. Early preclinical studies using blasts from patients with myeloid leukemias who relapsed after HSCT demonstrate that blocking PD-1 offers an appealing immunotherapeutic strategy in this setting.[62] Although similar data do not yet exist in patients with CLL, preclinical work from our laboratory suggests that immune responses can be restored by early antibody blockade of the PD-1/PD-L1 axis in mice with CLL after transplantation.[63] Whether this can be translated to the setting of relapse after HSCT should be confirmed in future clinical studies.

Paradigm Shifts in CLL Treatment Due to the Availability of Novel Treatments

The availability of novel treatments is dramatically changing the standard of care in CLL. These treatments include new monoclonal antibodies, immunomodulatory substances, agents blocking the BCR signaling pathway, and novel cellular therapies. Extensive reviews on these strategies have been published elsewhere; therefore, we will focus on highlighting some key points.

Monoclonal Antibodies

Although representing a 'passive' immunotherapeutic strategy, anti-CD20 monoclonal antibodies are now integral components of CLL therapy.[4,64-67] A variety of other monoclonal antibodies are currently being tested or have been introduced in the treatment of CLL, including

antibodies against receptor tyrosine kinase-like orphan receptor 1 (ROR-1)[68] and CD44.[69]

B-Cell Receptor Signaling Pathway Inhibitors

Recent clinical studies convincingly show that agents inhibiting BCR signaling are well tolerated and very active. BCR activation is a central stimulus in CLL cells and promotes malignant cell survival by activating multiple downstream kinases. To date, the most clinically successful BCR pathway inhibitor is the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib. In a phase 1/2 study of 85 heavily pretreated patients, the ORR was 71%, with a PFS of 75% and an OS of 83% at 26 months.[70] Importantly, these responses were independent of the presence of del(17p). Treatment was very well tolerated and toxicities included grade 1 or 2 transient diarrhea, fatigue, and upper respiratory tract infection. Grade 3 or 4 hematologic toxic effects were infrequent.

Ibrutinib monotherapy is also very well tolerated and effective in treatment-naive elderly CLL patients, producing an ORR of 71%.[71] A recently published update (median follow-up, 3 years) reported improved response qualities and durable responses in both treatment-naive and relapsed/refractory CLL patients after ibrutinib treatment.[72] Importantly, grade 3 or greater cytopenias, fatigue, and infections diminished with longer follow-up. Disease progression rarely occurred and was primarily observed in patients with del(17p). In a single-arm phase 2 study of single-agent ibrutinib in patients with *TP53* aberrations, the activity and safety profiles supported the consideration of this drug as a treatment option for high-risk CLL in the first- and second-line settings.[73] In a randomized phase 3 study of patients with relapsed/refractory CLL, ibrutinib demonstrated significantly improved ORR, PFS, and OS compared with ofatumumab (Arzerra, GlaxoSmithKline) monotherapy, and was able to overcome the adverse effect of del(17p).[74] In combination with rituximab, ibrutinib was well tolerated and active in patients with high-risk CLL and mainly produced mild to moderate toxicities.[75]

Idelalisib (Zydelig, Gilead Sciences; formerly known as GS-1101 and CAL-101) is an inhibitor of the phosphoinositide 3-kinase (PI3K) regulatory subunit p110-delta that is involved in CLL cell survival, clonal expansion, and retention in lymphoid tissues.[76,77] In a phase 1 study of 54 heavily pretreated patients with relapsed/refractory CLL, including patients with del(17p), 81% achieved nodal responses with an ORR of 72%.[78] The most commonly observed higher-grade adverse events were pneumonia, neutropenic fever, and diarrhea. A phase 3 trial was then initiated including 220 patients with relapsed CLL that compared rituximab with or without idelalisib.[79] Owing to the overwhelming improvement in efficacy in the idelalisib arm, the study was interrupted after the first interim analysis. However, more than 90% of patients had at least 1 adverse event, including rash, diarrhea, cytopenias, and hepatic aminotransferase elevations. At least 1 serious adverse event, which included pneumonia, pyrexia, and febrile neutropenia, occurred in 40% of patients receiving idelalisib and rituximab vs 35% of those receiving placebo and rituximab. Importantly, both ibrutinib and idelalisib are associated with a transient increase in blood lymphocyte levels, which is not a sign of progressive disease and occurs concomitantly with a notable reduction in lymph node and spleen sizes.

Multiple ongoing trials are now investigating various combinations of these substances, as well as with bendamustine and rituximab or FCR.[80] However, a recently published study evaluating the pharmaceutical costs of these treatments pointed out that individual out-of-pocket and societal costs are expected to increase dramatically.[81] In addition, patients who previously have responded can become resistant to ibrutinib because of mutations at drug binding sites within the BCR pathway.[14] A recent analysis of 127 patients enrolled in various clinical trials of ibrutinib at the MD Anderson Cancer Center demonstrated discontinuation of treatment in 26%, mostly because of disease transformation, progressive CLL, and adverse events.[15] Rescuing these patients has proven to be extremely difficult, and almost 75% died after discontinuation of treatment, with a median overall survival of just 3.1 months. The underlying mechanisms are still unclear and probably include the influence of other high-risk disease markers, other pathomechanisms relating to *TP53* mutations, and ibrutinib-driven resistance to therapy.

BCL-2 Antagonists

BCL-2 antagonists such as navitoclax (previously ABT-263) and GDC-0199 (also known as ABT-199) mainly work by triggering apoptosis via modulation of mitochondrial stability. In a phase 1 study of 29 patients with relapsed/refractory CLL treated with navitoclax, lymphocytosis was reduced by more than 50% in 19 of 21 patients with baseline lymphocytosis, and PR or stabilization of disease was achieved in almost half of the patients, including those with del(17p) CLL.[82] The major dose-limiting toxicity was thrombocytopenia. The newer agent GDC-0199 is even more promising, because it is more specific for BCL-2 and lacks the platelet-depleting activity of navitoclax.

CAR T Cells

Chimeric antigen receptor (CAR) technology specifically targets malignant cells using precisely engineered T cells.[13] The single-chain variable fragment from an antibody molecule is fused with an internal T-cell signaling domain to form a chimeric antigen receptor, which is then transduced into T cells.[83] A major advantage of this approach is that

Table 3. Overview of the Advantages and Disadvantages of Novel Substances and HSCT

	Advantages	Disadvantages
BCR signaling inhibitors	- Effective - Tolerable - Prolong PFS - Can reduce negative effect of fludarabine resistance and del(17p)	- Currently, short follow-up - Complete responses are rare - Generally only available in clinical trials - Very costly - Resistance mechanisms are emerging - Discontinuation observed in approximately 1/4 of patients - Dismal outcome after discontinuation - *TP53* abnormalities remain problematic to manage - Small numbers of patients in specific subgroups with known high-risk constellations - Probable lack of chemosensitivity in relapsed disease
HSCT	- Long-term follow-up is available - Effective - Curative potential in approximately 50% of patients - Overcomes negative prognostic impact of high-risk constellations - Low early mortality - Relapse after HSCT can be treated	- Only suitable for selected patients - High NRM - cGvHD - Reduced quality of life - Specialized transplant centers are required

BCR, B-cell receptor; GvHD, graft vs host disease; HSCT, hematopoietic stem cell transplantation; NRM, nonrelapse mortality; PFS, progression-free survival.

it eliminates major histocompatibility complex (MHC) restriction. Since the first pivotal report[84] on a CLL patient in 2011, several clinical trials have reported impressive results with anti-CD19 CARs.[85-87] However, the success of CAR therapy is dependent on the inclusion of lympho-reducing conditioning chemotherapy and the choice of CAR design. In addition, CAR T-cell therapy can be associated with severe complications such as cytokine release syndrome—a potentially lethal complication—and lasting normal B-cell depletion.[86,88] CD19 CAR-engineered and donor-derived allogeneic T cells also have been used for treatment of persistent or relapsed B-cell malignancies (including CLL) after HSCT.[89] Although early observations of this pilot study were encouraging, enthusiasm was tempered by the fact that the majority of patients did not exhibit an objective response, potentially because of increased expression of immune-inhibitory receptors such as PD-1. The next generation of CAR T cells, termed "armored CARs," are therefore designed to overcome an immune-suppressive tumor microenvironment.[90]

Summary: What Is the Place of HSCT in the Era of Novel Therapies?

Significant advances in understanding the pathogenesis of CLL have led to the development of a wide range of novel treatment options for CLL patients requiring therapy. Choosing the appropriate types and timing of therapy for an individual patient is therefore more challenging than ever, especially as prospective randomized trials on combination treatments are still rare. In addition, it is unknown whether the effects observed in most patients can be extrapolated to other subgroups with specific mutations or high-risk constellations known to confer an adverse prognosis or poor response to treatment. Therefore, few of these patients were included in study cohorts or these markers were not assessed. Sophisticated and technically advanced complex cellular therapeutic approaches such as CAR T-cell therapy are very intriguing, but generally only available in a few specialized CAR manufacturing and treatment centers, and are mostly reserved for patients lacking further therapeutic options.

Although novel agents are efficacious, are tolerable, and prolong PFS even in high-risk CLL patients, the existing data are not yet mature and the follow-up is still too short to allow any conclusions about their long-term efficacy. In addition, resistance mechanisms can emerge; approximately 25% of patients discontinue treatment because of disease transformation, progressive CLL, or adverse events, with a dismal outcome when treatment is stopped. Patients with *TP53* abnormalities seem to be especially affected by these resistance mechanisms, indicating that the natural dismal progression of high-risk CLL might be slowed, but not avoided. These observations are currently derived from ibrutinib-treated patients, and it is unknown whether similar problems will arise with other novel substances and whether they can be overcome by intelligent combinations of novel substances.

In contrast, long-term follow up from large prospective trials of HSCT have been ongoing for almost a decade in a few centers. These studies have shown that HSCT is effective and has curative potential in approximately half

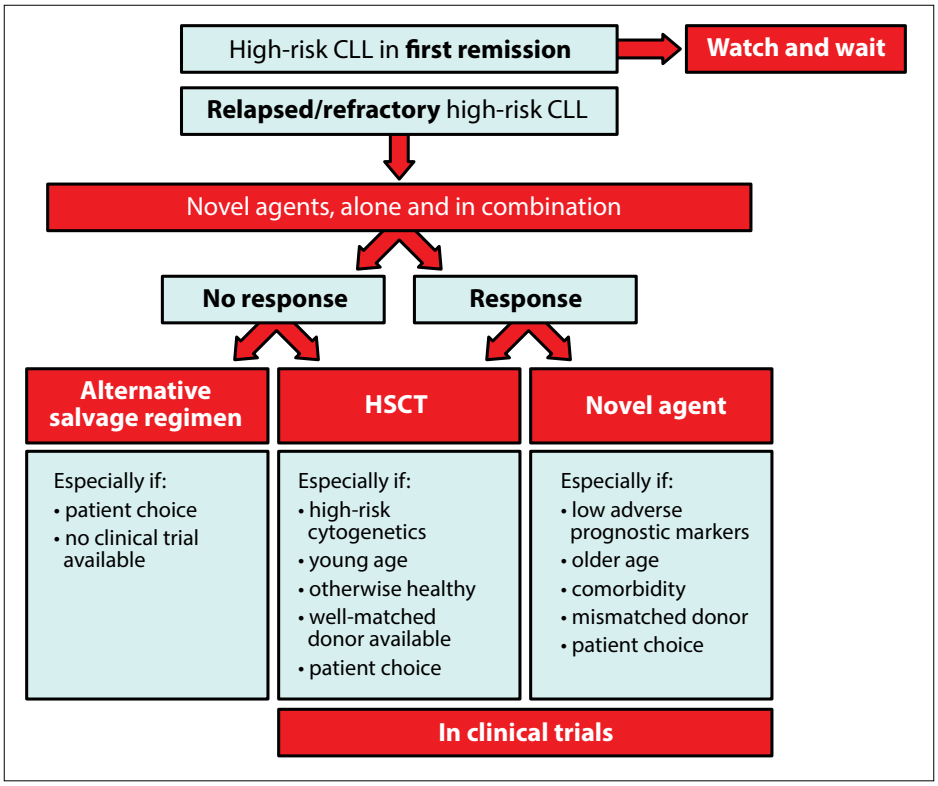

Figure. Potential treatment algorithm for the use of HSCT in the era of novel agents.
CLL, chronic lymphocytic leukemia; HSCT, hematopoietic stem cell transplantation.
Modified from the 2014/2015 EBMT/ERIC recommendations.[91,93]

of the patients. HSCT should be reserved for high-risk patients, given that it overcomes the negative prognostic impact of high-risk constellations known to confer an adverse prognosis. Although there are no prospective data on whether HSCT can change the natural biological course of high-risk CLL, some retrospective data indicate that OS was significantly improved in patients with a donor vs those without a donor.[91] However, HSCT can only be conducted in select groups of patients and can lead to cGvHD and reduced quality of life, both of which can significantly affect long-term mortality and morbidity. Although relapse after HSCT generally is considered difficult to treat and no standard approach exists, recently published data indicate that these patients can be rescued successfully and respond to immuno(chemo)therapy. A summary of the advantages and disadvantages of novel substances and HSCT is depicted in Table 3.

Because there are no direct comparisons between HSCT and novel agents, and because combinations with each other have not yet been tested within clinical trials, general evidence-based recommendations are very difficult to make. It is therefore essential to understand the limitations of each approach and carefully weigh the chance of benefits and risks on a case-to-case basis. This is reflected in the recently published updated recommendations from the EBMT and the European Research Initiative on CLL (ERIC).[92,93] Although it is feasible to withhold HSCT in high-risk patients in first remission, the lack of curative potential of novel agents in this subgroup must always be considered. This is particularly important in relapsed/refractory high-risk patients and in patients progressing under novel therapies. Because the success of HSCT is highly dependent on remission state at the time of HSCT, it therefore appears reasonable to consider HSCT after response to novel therapies and after careful consideration of individual treatment histories, patient characteristics, and preferences. These recommendations are summarized in the figure. Ideally, biomarkers will be developed to help identify which patients will not respond to novel agents and which patients are most suitable for HSCT, but such biomarkers are currently absent. Together, there are a number of very promising novel drugs and immunotherapy strategies, which leads us to believe that an intelligent and individualized combination of these approaches can benefit poor-risk CLL patients.

Disclosures

Dr Gribben has received honoraria from Roche/Genentech, Celgene, Gilead, Pharmacyclics, Janssen, Mundipharma, and Infinity. Dr McClanahan has no conflicts to disclose.

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