Role of allogeneic transplantation in patients with chronic lymphocytic leukemia in the era of novel therapies: a review

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Abstract: Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia and is characterized by a highly variable clinical course. In the past decade, several prognostic risk factors have been identified facilitating the classification of CLL into various risk groups. Patients with poor risk disease, such as poor cytogenetics or relapsing after purine-based analogues, had limited therapeutic options, with allogeneic hematopoietic cell transplantation (allo-SCT) the only known therapy with curative potential. More recently, the introduction of novel agents inhibiting the B-cell receptor pathway, and the early success with chimeric antigen receptor T cells offers an effective and relatively safe option for this poor prognostic group which holds promise in the future. Alternatively, the use of reduced intensity conditioning regimens in the allo-SCT setting has led to a significant decrease in nonrelapse mortality to 16–23%, making it an attractive therapeutic option. No recent guidelines have been developed since these novel therapies became available regarding the optimal time to allo-SCT in this patient population. The advent of these novel and highly active therapeutic agents, therefore, warrants a reappraisal of the role and timing of allo-SCT in patients with CLL. In this article, we summarize the literature regarding the novel therapeutic agents available today as well as focus on the efficacy and safety of allo-SCT.

Keywords: chimeric antigen receptor T cells, chronic lymphocytic leukemia, immunomodulatory drugs, targeted agents, transplant

Introduction

Chronic lymphocytic leukemia (CLL) is a post-germinal center neoplasm with clonal proliferation of mature lymphocytes in patients with mutated immunoglobulin heavy chain (IGHV) and is a pre-germinal center neoplasm in patients with unmutated IGHV. CLL accounts for one-third of all forms of adult leukemia [Siegel *et al.* 2013]. In 2013, 15,680 new cases of CLL were diagnosed while 4580 deaths were reported [American Cancer Society, 2013]. It is mainly a disease occurring in older people, with the median age of 70 years at diagnosis [Smith *et al.* 2011]. It is often indolent, characterized by progressive accumulation of monoclonal, small, mature appearing CD5+ B cells in the peripheral blood, bone marrow, and secondary lymphoid organs. However, in some patients it progresses rapidly with a fatal outcome within 2–3 years of diagnosis [Rai, 2008]. Most patients with newly diagnosed symptomatic CLL are treated with chemoimmunotherapy with good responses. There

have historically been limited options for long-term favorable outcomes in high-risk disease, which includes relapsed/refractory disease, purine analogue-refractory disease or poor prognostic cytogenetics, including 17p deletion, p53 mutation or 11q deletion. Dependence of CLL cells on the B-cell receptor (BCR) pathway and tissue microenvironment have presented opportunities for targeted therapies and resulted in the development of multiple novel therapeutic options which are efficacious in the relapsed and refractory setting, including those with poor risk features. Accordingly, we appraise the important role of allogeneic hematopoietic cell transplantation (allo-SCT) in CLL.

Prognostic factors in CLL

Traditional factors

Advanced stage according to the Binet and Rai staging systems and older age are considered as

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having a poor prognostic disease [Rai, 2008; Binet *et al.* 1981]. Additionally, a lymphocyte doubling time of less than 12 months is associated with a more aggressive course [Molica and Alberti, 1987; Montserrat *et al.* 1986]. Also higher levels of $\beta 2$ microglobulin are associated with worse prognosis [Wierda *et al.* 2009].

Newer prognostic factors

CD38 and zeta-associated protein

The presence of CD38 overexpression by flow cytometry independently correlates with worse prognosis. The cut off for significance ranges from more than 5% in some studies while others consider over 30% as positive for CD38 expression [Chevallier *et al.* 2002; Ibrahim *et al.* 2001; Hamblin *et al.* 2002]. Increased levels of zeta-associated protein 70 (ZAP-70) by flow cytometry in CLL are associated with worse prognosis as well [Rassenti *et al.* 2008]. A level of at least 20% ZAP-70-positive cells was associated with poorer outcomes with time to progression of 29 months and median survival of 90 months. CD38 expression and ZAP-70 status correlate with *IGHV* unmutated status. It is concordant in 70% of the cases [Crespo *et al.* 2003]. The lack of standardized methodology to determine ZAP-70 expression has made it less favorable for routine use in clinical practice.

IGHV gene mutation status

Expression of an unmutated *IGHC* variable (V_H) gene is associated with progressive disease with an inferior survival and higher risk of relapse. Median survival was significantly shorter: 117 months in patients with unmutated V_H versus 293 months in those with mutated V_H ($p=0.001$) [Kharfan-Dabaja *et al.* 2008].

Genetic abnormalities

In a single institution study, 325 CLL cases analyzed by fluorescence *in situ* hybridization showed that 17p deletion had an inferior overall survival (OS) of 32 months, followed by 11q deletion at 79 months [Döhner *et al.* 2000]. The presence of 17p deletion frequently results in abnormalities associated with the tumor suppressor gene *TP53* which are associated with poor outcomes often due to chemoresistance to purine analogues and alkylator therapy and consequently short disease free intervals [Rossi and Gaidano, 2012]. In another study, 637 previously untreated CLL

cases were evaluated for genetic mutations as determinants of prognosis and survival. Patients with mutations *TP53* and *BIRC3* were categorized into a high-risk group, given a 5-year OS of 51% and a 10-year OS of 29%. Patients with *NOTCH1* or *SF3B1* or 11q deletion were categorized as intermediate risk, with a 5-year OS of 66% and a 10-year OS of 37% [Rosenquist *et al.* 2013; Jeromin *et al.* 2013; Cuneo *et al.* 2014]. In a recent analysis of the UK CLL-4 trial that evaluated the role of chlorambucil versus fludarabine versus fludarabine and cyclophosphamide combination showed that both *NOTCH1* and *SF3B1* mutations were associated with a decreased OS. In another study, *NOTCH1* mutations were also found to be associated with increased risk for Richter's transformation. Recent studies have indicated that mutations in the *BIRC3*-negative regulator for nuclear factor κB were associated with chemotherapy-refractory disease [Rossi and Gaidano, 2012; Oscier *et al.* 2013; Schnaiter *et al.* 2013]. As next generation gene sequencing becomes more universally available, a broad range of mutations with prognostic significance would likely be identified. At the present time, routine testing of these novel mutations is recommended in the context of a clinical trial.

Management of high-risk CLL

High-risk CLL refers to disease that is refractory (relapse within 24 months of initial favorable response to therapy with a fludarabine-based regimen) with the presence of cytogenetic abnormalities as noted above, specifically 17p deletion or *TP53* mutations/deletions [Dreger *et al.* 2006]. These have a tendency to have a highly progressive nature, with reduced response to conventional therapy.

Conventional therapies

Conventional chemotherapy is still used as first-line therapy in high-risk patients who are eligible for therapy based on the International Workshop on Chronic Lymphocytic Leukemia. Table 1 refers to outcomes with the different regimens used, with a special note on the cytogenetic abnormalities.

In patients younger than 65 years with few or no comorbidities, fludarabine, cyclophosphamide and rituximab (FCR) has been shown to be superior to fludarabine and cyclophosphamide (FC) [Keating *et al.* 2005; Tam *et al.* 2008]. A phase III

Table 1. Conventional chemotherapy options.

Regimen	Survival expressed as PFS/OS (months)					References
	All groups	13q-	+12	11q-	17p-	
Chlorambucil	11.7/NR	13/NR	12.9/NR	8.5/NR	2.2/NR	Hillmen <i>et al.</i> [2007]
Alemtuzumab	14.6/NR	24.4/NR	18.3/NR	8.5/NR	10.7/NR	Hillmen <i>et al.</i> [2007]
FC (% at 3 years)	45/83	52/89	48/86	32/83	0/37	Hallek <i>et al.</i> [2010]
FCR (% at 3 years)	65/87	76/95	83/96	64/94	18/38	Hallek <i>et al.</i> [2010]
FCR + mitoxantrone	NR	NR	NR	NR	NR	Bosch <i>et al.</i> [2009]
FCR + alemtuzumab	38/NR	42/NR	42/NR	27/NR	15/NR	Parikh <i>et al.</i> [2011]
Bendamustine-Rituximab	33.8/NR	34.4/NR	34.4/NR	29.7/NR	7.9/NR	Fischer <i>et al.</i> [2011]
Alemtuzumab + methylprednisolone	NA	NR	NR	NR	18.3/39	Pettitt <i>et al.</i> [2012]
Rituximab + high-dose solumedrol	30.5/NR	NA	NA	NA	NA	Castro <i>et al.</i> [2008]

FC, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide and rituximab; NR, not reported; OS, overall survival; PFS, progression-free survival.

study conducted by the German CLL Study Group (GCLLSG) showed a significant improvement in overall response rate (ORR) and progression-free survival (PFS) with FCR *versus* FC. At 3-year follow up from randomization, the PFS was 65% *versus* 45% in the FC group. The OS is also higher in the FCR group, 87% *versus* 83%. The most common adverse event was myelotoxicity. However, in the subgroup analysis, patients with 17p deletion had an ORR of 68% with a PFS of 18% at 3 years [Hallek *et al.* 2010]. This therapy is thus of marginal benefit in patients with 17p deletion. At MD Anderson, a study done combining FCR with granulocyte macrophage colony-stimulating factor showed that the ORR was 100% with a significant reduction in infectious complications [Strati *et al.* 2014]. Reduced doses of FCR, such as FCR-lite, are also available which are well tolerated in the older population [Foon *et al.* 2009].

Alemtuzumab

An anti-CD52 antibody has been approved for the treatment of fludarabine-refractory CLL and as first-line therapy for those who are not expected to respond to fludarabine. One randomized trial investigated efficacy and safety of intravenous alemtuzumab compared with chlorambucil in 297 patients. Alemtuzumab was significantly superior regarding the ORR (83% *versus* 55%, $p < 0.0001$) and rate of complete remission (24% *versus* 2%, $p < 0.0001$) [Hillmen *et al.* 2007]. The CLL2H trial showed that subcutaneous administration of alemtuzumab in the refractory situation is equally effective as intravenous administration with fewer side effects. A

high number of patients with 17p deletion (30%) included in the study did not have significant differences in ORR, OS, PFS or time to treatment failure [Keating *et al.* 2002]. The addition of dexamethasone to alemtuzumab therapy in the CLL2O study did yield favorably improved outcomes in the high-risk patients with an ORR of 98% and 79%, median PFS of 38 months and 10.3 months, and OS not reached and 21.3 months in the previously untreated and refractory groups respectively. There is an increased risk of cytomegalovirus reactivation with the use of alemtuzumab [Stilgenbauer *et al.* 2012]. Alemtuzumab has currently been pulled from the market and is no longer being developed for the treatment of CLL.

Rituximab and high-dose methylprednisolone

Castro and colleagues studied the role of a combination of rituximab and high-dose methylprednisolone (R-HDMP) in patients with fludarabine-refractory disease. Fourteen patients received methylprednisolone at the dose of 1 g/m² daily for 5 days along with rituximab weekly for 4 weeks for a total of three cycles. The ORR was 93% and complete remission rate was 36%. The median time to progression was 15 months [Castro *et al.* 2008]. Dungarwalla and colleagues also reported similar responses. They reported 14 heavily pretreated patients who received R-HDMP. The ORR was 93% with a complete remission rate of 14% [Dungarwalla *et al.* 2008]. Thus R-HDMP is also a regimen which can be used in these patients as per NCCN guidelines.

Figure 1. Chronic lymphocytic leukemia (CLL) cell and interaction with microenvironment.

This figure shows the interaction between the CLL cell and the accessory cells in the bone marrow and lymphoid tissue microenvironment which facilitates the survival and development of drug-resistant pathways. Nurse-like cell (NLC) and bone marrow stromal cell (BMSC) release chemokines CXCL 12 and CXCL 13 and CXCL12 only. The CLL cell responds through CXCR4 and CXCR5 G-protein-coupled chemokine receptors. VLA-4 (CD-49d) integrin on CLL cells interacts with vascular cell adhesion protein 1 (VCAM-1) and fibronectin (FN), a ligand on the stromal cell. Interaction between B-cell activating factor (BAFF) a cytokine belonging to the tumor necrosis factor ligand family and a proliferation-inducing ligand (APRIL) and corresponding receptors BCMA (B-cell maturing antigen), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) and BAFF-R (B-cell activating factor-receptor) provide survival signals. CD38 interacts with CD31 on NLCs which activates ZAP-70 and downstream survival pathways. Activation of the B-cell receptor (BCR) pathway activates SYK (Spleen tyrosine kinase) a member of SYK family of tyrosine kinases, and zeta-associated protein 70 (ZAP-70), inducing release of high levels of chemokines CCL3/4 from the CLL cells, potentially attracting T cell. T cells with CD40L interact preferentially with CD40 on CLL cells, facilitating the release of T-cell cytokines interleukin 4 and tumor necrosis factor α which also help to regulate CLL cell survival. Figure modified from Burger *et al.* [2009].

Novel therapies

CLL and the microenvironment

The microenvironment plays a significant role in supporting CLL cell proliferation and survival, as well as facilitating chemoresistance (Figure 1). Hence attempts have been made to chemically remove CLL cells from the microenvironment by either blocking the extracellular triggers or by abrogating the intracellular signaling. Different compounds have been developed capable of antagonizing surface receptors or cytokines, including small molecules that target signaling kinases and antiapoptotic proteins. These have resulted in encouraging clinical responses.

Immunomodulatory agents

Lenalidomide, is an immunomodulating drug with antitumor activity in certain hematological disorders. It is reported that an important mechanism of action of this agent is to modulate immune effector cells by activating T and natural killer cells indirectly and inducing apoptosis in tumor cells. In a phase II study of 45 patients with advanced stage CLL

refractory to fludarabine, the ORR with lenalidomide was 47% with 9% attaining a complete response (CR) [Chanan-Khan *et al.* 2006]. Similarly the combination of lenalidomide and rituximab as salvage therapy for relapsed refractory CLL was evaluated in 49 patients. The ORR was 66%, with 12% attaining a CR. Fifteen patients with 17p deletion were included in the study and an ORR of 53% as reported by the authors is encouraging [Reddy *et al.* 2008; Badoux *et al.* 2013]. The ORIGIN trial which was a randomized controlled trial comparing safety and efficacy of lenalidomide *versus* chlorambucil as frontline therapy for older patients with CLL (> 65 years) was halted by the US Food and Drug Administration (FDA) for safety concerns due to an imbalance in the number of deaths in the lenalidomide arm [FDA, 2014 <http://www.fda.gov/Drugs/DrugSafety/ucm361444.htm>].

Targeting BCR

Small molecule drugs targeting spleen tyrosine kinase (SYK), Bruton tyrosine kinase (BTK), phosphoinositide 3-kinase isoform p110 delta (PI3K δ)

Figure 2. B-cell receptor (BCR) pathway and targeted agents. BCR has two components: a ligand-binding moiety, which is a membrane-bound antibody embedded in the phospholipid bilayer and recognizes antigen, and a signal-transduction moiety disulfide-linked heterodimer (CD79). Binding of antigen to the membrane-associated immunoglobulin triggers activation of the kinases LYN and SYK that initiates a second messenger cascade through activation of SYK, LYN and BTK, with subsequent propagation through PI3K/AKT, MAPK and NFκB pathways (not shown here), resulting in B-cell activation and proliferation. These serve as potential targets for inhibiting the BCR as shown above. BTK, Bruton tyrosine kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NFκB, nuclear factor κB; PI3K, phosphoinositide 3-kinase. Figure modified from Brown [2013]. The illustrations included in this manuscript are original compositions created by myself and based on a variety of artistic representations of the subject matter, drawn from various sources. Strictly speaking they are not direct reproductions of another work but as noted, are sourced from published diagrams. Is any permission necessary in this case? In communicating with the authors of some of the works that my diagrams are based on, they indicated that they had essentially done the same thing themselves.

Table 2. BCR pathway targeted agents in development.

Target	Agent	Manufacturer	Study phase
BTK	Ibrutinib (PCI-32765)	Pharmacyclics/Janssen	III
	CC-292 (AVL-292)	Celgene	Ib/II
	GDC-0834	Genentech	I
	ACP-196	Acerta	I
	Idelalisib (GS-1101, CAL-101)	Gilead Sciences	III
PI3Kδ	GS-9820	Gilead Sciences	II
	AMG-319	Amgen	I
	TGR-1202	TG Therapeutics	I
	IPI-145	Infinity	III
SYK	GS-9973	Gilead Sciences	II

BCR, B-cell receptor; BTK, Bruton tyrosine kinase; PI3K, phosphoinositide 3-kinase.

and Bcl-2 B-cell lymphoma 2 (BCL-2) show impressive results in relapsed or refractory CLL. In the first few weeks of treatment there is regression in lymphadenopathy with transient lymphocytosis, a gradual resolution of lymphocytosis and a deepening of responses, with a high rate of remission achieved

with increasing duration of time on therapy over 1 year or longer. The clinical responses are attributed to the combined effects of direct cell cytotoxicity, inhibition of survival pathways, and impairment of CLL cell trafficking and tissue homing. A few of the promising agents that exert their effect through the BCR pathway are discussed here (Figure 2). Table 2 shows select BCR-signaling pathway inhibitors in clinical development [Jones and Byrd, 2014]. Table 3 shows current therapies that have been studied and shown to have clinical response in CLL.

Ibrutinib

Ibrutinib is an orally administered irreversible and specific inhibitor of BTK that modulates BCR signaling which is activated in CLL [Herman *et al.* 2011]. A phase Ib/II multicenter study was conducted to assess the safety, efficacy, pharmacokinetics and pharmacodynamics in patients with CLL who were over the age of 65. The ORR irrespective of dose was 86–91%, with 15–20% having a partial response (PR) with persistent lymphocytosis. The response appeared independent of clinical and genomic risk factors present beforehand, including advanced-stage disease, the number of previous therapies, and 17p deletion. At 26 months, the estimated PFS rate was 75% and the rate of OS was 83%. Toxic effects were

Table 3. Current therapies in CLL.

Authors	Study agents	Other agents	Clinical trials
Hallek <i>et al.</i> [2010]	FCR		Phase III
Strati <i>et al.</i> [2014]	FCR	GM-CSF	Phase II
Woyach <i>et al.</i> [2011]	FR		Phase II
Byrd <i>et al.</i> [2013]	Ibrutinib		Phase Ib/II
Burger <i>et al.</i> [2012]	Ibrutinib	Rituximab	Phase II
Furman <i>et al.</i> [2014]	Idelalisib	Rituximab	Phase III
Flinn <i>et al.</i> [2012]	Ofatumumab		Phase II
Costa <i>et al.</i> [2012]	Ofatumumab	Lenalidomide	Phase II
Hillmen <i>et al.</i> [2013]	Ofatumumab	Chlorambucil	Phase III
Goede <i>et al.</i> [2014]	Obinutuzumab	Chlorambucil	Phase III
	Seymour <i>et al.</i> [2013] ABT-199		Phase I
Kochenderfer <i>et al.</i> [2012]	CAR-T cells		Phase I
Kalos <i>et al.</i> [2013]	CAR-T cells		Phase II

CAR-T cells, chimeric antigen receptor T cells; FC, fludarabine and cyclophosphamide; FCR, fludarabine, cyclophosphamide and rituximab; GM-CSF, granulocyte macrophage colony-stimulating factor.

Table 4. Selected RIC allogeneic transplantation in chronic lymphocytic leukemia.

	Dreger <i>et al.</i> [2010]	Sorrer <i>et al.</i> [2008]	Brown <i>et al.</i> [2012]	Khoury <i>et al.</i> [2011]
<i>N</i>	90	82	76	86
Conditioning chemotherapy	Nonmyeloablative (FluCy ± ATG)	Nonmyeloablative (FluTBI)	Reduced intensity (FluBu)	Nonmyeloablative (FluCyRit)
Alternative donors* (%)	59	37	63	50
Relapse incidence (%)	40 (4 years)	38 (5 years)	40 (5 years)	NR
PFS (%)	42 (4 years)	39 (5 years)	43 (5 years)	36 (5 years)
OS (%)	70 (4 years)	50 (5 years)	63 (5 years)	51 (5 years)
100-day mortality (%)	2	<10	<3	3
NRM (%)	23 (4 years)	23 (5 years)	16 (5 years)	17 (1 year)
Follow up (years)	3.8 (0.6–8.5)	5 (0.9–7.3)	5.1	3.1 (0.9–10.9)

*Donors other than HLA-matched siblings. FluCy, Fludarabine and Cyclophosphamide; ATG, Anti-thymocyte globulin; FluTBI, Fludarabine and Total Body Irradiation; FluBu, Fludarabine and Busulfan; FluCyRit, Fludarabine, Cyclophosphamide and Rituxan; RIC, Reduced Intensity Conditioning. HLA, human leucocyte antigen; NR, not reached; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival.

predominantly grade 1 or 2 and included transient diarrhea, fatigue and upper respiratory tract infection; thus, patients could receive extended treatment with minimal hematologic toxic effects. The median range of previous therapies in this patient cohort was 4 [Byrd *et al.* 2013]. Similar favorable outcomes were noted when used in the front-line setting in older patients. ORR was 71%, with four CRs (13%), 17 PRs (55%) and one nodal PR (3%) [O'Brien *et al.* 2014].

Ibrutinib was also studied in combination with rituximab in a phase II study in which 40 patients were enrolled: 20 patients were evaluated for an early response at 3 months, with ORR of 85%, although all had partial responses. The drug was very well tolerated with a favorable safety profile

and limited adverse events [Burger *et al.* 2012]. In a multicenter phase III study of 391 patients with relapsed refractory CLL or small lymphocytic lymphoma (SLL), patients were randomized to receive ibrutinib or ofatumumab. In this study ibrutinib significantly improved PFS, OS and response rates among patients with previously treated CLL. In patients with 17p deletion the median duration of PFS was not reached in the ibrutinib group compared with the median PFS of 5.8 months in the ofatumumab group [Byrd *et al.* 2014]. These studies show that the efficacy of ibrutinib is significantly better than the conventional treatments available for patients with 17p deletion but is still inferior to patients without 17p deletion [Byrd *et al.* 2013]. The Ohio State University experience showed that the PFS, ORR and OS were much better with

ibrutinib than other traditional treatments [Stephens *et al.* 2014]. The FDA approved use of ibrutinib in March 2014 for patients who had received at least one prior treatment. Ibrutinib has also received approval for expanded use in treating patients with CLL with 17p deletion based on the favorable results of a preplanned interim analysis of the data from the phase III RESONATE trial that showed a 75% reduction in risk of disease progression or death in this patient population.

Idelalisib

Idelalisib is an oral inhibitor of PI3K, especially the isoform p110 delta (PI3K δ) which is expressed on CLL cells [Lannutti *et al.* 2011]. A phase III multicenter, randomized, double-blind study was done in 220 patients (relapsed disease with comorbidities and at least two prior regimens or CD20 antibody), randomized to receive either rituximab or rituximab and idelalisib. The median PFS was 5.5 months in the placebo group and was not reached in the idelalisib group (hazard ratio for progression or death in the idelalisib group 0.15; 95% confidence interval 0.08–0.28; $p < 0.001$). Patients receiving idelalisib *versus* those receiving placebo had improved rates of overall response (81% *versus* 13%; odds ratio 29.92; $p < 0.001$) and OS at 12 months (92% *versus* 80%; hazard ratio for death 0.28; $p = 0.02$). Serious adverse events occurred in 40% of the patients receiving idelalisib and rituximab and in 35% of those receiving placebo and rituximab. A subgroup analysis showed that there was a significant benefit in the poor prognostic groups, including unmutated *IGHV* and 17p deletion [O'Brien *et al.* 2013; Furman *et al.* 2014]. The FDA approved the use of idelalisib in combination with rituximab for patients with relapsed CLL in July 2014.

ABT-199

ABT-199 is an oral selective BCL-2 inhibitor. Three patients with relapsed or refractory CLL developed tumor lysis in 24 h following a single dose of ABT-199 [Souers *et al.* 2013]. Various proteins in the BCL-2 family control programmed cell death. Altering this process can lead to apoptosis [Adams and Cory, 2007]. Due to its selective inhibition, it causes significantly less thrombocytopenia. An ongoing phase I study using ABT-199 in relapsed or treatment-resistant CLL or SLL released preliminary results showing an ORR of 84% among 67 evaluable subjects. At

a median follow up of 10.9 months, 23% patients achieved a CR while 61% achieved a PR. The ORR was 82% in 17p deletion cases and 89% in fludarabine-refractory cases. The most common side effects were diarrhea, neutropenia, fatigue, upper respiratory tract infection and cough [Seymour *et al.* 2013]. Updated results of a phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). *J Clin Oncol* 31, 2013 (suppl; abstr 7018) Ongoing phase II studies are evaluating single-agent ABT-199 in patients with relapsed CLL and 17p deletion. Another trial using a combination of ABT-199 and rituximab is also underway.

Targeted antibody therapy

Rituximab is the first monoclonal antibody approved for the treatment of B-cell neoplasms due to its action directed against CD20. It mediates complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and direct cell apoptosis in the treatment of B-cell malignancies. Several targeted antibodies have been subsequently developed which have been used as single-agent or as combination chemoimmunotherapy in CLL.

Ofatumumab

Ofatumumab is a fully humanized anti-CD20 molecule that binds to a different region than rituximab, with enhanced CDC, ADCC and direct cell death [Teeling *et al.* 2004]. A phase I/II study of single-agent ofatumumab in 33 patients with relapsed or refractory CLL showed an ORR of 50% [Coiffier *et al.* 2008]. The results of a landmark trial led to the approval of single-agent ofatumumab in relapsed or refractory CLL which showed an ORR of 58% and 47%, median PFS of 5.7 months and 5.9 month, and OS of 13.7 months and 15.4 months in patients who were fludarabine or alemtuzumab refractory and with bulky disease, respectively [Wierda *et al.* 2010]. Prior rituximab refractoriness or specific genomic groups did not impact the response [Wierda *et al.* 2011]. A phase III multicenter, randomized, open-label trial comparing ofatumumab in combination with chlorambucil (OF-Clb) with single-agent chlorambucil (Clb) in patients with previously untreated CLL who were not eligible for fludarabine-based therapy enrolled 447 patients. The study showed a median PFS of 22.4 months in the OF-Clb arm compared with 13.1 months in the

Clb arm. ORR was higher in the OF-Clb arm compared with the Clb arm (82% *versus* 69%; $p = .001$), with a superior CR rate (12% *versus* 1%). The OS was not reached in either study arm at 29 months. The most common adverse events were neutropenia and infection [Hillmen *et al.* 2013]. Ofatumumab was also studied in a phase II trial in combination with lenalidomide in patients with relapsed or refractory CLL which showed an ORR of 43% [Costa *et al.* 2012].

Obinutuzumab

Obinutuzumab is a novel humanized anti-CD20 type II monoclonal antibody. It mediates cell death through natural killer cell mediated antibody-dependent cellular cytotoxicity, which is 5–100 times greater than rituximab. In preclinical trials, obinutuzumab showed higher efficacy compared with rituximab [Herter *et al.* 2013]. Based on these results, a phase III multinational trial conducted in 781 patients, randomly assigned to receive chlorambucil (Cl) alone, chlorambucil + obinutuzumab (Cl-Ob) or chlorambucil + rituximab (Cl-R) showed a higher CR rate in the Cl-Ob arm compared with the Cl-R arm (20.7% *versus* 7%), resulting in higher ORR. There were infusion-related reactions in the Cl-Ob arm compared with the Cl-R arm. The rate of death was lower in the Cl-Ob arm compared with the Cl-R arm (8% *versus* 12%). This also resulted in longer remissions in the Cl-Ob arm. This study was done on treatment-naïve patients [Goede *et al.* 2014]. There are currently no data comparing obinutuzumab with rituximab in the relapsed refractory setting.

Chimeric antigen receptor therapy

Chimeric antigen receptor (CAR) T cells are autologous T lymphocytes that have been genetically modified to express the antigen-binding component of an immunoglobulin molecule fused to T-cell signaling domains. This strategy involves using a single chain variable fragment from an antibody with an internal signaling domain to form a CAR cell. CAR-T cells are then adoptively transferred into the patient to mediate destruction of malignant and normal B cells. It is important to identify a suitable tumor-associated antigen which is expressed only on tumor cells and are essential for tumor survival. CLL B cells express higher levels of CD19 compared with CD20 [Koehler *et al.* 2012]. Hence, several phase I/II clinical trials are underway using

antiCD19-CAR-T cells. The National Cancer Institute has investigated the use of antiCD19-CAR-T cells in four patients with CLL who received conditioning with cyclophosphamide and fludarabine, followed by infusion of antiCD19-CAR-T cells. They also received a post-infusion course of interleukin 2 to enhance *in vivo* T-cell expansion. One achieved a CR, two a PR, and one attained stable disease [Kochenderfer *et al.* 2012]. The University of Pennsylvania group studied 14 patients with CLL (6/14 patients had a p53 mutation) treated with antiCD19-CAR-T cells following lympho-depleting chemotherapy. Three achieved a CR, five (36%) achieved a PR and six showed no response, for an overall major response rate of 57%. Two of five patients with a PR had progressive disease 4 months after infusion with CD19+ CLL, and no patient with a CR had relapsed [Kalos *et al.* 2013]. The most significant side effect seen with this treatment is the cytokine release syndrome, with symptoms of fevers, myalgias, hypotension and dyspnea. An unavoidable disadvantage of this method is that it also affects the humoral immunity for a prolonged period of time.

Current role of allo-SCT in CLL

Allo-SCT is frequently noted to have the potential for durable remissions for CLL lasting over 5 years. The efficacy of allo-SCT is primarily due to the graft-*versus*-leukemia effect in CLL. This is evidenced by the decrease in relapse risk noted over time even in reduced-intensity conditioning allo-SCT [Michallet *et al.* 1996; Pavletic *et al.* 2005; Moreno *et al.* 2005; Schetelig *et al.* 2003; Dreger *et al.* 2005, 2008; Sorrow *et al.* 2008] and in the presence of chronic graft-*versus*-host disease (GVHD) [Dreger *et al.* 2005; Toze *et al.* 2005; Farina *et al.* 2009] and an increase in relapse risk associated with T-cell depletion [Gribben *et al.* 2005, Schetelig *et al.* 2008]. Previously with myeloablative transplantation, the treatment-related mortality was high. The treatment-related mortality has significantly reduced to as low as 15% with reduced intensity conditioning regimens [Sorrow *et al.* 2008]. Reduced intensity conditioning for allografting has significantly reduced the morbidity and mortality associated with the procedure. The 100-day as well as the 1-year nonrelapsed mortality after transplant has been significantly reduced [Dreger *et al.* 2010; Khouri *et al.* 2011; Brown *et al.* 2012; Sorrow *et al.* 2008; Kharfan-Dabaja *et al.* 2012] (Table 4). Conditioning regimens using FCR that also

target the disease have a low nonrelapse mortality of 17% at 1 year with early death as low as 3%. The main long-term effect seen is GVHD [Khoury *et al.* 2011]. Although not considered as first-line treatment except in cases of high-risk CLL with 17p deletion or *TP53* mutations or deletions, the recommendation is to consider it early during the course of the disease. RIC allo-SCT has made the procedure more suitable for older patients and those with comorbidities who would have been excluded in the past [Schetelig *et al.* 2008]. Although conventional therapies available for the treatment of relapsed or refractory or high-risk CLL (Table 1) induce positive responses, they are unable to provide long-term disease control, with PFS ranging from 3 to 15 months. Early relapses were noted in this patient population, possibly from the acquisition of new biological risk factors. Prospective phase II studies as well as a larger registry analysis of allo-SCT in patients with CLL suggest that long-term disease control can be achieved in 30–45% of patients with 17p deletion [Zenz *et al.* 2010] and *TP53* mutation in the absence of 17p deletion. Published phase II evidence also indicates that allo-SCT can overcome poor prognostic impact of purine-analog refractoriness if the patient can exhibit a state of chemosensitive disease by other measures before transplant [Michallet *et al.* 1996; Koehler *et al.* 2012; Kochenderfer *et al.* 2012; Kalos *et al.* 2013]. RIC allo-SCT has afforded long-term PFS in 30–60% of transplanted patients. In studies that included and evaluated high-risk patients, the outcomes were comparable. In the CLL3X trial of GCLLSG, the PFS was similar irrespective of the purine-analogue refractory status. Hence in a multivariate analysis, purine-analogue refractoriness did not adversely affect PFS [Dreger *et al.* 2008, 2010]. Similar observations were noted in a study by Schetelig and colleagues [Schetelig *et al.* 2003]. In the study of the Seattle Consortium, despite a high proportion (87%) of patients with a history of fludarabine refractoriness, a 5-year PFS of 39% was reported with only very few late events [Sorrer *et al.* 2008]. A retrospective analysis of the European Group for Blood and Marrow Transplantation on allo-SCT in 44 patients with 17p deletion CLL showed a 3-year PFS of 37% (95% confidence interval 22–52%) with no event occurring later than 3.5 years after transplant (median follow up 39 months, range 18–101). The majority of the patients studied (89%) had received RIC [Schetelig *et al.* 2008]. Similarly, in the CLL3X trial, five of 13 patients with 17p deletion prospectively followed became long-term

minimal residual disease (MRD)-negative survivors (maximum follow up 59 months). No event was observed from 24 months after allo-SCT onwards. Therefore it can be concluded that RIC allo-SCT seems to be effective in high-risk CLL by overcoming the adverse prognostic impact of purine analogue refractoriness and 17p deletion. The presence of active or unresponsive disease at the time of allo-SCT remains a predictor of an unfavorable outcome [Dreger *et al.* 2005; Sorror *et al.* 2008; Brown *et al.* 2012; Khouri *et al.* 2007]

Indications for allo-SCT

It is important to acknowledge that no randomized data exist to date which compare conventional chemotherapy against allo-SCT in patients with CLL. A donor *versus* no-donor analysis by Herth and colleagues showed a survival advantage in cases in which a suitable human leucocyte antigen donor was readily available [Herth *et al.* 2014]. Moreover, a Markovian decision model by Kharfan-Dabaja and colleagues showed a quality-adjusted life expectancy favoring allo-SCT (*versus* conventional chemotherapies or chemoimmunotherapies) [Kharfan-Dabaja and Bazarbachi, 2012]. According to the European Group for Blood and Marrow Transplantation (EBMT) consensus guidelines, allo-SCT should be considered in patients with previously treated poor-risk CLL. Criteria for high-risk disease as defined by the authors entailed nonresponse or early relapse within 12 months after purine analogue containing therapy, relapse within 24 months after having achieved a response with a purine analogue combination therapy or treatment of similar efficacy, and p53 deletion or mutation, or 17p deletion requiring treatment [Dreger *et al.* 2006]. An update by the EBMT in 2013 also suggested proceeding to transplant before a stage of refractoriness so favorable outcomes are still possible [Dreger, 2013; National Comprehensive Cancer Network, 2014]. It is to be noted that the consensus guidelines were developed before the availability of the novel agents. In addition to the principle disease risk, patient-related risk factors, such as age, comorbidity, and actual disease activity, have to be considered when the decision about allo-SCT is made.

Impact of novel therapies on allo-SCT

As previously noted, compared with as recent as 5 years ago, the impact of the available novel agents in poor prognostic groups less likely favors early

referral for allo-SCT. Patients with 17p deletion or *TP53* gene mutation have modest responses to most conventional regimens, with minimal long-term control, leaving allo-SCT the only option for these patients provided with minimal disease burden prior to the availability of newer agents. However, this has changed in the modern era with satisfactory long-term controls realistically plausible in poor-risk groups. The novel agents when combined together in the poor prognostic group may have a greater impact on tumor reduction and prolonged disease-free interval. However, there is concern for the long-term safety, development of resistant clones and ultimately transformation to a high-grade lymphoma with targeted agents.

Previously with the use of myeloablative conditioning regimens for allo-SCT, treatment-related mortality was prohibitive. This has improved significantly with the use of reduced intensity conditioning regimens, to as low as 15%. Nonmyeloablative conditioning regimens using FCR that also target the disease have a relatively low nonrelapse mortality of 17% at 1 year, with early mortality as low as 3%. This suggests incorporation of allo-SCT early during the treatment phase of CLL rather than awaiting exhaustion of available drugs.

There are no prospective trials comparing transplant *versus* nontransplant therapeutic options in high-risk patients with CLL. To date, allo-HCT remains the therapy with potentially long-term sustainable responses, especially in high-risk patients. The targeted therapies available today could potentially improve transplant-associated outcomes

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Conflict of interest statement

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