Chronic Lymphocytic Leukemia

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84.1 Introduction

CLL is a rare indication for HSCT since it usually follows an indolent course. Those patients who require treatment have the option of various combinations of chemoimmunotherapy (CIT), several non-cross-resistant pathway inhibitors, and cellular-based immunotherapy.

Three orally available pathway inhibitors with an attractive risk-benefit ratio have been approved for the treatment of CLL in the past 5 years, the Bruton's tyrosine kinase inhibitor ibrutinib, the phosphoinositide 3-kinase inhibitor idelalisib, and the BCL2 inhibitor, venetoclax. Second-generation compounds are under development.

While CAR treatment is still at an early stage of clinical developmental for CLL, already today the sequential use of the available treatment options offers chances for long-term survival. Only a minority of patients shows resistant disease with the current treatment options and requires allo-HSCT.

84.2 Principles of Treatment for CLL

The diagnosis of CLL does not justify the start of treatment. This holds true even for relapsing CLL. Criteria which should trigger treatment are, e.g., anemia or thrombocytopenia due to heavy marrow involvement, a lymphocyte doubling time of less than 6 months, severe constitutional symptoms, or bulky lymphadenopathy. Treatment of CLL should be stratified by the *TP53* genotype. Patients with CLL harboring a cytogenetic deletion 17p detected by FISH or karyotyping or with a *TP53* mutation detected by DNA sequencing (combined in this manuscript as *TP53* abnormalities) should not be treated with chemotherapy. While CIT used to be the standard of care for first-line treatment for several decades, this standard is now challenged also in patients with functional *TP53* by the treatment with pathway inhibitors with or without monoclonal B-cell antibodies.

84.3 Results of CLL Treatment with Pathway Inhibitors

Five-year disease control rates in treatment-naive elderly patients on ibrutinib monotherapy have been reported from two phase II trials (5-year PFS of 92% and 100%) (Ahn et al. 2018; O'Brien et al. 2018). Treatment-naive patients with a *TP53* abnormality had a 5-year PFS of 74% (95% CI, 60–92%).

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Five-year PFS in relapsed/refractory patients on ibrutinib was 44% (O'Brien et al. 2018). Outcome was worse in patients with a deletion 17p or a *TP53* mutation compared to patients without these abnormalities (O'Brien et al. 2018). In an NIH trial, patients with *TP53* abnormalities had a 5-year PFS of 19% (95% CI, 6–60%) compared to 65% (95% CI, 44–96%) without *TP53* abnormalities (Ahn et al. 2018).

Patients with relapsed/refractory (R/R) CLL with a deletion 17p who received the BCL inhibitor venetoclax had a 2-year PFS of 54% (95% CI: 45%, 62%) (Stilgenbauer et al. 2018). Notably, on venetoclax monotherapy, 20% of patients achieved a CR according to NCI criteria, and 30% reached MRD negativity measured by FACS at cutoff of 10^{-4} CLL cells. Patients who achieved a complete or MRD-negative remission had a very good prognosis despite previously relapsed/refractory CLL with a deletion 17p. Furthermore, venetoclax demonstrated activity in patients who failed on ibrutinib or idelalisib (Jones et al. 2018).

Finally, idelalisib in combination with RTX or ofatumumab has also demonstrated activity in patients with R/R high-risk CLL. For example, the median PFS for patients with del(17p) or *TP53* mutations who had received idelalisib plus ofatumumab was 16 months (95%-CI, 11–19 months) (Jones et al. 2017).

After failure of ibrutinib or idelalisib, sequential treatment with another pathway inhibitor is efficacious (Jones et al. 2017; Coutre et al. 2018; Mato et al. 2016). However, disease control generally is shorter compared to pathway-inhibitor-naïve patients.

84.4 Allogeneic HSCT

The indication for allo-HSCT requires high-risk disease and failure on at least one pathway inhibitor (Dreger et al. 2014). High-risk CLL can be defined clinically by refractory disease or relapse within 2 years after CIT and biologically by *TP53* abnormalities. Information on the IGVH mutation status, IGHV3-21 gene usage, deletion 11q, or complex karyotype adds to biological risk categorization, but only *TP53* abnormalities are broadly accepted for stratified treatment. However, even patients with high-risk disease should have failed at least one pathway inhibitor before being referred for allo-HSCT. Independent of PI exposure, patients with a history of Richter's transformation and patients with a therapy-related myeloid neoplasia have an indication of allo-HSCT.

Available evidence strongly suggests that allo-HSCT is currently the only therapy with curative potential in CLL (van Gelder et al. 2017; Kramer et al. 2017). Many patients reach CR without MRD after allo-HSCT. Allo-HSCT can provide long-term disease control even in patients with an unfavorable biological and clinical risk profile. The timing of allo-HSCT should be individually discussed with the patients by taking into consideration the risk of complications after allo-HSCT and the chances of sequential treatment with pathway inhibitors and or CIT. Standard risk scores like the HCT-CI, the PAM-score, or the EBMT risk score can be used to assess the risk of non-relapse mortality of an individual patient (Schetelig et al. 2017a, b). When assessing the chances of continued conventional treatment, several factors have to be considered:

1. The risk of adverse events during prolonged conventional treatment which affect the eligibility for allo-HSCT
2. The risk of a Richter's transformation
3. The risk of a failed salvage attempt at the next relapse/progression of CLL
4. The risk of worse outcome after allo-HSCT in patients with more resistant CLL

84.4.1 Remission Induction Prior to Start of the Conditioning Regimen

Large prospective and retrospective studies uniformly show that the results of allo-HSCT deteriorate if the disease is not in remission at the time of transplant. Thus, allo-HSCT should be performed in remission of CLL. Different options exist for remission induction and bridging to allo-HSCT. Abundant information exists for CIT prior to allo-HSCT. Data from retrospective registry studies also supports the use of ibrutinib or idelal-

isib plus RTX for remission induction prior to transplantation (Dreger et al. 2018; Schetelig et al. 2017c). So far, no systematic studies addressed the use of venetoclax prior to allo-HSCT. However, since this drug does not modulate the immune responses, no adverse carry-over effects have to be suspected. As a general rule, the treatment with the highest chance of short-term tumor debulking should be used for remission induction prior to allo-HSCT (van Gelder et al. 2016).

84.4.2 Conditioning Regimens

The crucial therapeutic principle of allo-HSCT in CLL is GVL activity. Evidence for this comes from the observation that even some patients with refractory disease benefit from allo-HSCT. The impact of GVL is reflected by a reduced relapse risk in the presence of cGVHD and the efficacy of immune modulation for the eradication of MRD (Ritgen et al. 2008; Hahn et al. 2015).

Accordingly, long-term disease control can be achieved with a broad range of conditioning regimens. Current evidence does not allow the definition of one standard conditioning regimen for CLL. The most convincing data supporting allo-HSCT in CLL come from studies of NMA conditioning or RIC (Kramer et al. 2017; Schetelig et al. 2017b; Sorror et al. 2008). The choice of conditioning intensity may vary according to the individual situation. In the presence of comorbidity and chemosensitive disease, RIC or NMA conditioning appear to be more appropriate, whereas high-intensity regimens might be preferable in younger patients with good performance status but poorly controlled disease.

84.4.3 Outcome After Allo-HSCT for CLL

Based on a large registry cohort, estimated event-free survival, overall survival, and NRM 10 years after allo-HCT were 28% (95% confidence interval (CI), 25–31), 35% (95% CI, 32–38), and 40% (95% CI, 37–42), respectively (van Gelder et al. 2017). Patients who passed the 5-year landmark EFS (N = 394) had a 79% probability (95% CI, 73–85) of surviving the subsequent 5 years without an event. Relapse and NRM contributed equally to late treatment failure. Higher age, lower performance status, unrelated donor type, and unfavorable sex mismatch have an adverse impact on 2-year NRM. Despite the risks of NRM and even late relapse/progression, the prospect of long-term DFS on average in almost one out of three patients remains an argument to consider allo-HCT especially for young patients with high-risk CLL.

84.4.4 Post transplant Minimal Residual Disease Monitoring and Immune Intervention in CLL

In CLL, sensitive MRD quantification (i.e., 1 cell in 10^4 or less) can be obtained by PCR- or flow cytometry-based assays. The decline of the MRD level is often delayed and is closely related to immuno-reconstitution after allo-HSCT. GVL-induced MRD negativity after allo-HSCT is sustained in the majority of patients and is highly predictive of freedom from relapse. MRD monitoring is a valid instrument for the guidance of preemptive immune interventions directed at disease eradication after allo-HSCT, such as the tapering of IS and the use of DLI. The published evidence suggests that CLL is sensitive to timely preemptive immune intervention by modulation of systemic IS (Ritgen et al. 2008; Moreno et al. 2006).

84.5 Summary and Perspectives

Allo-HSCT from MRD or MUD can induce long-term DFS in patients with high-risk CLL. It is a standard treatment option for patients with high-risk CLL who have failed at least one pathway inhibitor. Generally, allo-HSCT should be considered before the disease has advanced to a status of complete refractoriness. At the same time, allo-HSCT should not be recommended for patients who face a higher short-term risk of mortality after transplantation compared to conventional therapy. In the absence of randomized

controlled comparisons of these treatment strategies, the outcome of an individual patient has to be predicted based on published data. This requires careful individual assessment of the risk of allo-HSCT versus prolonged conventional treatment. Patients should be referred to a transplant center once their disease proved refractory to at least one pathway inhibitor in order to get consultation with an expert in the field. Finally, all approved drugs for CLL can also be used for the treatment of post transplant relapse, and further improvements of donor selection, patient care, and prevention of complications can be expected; thus, overall outcome after transplantation will continue to improve.

Key Points

Indications for allo-HSCT	• High-risk CLL after failure of pathway inhibitor treatment • CLL in combination with therapy-related MDS • History of Richter's transformation
Remission induction prior to start of conditioning	Patient who receive allo-HSCT in remission enjoy a lower risk of relapse. The most potent option for remission induction should be chosen. This can be any pathway inhibitor or CIT
Donor, graft source, and GVHD-prophylaxis	No disease-specific criteria have to be considered (Michallet et al. 2010; van Gorkom et al. 2018)
Conditioning	Patients should receive either NMA conditioning or alkylator-based RIC. A history of a Richter's transformation or concomitant MDS may justify dose intensification (Schetelig et al. 2017b; Sorror et al. 2008)
MRD monitoring	At least quarterly assessments of MRD by FACS or PCR should be offered after allo-HSCT. Early taper of IS with or without administration of DLI, especially in patients without GVHD but with persistent disease, may result in MRD-negative CR in this group of patients (Ritgen et al. 2008)
Risk factors for non-relapse mortality	• Advanced age • Poor performance status and/or high HCT-CI score • Partially matched as compared to matched donor HSCT
Outcomes	Estimates based on HSCT performed between 2000 and 2010 reported to EBMT registry (van Gelder et al. 2017): 2-year and 5-year NRM, 30% and 36% 2-year and 5-year CI of relapse/progression, 21% and 29% 2-year and 10-year EFS, 49% and 28% 2-year and 10-year OS, 62% and 35%
Relapse after allo-HSCT	Relapse after allo-HSCT may be treated successfully. To current knowledge the history of allo-HSCT does not restrict treatment options for patients with relapsed CLL. Ibrutinib appears to be especially favorable for the treatment of first relapse after transplantation in patients without proven ibrutinib resistance

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