Current strategies for the diagnosis and management of chronic lymphocytic leukemia (CLL), with a focus on poor-risk CLL: A review

Kronik lenfositik lösemi (KLL) tanı ve tedavisine ilişkin, özellikle yüksek riskli KLL'ye odaklanan güncel stratejiler: Derleyici bir inceleme

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Abstract

Despite substantial advancement in the understanding and treatment of chronic lymphocytic leukemia (CLL), a standard curative approach does not exist. The choice of treatment is generally based on the existence of biological and genetic factors associated with the prediction of prognosis, individual response to therapy, and duration of remission. About 20% of patients that require treatment have an aggressive disease course and die within a few years, despite early initiation of intensive therapy (poor-risk CLL). Poor-risk CLL can be predicted by the presence of genomic markers, and the quality and duration of response to purine-analogue-based treatment. Within this patient subgroup alternative treatment approaches such as alemtuzumab or new substances such as flavopiridol or IMiDs® should be considered. To date, the only treatment bearing curative potential is allogeneic stem cell transplantation; in contrast to conventional immunochemotherapy, it can provide long-term disease control, even in patients with del 17p or other unfavorable biological and clinical risk factors. The aim of this review was to outline the current strategies for the diagnosis and management of CLL, with a focus on high-risk CLL.

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Key words: CLL, genetics, poor-risk, treatment, allogeneic stem cell transplantation

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Özet

Kronik lenfositik löseminin (KLL) tanı ve tedavisine yönelik önemli gelişmelere karşın, şifa sağlayıcı (küratif) standart bir yaklaşım henüz bulunmamaktadır. Tedavi seçimi genellikle prognozu öngören biyolojik ve genetik faktörlerin varlığına, tedaviye alınan bireysel yanıt ve iyileşme (remisyon) süresine dayanır. Tedavi edilmesi gereken hastaların yaklaşık %20'si hızla ilerleyen bir klinik gidiş gösterirler ve yoğun tedaviye erkenden başlanmasına karşın birkaç yıl içerisinde yaşamlarını yitirirler (yüksek riskli KLL). Yüksek riskli KLL olasılığı, genomik belirteçler yanında purin-analogu temelli tedaviye alınan yanıtın niteliği ve süresiyle önceden kestirilebilir. Bu hasta altgrubunda, alemtuzumab gibi alternatif tedavi yaklaşımları ya da flavopiridol ve IMiD® grubu gibi yeni ilaçlar göz önüne alınmalıdır. Günümüzde bu hastalarda şifa sağlayıcı potansiyele sahip tek tedavi seçeneği allogeneik kök hücre naklidir. Bu yöntemle, geleneksel immünokemoterapinin aksine, del 17p veya diğer olumsuz biyolojik ve klinik risk faktörlerine sahip hastalarda bile hastalığın uzun süreli denetimi sağlanabilir. Bu derleyici incelemede, yüksek riskli KLL'ye odaklanarak KLL tanı ve tedavisine ilişkin güncel stratejilerin özetlenmesi amaçlanmıştır. *(Turk J Hematol 2011; 28: 86-96)*

Anahtar kelimeler: KLL, genetik, yüksek risk, tedavi, allogeneik kök hücre transplantasyonu

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Epidemiology and Clinical Features

Chronic lymphocytic leukemia (CLL) is one of the most common lymphoid malignancies, accounting for more than 10% of all lymphoid neoplasms, and is the most common adult leukemia in Western countries, with an age-adjusted annual incidence rate of about 4 cases per 100.000 men and women [1,2]. While the median age at diagnosis is over 70 years, approximately 30% of patients are diagnosed at an age of ≤65 years. The disease has a slight male predominance (male:female ratio: 1.5-2:1). Clinical features are highly variable, and most patients are asymptomatic. As the disease proceeds, fatigue, splenomegaly, hepatomegaly, lymphadenopathy, and extranodal infiltrates are observed. Another hallmark is immune suppression and deficiency, including hypogammaglobulinemia, autoimmune phenomena, and impaired response to vaccination, which is further exacerbated by therapy-related immunosuppression [3].

Diagnosis

To unify the criteria for diagnosis and response assessment a working group sponsored by the National Cancer Institute first published guidelines for the design and conduct of clinical trials on CLL in 1988 [4]. Following an update in 1996, the International Workshop on CLL (iwCLL) revised the guidelines, taking into account the substantial progress that had been made in the understanding and treatment of the disease [5]. The recommendations for diagnosis and treatment discussed in this review are based on the iwCLL criteria.

The diagnosis of CLL requires the presence of cells with a CLL-specific immunophenotype, along with ≥5.000 B-lymphocytes μL^{-1} in peripheral blood [5]. The presence of CLL cells with a lower B-lymphocyte count in the absence of lymphadenopathy, organomegaly, or cytopenia is now defined as monoclonal B-lymphocytosis (MBL) [6]. The presence of lymphadenopathy or splenomegaly, and a B-lymphocyte count ≤5.000 μL^{-1} is defined as small lymphocytic lymphoma (SLL). More than 55% prolymphocytes in the blood suggests a diagnosis of B-cell prolymphocytic leukemia (B-PLL) [7].

Flow cytometry is essential for determining the clonality of B-lymphocytes and the following characteristic CLL-cell-surface phenotypes: the presence of CD19, CD5, CD23 and CD43, weak expression of CD20 and CD79b, and kappa or lambda immunoglobulin light chains [8,9]. The expression of CD38 is variable, but has prognostic significance and should therefore be evaluated [10,11]. Flow cytometry is also indispensable for differentiating CLL from other lymphoproliferative diseases, such as hairy cell leukemia, leukemic manifestations of mantle cell lymphoma, marginal zone lymphoma, splenic marginal zone lymphoma, and follicular lymphoma.

Bone marrow investigation is generally not required for the diagnosis of CLL, especially in patients without cytopenia and those not requiring treatment. Bone marrow aspiration and biopsy may be indicated, however, when treatment is required, as the extent and pattern (diffuse vs. non-diffuse) of bone marrow infiltration can provide valuable information on tumor burden and factors that may contribute to cytopenia. Post-treatment bone marrow investigation is recommended in patients with persisting cytopenia of unknown origin. In SLL the diagnosis should be verified via histopathological evaluation of a lymph node biopsy specimen.

Clinical Staging and Prognosis

As the clinical course of CLL varies widely, staging systems have been developed to stratify patients into different risks groups for predicting survival. The 2 most commonly used are the Rai and Binet staging systems [12,13]. Both systems consist of parameters that are obtained via clinical examination and standard laboratory tests, and are therefore easy to obtain. Ultrasound and computed tomography are not required, although they increase the accuracy of the assessment of intra-abdominal lymph nodes and organomegaly. Table 1 outlines the parameters that define the clinical stages. To account for extreme heterogeneities observed within each risk group, Wierda et al. proposed a new prognostic index for previously untreated CLL patients for predicting overall survival (OS) [14]: in the Rai staging system age, absolute lymphocyte count, gender, β2-microglobulin concentration, and the number of involved lymph nodes were independently associated with OS. This index was validated in an independent patient cohort by a Mayo Clinic study [15]. A recent observational database study by GIMEMA (Gruppo Italiano Malattie EMatologiche dell´Adulto) also confirmed the utility of the index for predicting time to first treatment [16].

Indications for Treatment

As there is no standard curative approach for CLL, the decision to begin treatment is based on the development of symptoms and disease activity. Newly diagnosed asymptomatic patients should be monitored without therapy, as there is no documented benefit from early anti-leukemic treatment [5]. Patients with symptomatic, advanced, or rapidly pro-

Table 1. Rai and Binet clinical staging

Risk group	Rai	Binet
Low	0: lymphocytosis with CLL cells in PB and/or BM, lymphoid cells >30%	A: Hb ≥100 g L^{-1} (10 g dL^{-1}), platelet count ≥100×10^9 L^{-1}, and up to 2 lymph node areas involved*
Intermediate	1/2: Lymphocytosis, enlarged lymph nodes at any site, splenomegaly and/ or hepatomegaly	B: Hb ≥100 g L^{-1} (10 g dL^{-1}), platelet count ≥100x10^9 L^{-1}, and organomegaly greater than that defined for stage A (i.e. ≥3 areas of nodal or organ enlargement)
High	3/4: Disease-related anemia (Hb <110 g L^{-1} [11 g dL^{-1}]) or thrombocytopenia (plt <100x10^9 L^{-1})	C: Hb <100 g L^{-1} (10 g dL^{-1}) and/or a platelet count <100x10^9 L^{-1}, irrespective of organomegaly

*Areas of involvement considered for staging
1. Head and neck, including the Waldeyer ring (this counts as 1 area, even if >1 group of nodes is enlarged)
2. Axillae (involvement of both axillae counts as 1 area)
3. Groins, including superficial femorals (involvement of both groins counts as 1 area)
4. Palpable spleen
5. Palpable liver

gressive disease usually benefit from treatment. Definitions of disease activity are listed in Table 2. The decision to begin second-line treatment generally follows the same guidelines.

Factors Guiding the Choice of Treatment

Physical fitness and comorbidity

Once treatment is indicated, each patient's individual physical condition and degree of co-morbidity should be evaluated. In completely independent patients with no comorbidity and otherwise normal life expectancy (go-go patients) aggressive chemotherapy aimed at the prolongation of survival is recommended. The goal in patients with some co-morbidity, impaired organ function, and reduced performance status (slow-go patients) is to achieve disease remission via a less aggressive approach. Patients that are severely handicapped and have high co-morbidity (no-go patients) might often fare best with supportive palliative care only. Physical fitness can be determined empirically or by using the cumulative illness rating scale (CIRS) [17].

Biological prognostic factors

Substantial progress has been made in the identification of biological and genetic factors that are strongly associated with the prediction of prognosis, individual response to therapy, and duration of remission. Several studies reported that elevated serum thymidine kinase (sTK), β2-microglobulin, and soluble CD23 may predict OS or progression-free survival (PFS) [18-21]. Using fluorescence in-situ hybridization (FISH) cytogenetic aberrations can be identified in more than 80% of CLL patients [22]. The most common chromosomal aberrations are del 13q, del 11q, trisomy 12, del 17p, and del 6q, with 13q deletion indicating the best prognosis with a median survival of >10 years and 17p deletion indicating a particularly poor prognosis with a median survival of <3 years, even with modern fludarabine/rituximab-based frontline treatments.

Table 2. Definitions of disease activity

At least 1 of the following:
1. Evidence of progressive marrow failure: anemia and/or thrombocytopenia
2. Massive (i.e. ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly
3. Massive nodes (i.e. ≥10 cm in diameter), or progressive or symptomatic lymphadenopathy
4. Progressive lymphocytosis with an increase >50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months.
5. Autoimmune anemia and/or thrombocytopenia
6. Constitutional symptoms: unintentional weight loss, significant fatigue, fevers, night sweats

Somatic mutations in the gene encoding the variable region of the heavy chain of immunoglobulins (IGHV) occur in approximately 50% of CLL patients [23]. Patients lacking a mutation in this region (unmutated IGHV) tend to have a more progressive and advanced form of CLL than patients with mutated IGHV. This was first shown retrospectively in patients treated in the pre-purine-analogue era, but has been confirmed in prospective studies using fludarabine combination regimens [11,24]. As testing for IGHV mutation status is complex and expensive, ZAP-70 expression was reported to correlate with the expression of unmutated IGHV [11,24,25]; however, the association between ZAP-70 and IGHV is not definitive. According to the iwCLL guidelines, with the exception of del 17p FISH, these tests should not

be used in general practice to guide clinical decision-making; however, it is essential to consider the existence and importance of these tests at the time of first diagnosis.

First-line Treatment

Go-go patients without del 17p

Following traditional treatment approaches consisting of alkylating agents (mostly cyclophosphamide or chlorambucil) with or without nucleoside analogue-based substances, the combination of monoclonal antibodies with chemotherapy increased the complete response (CR) rate from 4% [26] to 70% [27-30]. A large phase III trial that randomly assigned patients to 6 courses of fludarabine and cyclophosphamide (FC), or rituximab-FC (R-FC) was conducted by the German CLL Study Group (GCLLSG) (CLL8 trial). At 3 years post treatment, 65% of the patients in the chemoimmunotherapy group were progression free, compared to 45% in the chemotherapy group (HR:.56; 95% CI: .46-.69; $p<0.0001$) [31]. Additionally, 3-year OS was significantly longer in the R-FC group (87% vs. 83%, $p=0.01$), and R-FC treatment was associated with a significantly higher complete remission (CR) rate and longer duration of response. Although R-FC was more frequently associated with grade 3 and 4 neutropenia and leucopenia, it is now considered the gold standard treatment for physically fit patients without 17p deletion. In another GCLLSG phase II trial previously untreated patients received 6 cycles of bendamustine (90 mg m^{-2} on d 1 and 2) with rituximab (375 mg m^{-2} for the first cycle and 500 mg m^{-2} for subsequent cycles, repeated every 28 d) (R-B regimen) [32]. The overall response (OR) rate was 91%, including 33% of patients with CR. Hematopoietic and overall toxicity of R-B was modest. After 18 months 76% of the patients were still in remission, while median progression-free survival (PFS) had not been reached. R-B can therefore be considered safe and effective. The GCLLSG is currently conducting a randomized phase III trial to make a direct comparison of R-B and R-FC.

Variations of the R-FC regimen have been tested extensively. For example, Bosch et al. conducted a phase II trial with 29 previously untreated CLL patients receiving rituximab plus FCM (mitoxantrone), followed by rituximab maintenance every 3 months for up to 2 years [33]. The OR, MRD- (minimal residual disease) negative CR, MRD-positive CR, and PR rates were 93%, 46%, 36%, and 11%, respectively, proving the efficacy of the regimen. Another approach was substitution of fludarabine by pentostatine (R-PC). A phase III randomized trial of R-FC versus R-PC in previously untreated and minimally treated CLL patients showed that there weren't any statistical differences between OS, response, or infection rates [34].

The role of autologous stem cell transplantation

Autologous hematopoietic stem cell transplantation (autoHSCT) is considered an attractive treatment alternative for a select group of patients. Pioneers in the field of autoHSCT for CLL are Gribben et al. from the Dana Faber Cancr Center [35]. An update published in 2005 showed that relapses continued to occur after 10 years of follow-up, translating into a 6-year PFS of 30% and a 6-year OS of 58% [36]. In the MRC pilot study, a large multicenter phase II trial on autoHSCT as a coponent of first-line CLL treatment, the 5-year OS and PFS rates were 78% and 52%, respectively [37]. An update of the GCLLSG CLL3 study, which had a similar design, reported a median OS of 10.5 years and a median PFS of 6.8 years after early autoHSCT [38]. The first, and to date, only phase III randomized trial was conducted by the EBMT; 39 patients with CR after first- or second-line treatment were randomized to consolidating autoHSCT or observation. Median event-free survival (EFS) was 24.4 months (range: 16.7-32 months) in the observation group and 51.2 months (range: 39.8-62.5 months) in the autoHSCT group, indicating a 5-year EFS of 24% and 42%, respectively. While autoHSCT almost doubled event-free survival (EFS) and time to retreatment, there wasn't a significant difference in OS (5-year OS was 84% and 86%, respectively). In addition, several studies indicate that autoHSCT fails to achieve durable MRD negativity [40,41], which means that autoHSCT cannot be considered as a curative treatment in CLL. Moreover, long-term follow-up observations have raised concerns about the increased incidence of therapy-related myeloid neoplasms (MDS and AML) following autoHSCT. In the Dana Faber and MRC series the 5- and 8-year incidence of therapy-related myeloid neoplasms was 12% [36,42], versus a 10-year incidence rate of 8% in the CLL3 trial [38]. Due to these limitations, autoHSCT cannot be recommended as a standard approach in CLL and should only be used in clinical trials.

Go-go patients with del 17p

As patients carrying del 17p have a high risk of very poor outcome with fludarabine-based regimens that include bendamustine, alternative treatment

approaches should be considered. It is well known that alemtuzumab has a similar affect in del 17p and non-del 17p CLL patients [43]. In the ongoing prospective GCLLSG CLL2o study patients with del 17p or refractoriness to fludarabine received subcutaneous alemtuzumab combined with oral dexamethasone, followed by alemtuzumab maintenance or allogeneic hematopoietic stem cell transplantation (alloHSCT). As of September 2010, 80 patients were enrolled in the protocol, of which 31 without prior therapy had del 17p and 17 that relapsed had del 17p [44]. OR and CR were 100% and 23%, respectively, in the del 17p first-line group, which are considerably higher than those in the CLL8 study F-CR group (71% and 5%, respectively). Adverse events were hematotoxicity and grade 3/4 cytomegaly virus (CMV) infection (16%); however, the response duration following alemtuzumab is usually limited, making the search for effective first-line consolidation mandatory. To date, the only treatment with the potential for long-term disease control in the del 17p patient subgroup is alloHSCT, which will be discussed in detail below.

Slow-go patients with and without del 17p

Patients with relevant comorbidity may be offered chlorambucil, bendamustine, or a dose-reduced fludarabine-containing regimen, with or without rituximab, depending on the fragility of the patient [45,46]. Alemtuzumab can also be considered in appropriate patients (i.e. those with del 17p). The GCLLSG is currently conducting an open-label 3-arm randomized phase III trial to compare the efficacy and safety of the new monoclonal CD20 antibody RO5072759 (GA101) plus chlorambucil (GClb) to those of rituximab plus chlorambucil (RClb) or chlorambucil only (Clb) in previously untreated patients with comorbidity.

Second-line Treatment

For selecting the appropriate indication and regimen for salvage treatment, the same criteria for first-line therapy primarily apply; start only if symptoms or rapid lymphoproliferation are present, and consider comorbidity and the presence of del 17p. In addition, an important factor guiding the choice of salvage treatment is the quality and duration of response to the previous treatment line; patients that relapse >12 months after purine analogue monotherapy or 24 months after completion of a modern combination treatment might benefit from repetition or modest escalation of the previous regimen, e.g. R-FC after F or FC, and R-B after R-FC. Before starting second-line treatment reassessment of 17p status is highly recommended to avoid unnecessary exposure to ineffective drugs in cases of clonal evolution. In contrast, all patients that relapse sooner must be regarded as having poor-risk CLL and treated accordingly.

Definition of Poor-Risk CLL

About 20% of patients with CLL that require treatment have an aggressive course and die within a few years of diagnosis, despite early initiation of intensive therapy. The hallmark of this so called poor-risk CLL is pre-existent or rapid development of resistance to the current standard combination regimens. Poor-risk CLL can be partially predicted by the presence of defined genomic markers.

Molecular markers

As outlined above, the existence of del 17p is associated with poor prognosis [22]. Patients with 17p deletion are often resistant to standard chemotherapy regimens. Following initial results of retrospective analyses [47], the adverse impact of del 17p was confirmed by several prospective phase III clinical trials using purine-analogue-based therapy. The LRF CLL4 trial that included 777 CLL patients that required treatment reported that patients with del 17p had significantly poorer response to fludarabine-based treatment and shorter PFS [28]. In a Spanish trial del 17p was associated with a significantly lower CR rate [33], and in the GCLLSG CLL4 (F vs. FC) and CLL8 trials (FC vs. FCR) del 17p was associated with dramatically lower CR, OR, OS, and PFS [31].

Recent data suggest that the vast majority of patients with del 17p had mutations of the remaining allele of the TP53 gene located in the deleted region of 17p [48]. Whereas TP53 mutations in general led to significantly shorter survival ($p=0.002$), survival was equally poor in patients with TP53 mutation only (5.5 months), TP53 mutation plus del 17p (7.6 months), and del 17p only (5.4 months). In a recent analysis of the GCLLSG CLL4 trial (F vs. FC) TP53 mutation was observed in 8.5% of the patients, of which 4.5% did not have del 17p [49]. None of the patients with TP53 mutation achieved CR, and median PFS and OS were significantly shorter in the group with TP53 mutation ($p<0.001$). As the outcome of patients with del 17p and/or TP53 mutation-both individually and combined-was very poor, it was recently proposed that these patients be considered as ultra-high risk [50].

In 2010 Oscier et al. published a comprehensive report on the prognostic significance of age, gender, and biomarkers in the prediction of treatment

response, PFS, and OS reported by a prospective randomized British CLL4 trial [51]. Using the factors identified as independent predictors for PFS, they subdivided CLL4 patients into 3 risk groups: 6% with known TP53 loss >10% were considered poor risk and 72% without TP53 loss and at least 1 of the following factors-unmutated IGHV, IGHV3-21 usage, 11q deletion, and/ or β-2 microglobulin >4 m L^{-1}-were considered intermediate risk. In all, 22% of patients were considered good risk, defined as none of the above factors and mutated IGHV. The 5-year PFS rates in these 3 groups were 0%, 12%, and 34%, respectively, and the corresponding 5-year OS rates were 9%, 53% and 79%, respectively, which confirmed the poor outcome of patients with del 17p and the prognostic impact of unmutated IGHV, β2-microglobulin, and 11q deletion. As this is a novel approach to risk stratification in CLL, it needs to be validated in patient cohorts treated with newer combination therapies, including monoclonal antibodies.

Response to treatment and duration of remission Independent of the presence of genomic poor-risk markers, the overriding predictor of poor-risk disease is the response to purine-analogue-based treatment. According to the iwCLL guidelines, every clinical response that is not CR or PR (e.g. stable disease, non-response, or progressive disease) should be rated as a treatment failure. Refractory disease is defined as treatment failure or disease progression within 6 months of the completion of the last antileukemic treatment. Early data from the M.D. Anderson Cancer Center on 174 patients with progressive or advanced CLL that received first-line therapy with fludarabine or fludarabine combined with prednisone showed that patients that did not achieve a clinical response had significantly shorter OS [52]. Patients with residual disease or non-response after fludarabine combined with cyclophosphamide and rituximab (R-FC) also had significantly reduced OS [30].

Median survival was also significantly reduced in patients that initially responded to R-FC, but then relapsed within 36 months, as compared to those that relapsed ≥36 months after R-FC treatment ($p<0.0001$) [53]. In an analysis of the CLL8 trial R-FC patients with PFS of 12-24 months (n=43) had a median post-relapse OS of <40 months. Outcomes for relapsing patients treated with FC within the same time interval were even worse [54].

The poor-risk associated with resistant disease is reflected in both the iwCLL guidelines and the EBMT (European Group for Blood and Marrow Transplantation) transplant consensus. According to iwCLL, patients with resistant disease (defined as a short time to progression after the first treatment) and/or leukemia cells with del 17p should be offered alternative treatment approaches such as alloHSCT. According to the EBMT consensus, patients with non-response or early relapse (within 12 months) after purine analogue treatment relapse within 24 months of having achieved a response with purine-analogue-based combination therapy, or autologous transplantation and TP53 abnormalities requiring treatment are potential candidates for alloHSCT [55].

Treatment of Poor-Risk CLL

As outlined in detail above, stable disease, non-response, progressive disease, and refractory disease are predictors of poor survival, and such patients should be considered high-risk, regardless of pre-existing biomarkers. This means that patients that have not been considered for alemtuzumab or alloHSCT pre-treatment based on their cytogenetic risk profile are candidates for a more intensive approach based on their inadequate response to first-line treatment. Most importantly, it is crucial to change the treatment components used in the initial failed approach. There are several treatment options, including alemtuzumab, ofatumumab, experimental drugs, and alloHSCT.

The phase II GCLLSG CLL2H trial evaluated the safety and efficacy of subcutaneous alemtuzumab in patients with fludarabine-refractory CLL, and reported that OR was 34% (4% CR and 30% PR), median PFS was 7.7 months, and median OS was 19.1 months [56]. Efficacy did not vary significantly between genetic subgroups, indicating that alemtuzumab treatment could overcome the adverse prognostic impact of IGHV mutation status, TP53 mutation, and genomic aberrations. The potential benefit of alemtuzumab in combination with chemotherapy was first observed in 6 patients by Kennedy et al. [57]; their findings were confirmed by a phase II trial on relapsed or refractory CLL, which reported an OR of 83%, including 11 patients with CR, and resolution of disease in all affected sites [58].

In the ongoing GCLLSG CLL2o trial on the combination of alemtuzumab and high-dose dexamethasone, 31 of the 80 patient enrolled to date were fludarabine-resistant; their OR rate was 47%, none achieved CR, and 12-month OS was 54% [44]. A recently published interim analysis of an international phase II study on the efficacy of the human monoclonal CD20 antibody ofatumumab in 138 patients that were fludarabine- and alemtuzumab-

refractory reported an OR rate of 58%; median PFS and OS were 5.7 and 13.7 months, respectively, indicating that ofatumumab might be a promising treatment option for fludarabine-refractory patients with poor-prognosis CLL [59]. Alternative treatment approaches using new substances, such as flavopiridol or IMiDs®, are currently being tested in clinical trials, and some patients might be eligible for inclusion in phase I or II clinical studies; however, none of the current or novel approaches has the potential for long-term disease control, highlighting the need for effective consolidation once remission is achieved.

The role of Allogeneic Stem Cell Transplantation

On the basis of its capacity to induce graft-versus-leukemia (GVL) effects [60], alloHSCT has been shown to provide long-term disease control in selected CLL patients [36,61-68]. Key outcome data from selected prospective clinical trials on reduced-intensity conditioning (RIC) are summarized in Table 3. To elucidate the effect of alloHSCT in patients with del 17p, the EBMT performed a retrospective database analysis in which 44 patients with del 17p that received alloHSCT were identified [69]. After a median post-alloHSCT observation time of 39 months, 19 patients were still alive. Three-year OS and PFS rates were 44% and 37%, respectively, and the cumulative incidence of disease progression at 4 years was 34%. During 4 years of follow-up no late relapses occurred in 9 patients, indicating that alloHSCT might have curative potential in patients with del 17p.

The final results of the prospective GCLLSG CLL3X trial on the feasibility and efficacy of RIC alloHSCT in patients with poor-risk CLL were recently published [70]. After a median follow-up of 46 months (7-102 months), 4-year non-relapse mortality (NRM), EFS, and OS were 23%, 42%, and 65%, respectively. Among the 52 patients for whom MRD monitoring results were available, 27 (52%) were alive and MRD negative 12 months after transplantation. EFS was similar in all genetic subgroups, including patients with del 17p. Multivariate analysis showed that uncontrolled disease at the time of alloHSCT and *in vivo* T-cell depletion with alemtuzumab, but no del 17p, previous purine analogue refractoriness, and donor source (human leukocyte antigen-identical siblings or unrelated donors) had an adverse impact on EFS and OS, indicating that alloHSCT can result in long-term MRD-negative survival in up to 50% of patients, independent of the underlying genomic risk profile. A recent update of the CLL3X data with work-up of TP53 mutation status showed that the adverse impact of TP53 mutation, similarly as del 17p, can be overcome by alloHSCT [71].

Although controlled trials are lacking, currently available data strongly suggest that alloHSCT is the only therapy with curative potential in high-risk CLL. In contrast to conventional immunochemotherapy, it can provide long-term disease control, even in patients with del 17p or other unfavorable biological and clinical risk factors.

Conclusions

Substantial progress has been made in the understanding and treatment of CLL, and advances in

Table 3. Results of prospective clinical trials on reduced-intensity conditioning (RIC) alloHSCT in CLL

	Schetelig et al. (61)	Sorror et al. (67)	Khouri et al. (65)	Brown et al. (66)	Delgado et al. (68)	Dreger et al. (70)
Number of patients	30	82	39	46	41	90
Conditioning regimen	FB/ATG[a]	F/TBI2[b]	FCR +/– ATG[c]	FB[d]	FM/CD52[e]	F/C +/–ATG[f]
Proportion of alternative donors[g]	57%	37%	18%	67%	41%	60%
4-year PFS	58%	39% (5y)	44%	34% (2y)	45% (2y)	42%
4-year OS	69%	50% (5y)	48%	54% (2y)	51% (2y)	65%
4-year NRM	15%	23% (5y)	n.r.	17% (2y)	26% (2y)	23%
Extensive chronic GVHD	21%	49-53%	58%	38%	5%	14%
Median follow-up [years] (range)	3.7 (2.1-5.6)	5	2.3 (.3-6.7)	1.7	1.3 (0-5.2)	3.8 (0.6-8.5)

[a]Fludarabine, busulfan, anti-thymocyte globulin (ATG)
[b]Fludarabine, total body irradiation 2Gy
[c]Fludarabine, cyclophosphamide, rituximab plus ATG in alternative donor transplants
[d]Fludarabine, busulfan
[e]Fludarabine, melphalan, alemtuzumab
[f]Fludarabine, cyclophosphamide plus ATG in alternative donor transplants
[g]Donor other than HLA-identical siblings
NRM: non-relapse mortality, GVHD: graft-versus-host disease

molecular profiling of the disease have enabled physicians to better predict patient risk profiles and response to therapy. Several studies have validated the components and impact of poor-risk CLL, and international guidelines have implemented these criteria in their treatment recommendations. As a result, Poor-risk patients can now be identified with greater accuracy and offered intensified treatment options, such as allo HSCT or alemtuzumab. Depending on patient performance status, personal preference, and the availability of a stem cell donor, these treatment options offer a tailored treatment approach, providing an opportunity to cure CLL in this poor-risk population.

Conflict of interest statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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