Chapter

Chronic Lymphocytic Leukemia: Rapidly Changing Treatment Landscape

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in developed countries. CLL is diagnosed with absolute B lymphocyte count (B-ALC) >5000/micrL sustained for at least 3 months, morphologically mature-appearing small lymphocytes, and flow cytometry showing the typical immunophenotype of CLL cells. Different prognostic parameters are used to differentiate between low-and high-risk patients, which would affect treatment decisions. Rai and Binet staging systems are the two most commonly used in practice. There has been a significant change in how we manage patients in CLL over the last 5 years. We have shifted away from chemoimmunotherapy toward novel agents such as BTK, PIK3, and BCL-2 inhibitors, which are not only more efficacious but are also safer and better tolerated. New prognostic models are being developed, and it appears that minima residual disease (MRD) directed therapy will become the norm in the future. Many clinical trials are looking at various combinations of novel therapies, with a defined period of treatment based on MRD analysis, to enable patients to have a period of treatment-free remission instead of continuous therapy. In this chapter, we summarize the latest updates in CLL management.

Keywords: CLL, leukemia, treatment, chemoimmunotherapy, MRD, novel agents

1. Introduction

With an age-adjusted incidence of 4–5 per 100,000 population, chronic lymphocytic leukemia (CLL) is the most common type of leukemia in developed countries. The median age at diagnosis is 72 years, and more men than women (2:1) are affected [1]. CLL is one of the B-cell chronic lymphoproliferative disorders. It is characterized by a progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin.

2. Diagnosis

CLL diagnosis depends on the presentation. For patients presenting with absolute lymphocytosis; CBC, flow cytometry of the peripheral blood, and examination of the peripheral smear are adequate to diagnose CLL [2]. Diagnosis of CLL using these tests requires identification of absolute B lymphocyte count (B-ALC) >5000/micrL sustained for at least 3 months, morphologically mature-appearing

small lymphocytes, and flow cytometry showing the typical immunophenotype of CLL cells: extremely low levels of surface membrane immunoglobulin (SmIg) and either Kappa or Lambda (but not both), CD19, CD20, CD23 and CD5 positive cells. Evaluation of the bone marrow is not usually necessary, but is included in the evaluation of patients with unexplained cytopenias. Patients presenting with lymphadenopathy without lymphocytosis will need ideally an excisional lymph node biopsy or alternatively a needle biopsy showing mature lymphocytes with the previously mentioned phenotype to diagnose small lymphocytic lymphoma (SLL) which is considered by WHO the same disease as CLL with different manifestations [3].

Monoclonal B cell lymphocytosis is diagnosed when B-ALC is <5000/micrL persistently with no other manifestations of disease activity such as lymphadenopathy, hepatosplenomegaly, disease related cytopenias, or disease related symptoms. Patients with disease related cytopenias are diagnosed with CLL regardless of B-ALC and patients with any of the other manifestations are considered to have SLL [2]. Before 2008, the diagnosis of CLL was based on ALC equal or more than 5000/microL in the setting of appropriate immunophenotype. Patients with an absolute B lymphocyte count (B-ALC) less than 5000/microL and an ALC more than 5000/microL represented an overlap between CLL and monoclonal B cell lymphocytosis. The switch to using B-ALC for the diagnosis of CLL in 2008 eliminated this overlap [4, 5].

3. Prognostication

CLL is commonly thought of as an indolent disease associated with a prolonged clinical course and that patients with CLL will die from unrelated cause rather than the disease itself. It is important to know that this only happens in one third of the patients. More commonly, patients will have two phases of the disease: an initial asymptomatic phase (5–10 years) where the course will be benign, followed by the terminal phase (1–2 years) where performance status will decline due to recurring need for hospitalization. Some patients die quickly within 1–2 years of the diagnosis. Because of this variable natural clinical course of CLL, there have been always efforts to come up with reliable and clinically applicable criteria that would allow recognizing those patients with poor prognosis to start treatment as soon as possible and improve their survival and differentiate them from the other group where the prognosis is good and treatment can be delayed to avoid treatment toxicity [6–8].

3.1 Rai and Binet staging systems

Rai and Binet staging systems are the most commonly used systems in practice and the international workshop Group on CLL (iwCLL) recommends using an integrated system using both methods [9]. Both systems depend on findings of CBC and physical exam findings only, addition of CT scan of the chest, abdomen, and pelvis is not routinely recommended to stratify patients.

Rai staging system divides patients into 5 groups (**Table 1**). It was published initially in 1975, with initial reports showing one quarter of patients fall in stage 0 on presentation, half of patients fall in stages 1 and 2, and a quarter of them fall in stages 3 and 4. Later reports showed that more patients fall in earlier stages because of earlier diagnosis due to the more routine testing being done in recent years including CBC [10]. Median survival decreases from almost 12 years in stage 0 to a year and a half in stages 3 and 4 [11]. In 1980s, this staging system was modified to include three stages based on actuarial survival pattern: Low risk (Rai stage 0), intermediate risk (Rai stages 1 and 2), and high risk (Rai stage 3 and 4). Of note,

Stage	Clinical features	Median survival (in years)
0 (low risk)	Lymphocytosis only	>10
I and II (intermediate risk)	Lymphadenopathy (I) and hepatosplenomegaly (II)	5–8
III and IV (high risk)	Anemia (III), thrombocytopenia (IV)	1.5

Table 1.
Rai staging system.

Stage	Clinical features	Median survival (in years)
A	<3 areas of lymphadenopathy; no anemia or thrombocytopenia	Comparable to age-matched controls
B	Three or more areas of lymphadenopathy; no anemia or thrombocytopenia	7
C	Hemoglobin <100 g/L or platelets <100 x 10^9 g/L	2

Table 2.
Binet staging system.

if complete or partial remission is achieved with successful therapy, and a patient's stage shifts from a higher risk to a lower risk category, the outlook for survival improves accordingly [12].

Binet staging system takes into consideration five potential sites of involvement: cervical, axillary, and inguinal lymphadenopathy (each area counts as one either unilateral or bilateral), spleen, and liver, in addition to the presence of anemia and/or thrombocytopenia. Based on these factors, Binet staging system divide patients into three groups (**Table 2**) [13].

One important practical concept is to reliably differentiate between autoimmune cytopenias and cytopenias related to CLL because patients with autoimmune cytopenias have better outcome than Binet stage C patients although still worse than stage A and they can normalize their counts with treatments directed at the autoimmune cytopenia thus delay CLL treatment [14, 15].

Both systems are not very effective for predicting early disease progression. Although routine imaging is not recommended for staging of patients with CLL, visceral adenopathy may occur in early-stage disease and might predict an early disease progression. It is not known if the presence of visceral adenopathy warrants any specific change in therapy [16].

3.2 Other prognostic factors

Historically, the presence of CD38 by flow cytometry appeared to be independently associated with an adverse prognosis as well as Increased levels of ZAP-70 detected by flow cytometry [17]. It is a tyrosine kinase normally expressed by NK and T cells, and required for normal T cell receptor signaling. ZAP-70 is not normally expressed in B lymphocytes, but has been found in a subset of patients with CLL. The clinical significance of CD38 and ZAP-70 have declined overtime with better understanding of CLL cytogenetics.

Currently, we use cytogenetics, molecular studies, lymphocyte doubling time, and beta-2 microglobulin [18]. Patients with del(13q) have favorable outcome, patients with trisomy 12 have intermediate outcome while patients with del(11q) and del(17p)/P53 have poor outcome. The prognosis of patients with del(11q) has

improved with the use of certain treatment regimens (e.g., fludarabine, cyclophosphamide, rituximab) while that of del(17p) or TP53 mutations remains poor despite such treatments. Analysis of CLL8 trial showed worse outcome in patients with SF3B1 and RPS15 gene mutations. Also, patients with complex karyotype and NOTCH1 mutations have more aggressive course.

The lymphocyte doubling time is the number of months it takes the absolute lymphocyte count to double. Doubling time <12 months is associated with a progressive course and a longer doubling time is associated with an indolent course. This factor is somewhat limited in usefulness because it takes time to measure. In patients with early stage disease, the presence of a short doubling time may favor more aggressive therapy. Higher levels of Beta-2 microglobulin (B2M) are associated with poorer outcome. B2M should be interpreted with caution in the context of renal disease, or alternatively GFR-adjusted B2M can be used although lacks validation in prospective studies [19]. Moreover, approximately half of CLL clones will demonstrate unmutated immunoglobulin heavy chain variable regions (IGHV), a finding associated with shorter survival overall and a higher risk of relapse following conventional treatment, including chemoimmunotherapy and hematopoietic cell transplantation [20].

3.3 International prognostic index for chronic lymphocytic leukemia (CLL-IPI)

An international group of investigators did a comprehensive analysis [21] to develop a prognostic index for CLL. Using data from 3472 treatment naive patients participating in prospective, randomized clinical trials, five independent prognostic factors were identified: TP53 deletion or mutation, or both, IGHV mutational status, serum B2M concentration, clinical stage, and age. Using weighted grading of the independent factors, a prognostic index was derived that separated patients into four risk groups with significantly different overall survival at 5 years: low (93%), intermediate (79%), high (63%), and very high risk (23%). This chronic lymphocytic leukemia international prognostic index (CLL-IPI) has now been validated by several other groups and is expected to improve patient counseling and the planning of clinical trials. Other risk scores have been proposed, but none of them has been generally accepted. Of note, none of the scores (including the CLL-IPI) affects the decision of when to initiate therapy.

4. CLL therapy

4.1 Early evolution

In the 1940's, steroids were the first systemic therapy for CLL. The risk of infection, other adverse effects from long term steroid use as well as transient nature of responses, steroids do not have a central role in the treatment of CLL. They can be used along with anti-CD 20 Ab to achieve remission in some patients.

Steroids were followed by the use of alkylating agent chlorambucil in the treatment of CLL, either in combination or as a single agent. These treatments produced objective response rates but mostly resulted on partial responses [22, 23]. This was followed by a long time period before newer drugs were introduced in the treatment of CLL. Fludarabine has been used in various combinations to improve outcomes in CLL. When compared to CAP (cyclophosphamide, doxorubicin and prednisone), fludarabine showed favorable results [24]. Even when it was compared to chlorambucil, fludarabine induced higher response rates but did not offer any survival advantage at the expense of higher toxicities especially from infection and neutropenia [25]. Cladribine in combination with prednisone achieved response rates

similar to fludarabine when compared to chlorambucil but failed to demonstrate any survival benefit [26, 27]. Cyclophosphamide combined with fludarabine in previously untreated patients showed lower prevalence of residual disease and increased progression free survival (PFS) but again no benefit in overall survival (OS) [28]. When rituximab was combined with fludarabine and cyclophosphamide there was an improvement in PFS as well as OS [29]. This was observed across multiple phase 3 randomized trials [30, 31]. Subset analysis of these trials led to the discovery that patients with mutated IGHV status, FCR led to long term remissions [30, 32].

4.2 Upfront treatment

Indication for treatment of CLL include severe fatigue, weight loss, night sweats, fever without infection, threatened organ function, progressive lymphadenopathy, anemia or thrombocytopenia that is progressive in nature, autoimmune anemia or thrombocytopenia not responsive to steroids [2]. In addition to these factors, patient age, performance status, presence or absence of del(17p) or TP53 mutation, IGHV mutation status should be assessed prior to initiating treatment in patients with indications to treat. Imaging should be considered as well to evaluate disease burden.

4.2.1 CLL without del(17p) or TP53 mutation

The CLL 8 trial was a pivotal one that established chemoimmunotherapy as the standard of care for patients that can tolerate it. The FCR regimen (fludarabine, cyclophosphamide and rituxan) was compared against FC (fludarabine, cyclophosphamide). Previously untreated CLL patients were randomized to either receive 6 cycles of FCR or FC. The FCR regimen resulted in higher ORR (90% v/s 80%) and CR rates 94% v/s 22%). The median OS was not reached for FCR and was about 86 months for the FC regimen. Subset analysis showed that the maximal benefit was derived by fit patients with CLL, especially those with mutated IGHV [32]. The FCR regimen however has its share of side effects and cannot be given to older patients.

The CCL2M trial looked at the feasibility of Bendamustine-Rituxan (BR) in untreated CLL patients and the results were found to be encouraging [33]. This prompted its comparison to other treatment regimens. The MABLE study looked at BR versus Chlorambucil-Rituxan in patients ineligible to receive fludarabine. Complete response rates were higher in the BR arm (24%) as compared to the chlorambucil-rituxan arm. Overall response rate and overall survival were not different among the two arms. However the PFS (40 months v/s 30 months) and Minimal Residual Disease (MRD) negativity (66% v/s 36%) were higher in the BR arm as compared to the Chlorambucil- rituxan arm [34].

CLL10 trial compared BR with FCR. The primary end point was PFS with the objective to assess non inferiority of BR as compared to FCR. The trial confirmed the superiority of FCR therapy (Median PFS 55 vs. 42 months) in fit patients and in patients with IGHV mutated status. However, in patients over 65 years of age the toxicity profile was better with BR.

The CLL11 trial found that chlorambucil-obinutuzumab had better PFS (26.7 months) as compared to rituximab-chlorambucil (16.3 months). The PFS for chlorambucil monotherapy was the shortest (11.1 months). The obinutuzumab-chlorambucil arm also had trend towards OS benefit as compared to the other 2 arms. The study population included CLL patients with comorbidities [35]. Based on these 2 trials both BR and chlorambucil- rituxan or obinutuzumab-chlorambucil are acceptable alternatives in elderly patients or those with comorbidities.

On a similar note, the COMPLEMENT 1 trial showed the combining ofatumumab to chlorambucil in fludarabine ineligible patients showed better PFS (22.4 months) as compared to the monotherapy arm (13.1 months) [36].

However, with the advent of novel agents the landscape of treatment in CLL has significantly changed. The RESONATE-2 study compared single agent chlorambucil to ibrutinib which is a Bruton's Tyrosine Kinase inhibitor. The ORR (92% v/s 36%) as well as PFS at 2 years (89% v/s 34%) in favor of ibrutinib (**Figure 1**). Based on the results of this study ibrutinib was approved for use in the first line setting of CLL. Results from the ECOG ACRIN Cancer research group trial E1912 were recently published. The study compared FCR versus Ibrutinib + Rituxan (IR) in treatment naive patients without deletion 17p. IR was found to be superior to FCR in all subgroups except for the IGHV mutated group. IR group saw significant less neutropenia and infectious complications as well as compared to FCR [38].

The alliance intergroup study showed that in older patients above 65, ibrutinib should be the standard of care as PFS was better in the ibrutinib arms then the BR arms [39]. However this study did not suggest a benefit of adding anti-CD 20 MAB therapy to ibrutinib monotherapy. In the older patient group, where chlorambucil is a treatment option, the iLLUMINATE trial showed that ibrutinib plus obinutuzumab combination resulted in better PFS as compared to chlorambucil plus obinutuzumab, albeit with greater serious adverse events [40]. Between the RESONATE-2 study and ECOG ACRIN study, ibrutinib has been established a first line recommendation in both younger as well as older patients with CLL.

Recently, CLL14 trial studied the combination of fixed-duration venetoclax and obinutuzumab versus obinutuzumab and chlorambucil in 432 treatment-naïve patients with CLL and coexisting medical conditions. Patients were evenly randomized to receive 12 months of venetoclax alongside 6 months of obinutuzumab or 6 months of obinutuzumab followed by 6 months of chlorambucil. Results from the trial showed the venetoclax combination reduced the risk of disease progression or death by 67% versus obinutuzumab plus chlorambucil in patients with treatment-naïve CLL and co-existing medical conditions (HR, 0.33; 95% CI, 0.22-0.51; P < .0001). The overall response rate (ORR) was 85% with venetoclax/obinutuzumab versus 71% in the control arm (P = .0007). The complete response (CR) or CR with incomplete hematologic recovery (CRi) rates were 50% versus 23%, respectively. The rate of minimal residual disease (MRD)-negativity in the bone marrow was 57% in the venetoclax arm compared with 17% in the obinutuzumab/chlorambucil arm. The MRD-negativity rates in the peripheral blood were

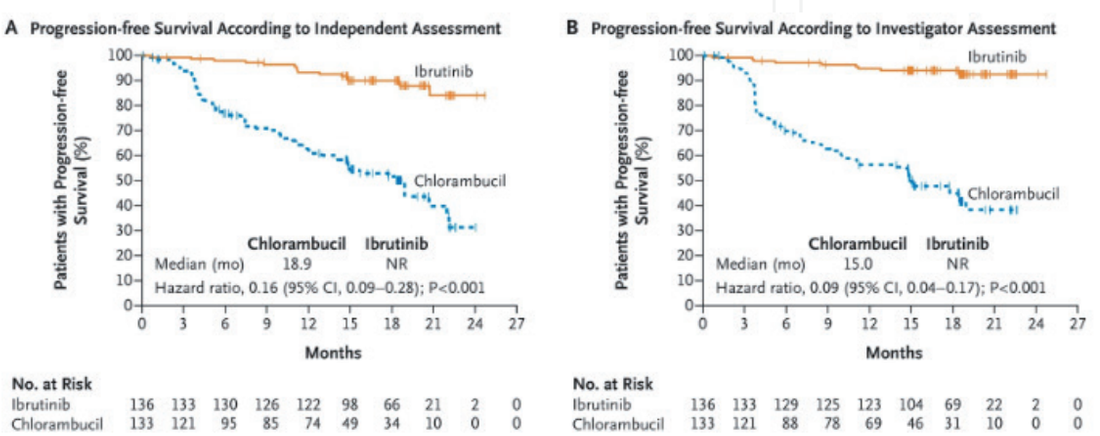

Figure 1.
Progression-free survival of Ibrutinib vs. Chlorambucil [37].

76% versus 35%, respectively. Venetoclax and obinutuzumab combination is the only chemotherapy-free option with fixed duration that proven to provide such a durable response.

4.2.2 CLL with del(17p) or TP53 mutation

Ibrutinib provides durable responses and is well tolerated in patients with del(17p). Historically this group of patients generally have poorer outcomes as compared to patients with CLL but without del(17p) [41]. Other treatments in the front-line setting are listed in NCCN for these patients however none of them are very effective. The CAPTIVATE trial is currently on going looking at venetoclax along with ibrutinib in the upfront setting.

Is summary, as far as front line therapy is concerned, for fit patients with IGVH mutated status it is reasonable to use chemo-immunotherapy such as FCR or BR. All other patients including young or older patients with high risk disease such as those with unmutated IGHD, 17p del or p53 mutation or 11q deletion it's recommended to treat with a novel agent such as ibrutinib as there has been accumulating evidence of better efficacy when compared to chemoimmunotherapy alone.

4.3 Relapsed or refractory chronic lymphocytic leukemia

4.3.1 Definitions

The International Workshop on CLL (iwCLL) defines relapsed disease when it occurs in patients who have previously achieved either a complete or partial remission but then develop progressive disease after a period of 6 months or more. Patients who fail to achieve either a partial or complete remission with therapy or those who develop disease progression within 6 months of last therapy are defined to have refractory disease. This distinction is principally made because many patients with progressive disease occurring later after the discontinuation of treatment can be successfully retreated using the same medication, or by switching to other available treatments. In contrast, patients who have refractory disease are unlikely to respond to a trial of the previously used therapy and have a much poorer prognosis [2]. Of note, The iwCLL response criteria were originally developed using data from patients treated with single agents (i.e., fludarabine, chlorambucil). As first-line therapy has evolved, the overall response rate and median progression-free survival have increased. The definitions of relapsed and refractory disease will likely change as therapy improves especially that we depend on expected progression free survival (PFS) in practice more than the 6 months rule to choose the next regimen as illustrated below.

The choice of treatment at relapse should consider how soon the relapse happens after initial treatment. If it happens sooner than the expected median PFS for the specific regimen is considered "Early relapse", while it is considered "Late relapse" when it happens after the expected median PFS [42]. Prospective trials have reported median PFS for different regimens, as a rule of thumb, progression within 2–3 years of initial treatment with fludarabine, cyclophosphamide, and rituximab (FCR) or within 1 year of other chemoimmunotherapy regimens may be considered to have early relapse.

4.3.2 Targeted therapies of relapsing or refractory CLL

For early relapsing CLL, it's recommended to start a targeted therapy with either ibrutinib, idelalisib plus rituximab, or venetoclax with or without rituximab rather than retreatment with the prior therapy or a trial of another chemoimmunotherapy

regimen. One series reported the median survival of 42 patients unresponsive to fludarabine as 48 weeks and only 11% responded to other chemoimmunotherapies [43]. The optimal length of treatment has not been defined but common practice to continue until disease progression or unacceptable toxicity.

Ibrutinib: it is a common treatment of choice for patients with refractory or early relapsing disease. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor [44]. The RESONATE trial which is a multicenter open label phase III trial showed better overall response rate (ORR), PFS, and overall survival (OS) compared to ofatumumab (an anti-CD20 monoclonal antibody) in patients with refractory/relapsed CLL, these benefits were found across all subgroups of patients, including those with high-risk features such as del(17p). This late observation was confirmed in the RENONATE-17 trial in 2016 where ORR was 83% at a median follow up of 28 months in 144 patients with relapsed/refractory CLL/SLL with del(17p) [45, 46]. Expected side effects from ibrutinib include diarrhea, fever, and nausea. Higher rates of atrial fibrillation (6–16%) and pneumonitis were noted in the clinical trials [47], atrial fibrillation is usually manageable without discontinuation of the drug. Another important side effect is increased risk of bleeding, ibrutinib should be used with caution if patient is on one anti-platelet medicine and should be avoided if on two anti-platelets or anticoagulants as fatal cases of bleeding happened in those scenarios. Also, Ibrutinib should be discontinued 3–7 days before and after surgery to decrease risk of perioperative bleeding. Patients should be also reminded to avoid NSAIDs [48]. Ibrutinib is associated with a usually "transient" lymphocytosis that peaks after approximately 4–8 weeks and resolves in the majority despite continued drug exposure with a median duration of 14 weeks. The starting dose of ibrutinib is 420 mg orally once daily, except for patients with mild liver impairment (child-pugh class A), the starting dose is reduced to 140 mg daily since it's metabolized in the liver and is contraindicated in moderate to severe liver impairment.

Idelalisib: It is an oral inhibitor of phosphoinositide 3′-kinase (PI3K) delta. It is given in combination with Rituximab. A phase 3 multicenter trial compared Idelalisib and rituximab vs. placebo and rituximab in 220 patients with relapsed CLL showed superior ORR, PFS, and OS (81%, 93%, and 92%, respectively), these benefits were seen in all prespecified subgroups, including those with 17p deletion, TP53 mutation, and IGHV mutations [49]. Possible side effects include: pneumonia and febrile neutropenia most commonly, but also fatigue, nausea, and diarrhea have been reported. Idelalisib can cause severe elevations in AST and ALT, it is reversible on holding the drug and never led to permanent discontinuation in clinical trials. The starting dose is 150 mg twice daily. Other possible combinations are Idelalisib plus Bendamustine plus Rituxan or idelalisib plus ofatumumab, those combinations led to more grade 3 toxicities and treatment related deaths, respectively, so extreme caution should be paid while choosing patients for these combinations [50, 51]. As with ibrutinib, idelalisib can cause transient lymphocytosis that peaks in the second week of treatment and resolves spontaneously by week 12, adding Rituximab decrease its severity and shortens its duration. CMV monitoring and prophylaxis against Pneumocystis pneumonia (PCP) are important with idelalisib use. It carries a boxed warning regarding hepatotoxicity, colitis, and pneumonitis.

Duvelisib: it is an oral inhibitor of PI3K delta and gamma isoforms. The phase 3 DUO trial was the largest trial to study the efficacy of duvelisib, it included 319 patients assigned to duvelisib vs. ofatumumab. Duvelisib had higher ORR and median PFS (74% and 13.3 months, respectively) [52]. Duvelisib is usually reserved for patients with multiply relapsed disease, usually after treatment with ibrutinib and venetoclax, with or without prior chemoimmunotherapy. The starting dose is 25 mg administered orally twice a day over a 28-day treatment cycle. Toxicities

include opportunistic infections, diarrhea or colitis, cutaneous reactions, and pneumonitis. Hepatic function and blood counts must be monitored for hepatotoxicity and neutropenia. Like idelalisib, it is recommended to use PCP and CMV prophylaxis.

Venetoclax: it is an oral inhibitor of BCL2, an antiapoptotic protein that is pathologically overexpressed and that is central to the survival of CLL cells. Initial phase 2 trials showed ORR more than 65% for venetoclax [53, 54]. The MURANO trial, an international phase 3 trial, compared Venetoclax plus rituximab vs. bendamustine plus rituximab in 389 patients with relapsed/refractory CLL showed higher PFS of 85% and OS of 92% at 2 years for the venetoclax arm, this effect was maintained in high risk patients and older adults. Patients assigned to venetoclax arm were also more likely to achieve undetectable minimal residual disease (uMRD) which is a status predictive of superior PFS [55]. The most common toxicities are pancytopenia, diarrhea, and upper respiratory tract infection. Because venetoclax increases risk of TLS, high risk patients (i.e. any lymph node >10 cm or lymph node >5 cm and ALC >25 x 109/L) should receive the first few doses in the inpatient setting with IV hydration, use of allopurinol or rasburicase, and frequent monitoring of TLS labs. Venetoclax is started at 20 mg daily and increased gradually over 5 weeks to a final daily dose of 400 mg. Rituximab is started after the patient has completed the escalation schedule and received the 400 mg dose for 7 days. It is common practice to use venetoclax after ibrutinib failure.

4.3.3 Late relapse: Retreatment versus targeted therapy

Although both options are valid in late relapsed CLL patients, each option has its advantages and disadvantages. Targeted therapy is generally the preferred option because they have better PFS and may improve OS, the best example on that is the MURANO trial mentioned above, patients who relapsed after 24 months of initial treatment with bendamustine and rituximab were included in the study, and still they had better PFS and OS [55]. Targeted therapy also offers the convenience of an oral regimen. On the other hand, retreatment with initial chemoimmunotherapy regimen may be considered for patients who experienced minimal toxicity with the initial treatment, targeted therapy is associated with unique toxicities and is often administered without breaks until the time of progression. In a phase 2 study, patients who were initially treated with FCR and relapsed after 3 years showed median survival of 5 years and estimated five-year survival rate of 70% when they were retreated with FCR, although the toxicities, especially myelosuppression, were more frequent [56].

Fludarabine-based therapy: Fludarabine, cyclophosphamide, plus rituximab (FCR) is a preferred treatment option for younger patients (<70 years) with standard-risk CLL. Patients with del(17p) or *TP53* mutations have particularly poor outcomes following fludarabine-based therapy and should be considered for targeted therapy.

Bendamustine-based therapy: Bendamustine plus rituximab (BR) is an acceptable alternative to fludarabine-based regimens among patients with decreased renal function or other comorbidities. BR is well tolerated, but appears to be slightly less effective than fludarabine-based regimens [57]. The most common toxicities are neutropenia, thrombocytopenia, and anemia [58]. Infusion is associated with a hypersensitivity reaction in approximately 5% of patients.

Ofatumumab-based therapy: Single agent ofatumumab has demonstrated partial response rates of approximately 50% in patients with relapsed or refractory CLL, although response duration is usually short [59]. The combination of ofatumumab plus chlorambucil is expected to result in higher response rates.

Patients with CLL experience serial relapses and many will be treated with each of these agents at some point during their disease course. A preferred order for their use has not been established. A choice is primarily made based on the patient's prior treatment and the regimens' expected toxicities.

5. Role of transplant in CLL

In the setting of approval of novel agents in the treatment of CLL the number of transplants that are being performed in Europe and the United States are decreasing. In the chemoimmunotherapy era, patients with TP53 deletion/mutation, fludarabine refractoriness, early relapse (<24 months) after FCR treatment were in the highest risk group. Allogeneic Stem Cell Transplant (SCT) would be considered in these patients as the only viable treatment option. Today however, these patients have ibrutinib, idelalisib and venetoclax and various combination of novel agents with immunotherapy as possible treatment options. There are no randomized clinical trials that compare the outcomes of allogeneic SCT with conventional chemotherapy, chemoimmunotherapy or novel therapy regimens. Most transplants offered for CLL use reduced intensity conditioning (RIC), however no trials have been conducted to compare it to myeloablative conditioning. RIC resulted in reduced toxicity without compromising engraftment and anti-tumor activity [60]. Follow up results for studies with RIC indicate that about 40% of patients achieve long term disease control and RIC also overcomes the negative prognostic effect of TP53, fludarabine refractoriness as well as that of SF3B1 and NOTCH gene mutations [61–63]. Generally, allogeneic transplants are no longer offered to patients with del(17p) in first remission. In the relapsed setting the role of SCT must be weighed against the comorbidities, prior therapies, and duration of response to prior therapies as well as current mutation status including TP53, NOTCH1 and SF3B1. Patient must be informed about the side effect profile and non-relapse mortality associated with allogeneic transplant compared to the toxicity and side effect profile of novel agents. (**Figure 2**).

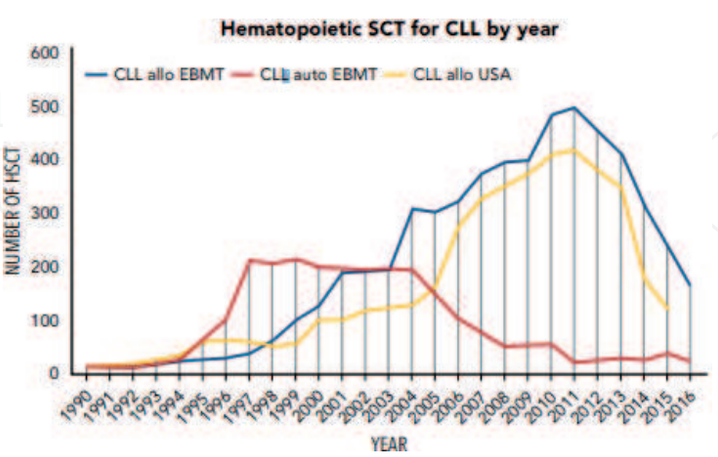

Figure 2.
Hematopoietic SCT for CLL by year [64, 65].

6. Role of minimal residual disease (MRD) testing in CLL

MRD in CLL is assessed most commonly using multiparametric flow cytometry with a sensitivity to detect <1 CLL cell in 10,000 leukocytes. MRD – undetectable (MRD-U) has been defined detection of <1 CLL cell per 10,000 leukocytes [2].

MRD-U in the blood or bone marrow strongly correlates with longer PFS in the patients treated with chemoimmunotherapy has been noted in numerous studies [30, 57, 64]. However, MRD- U is rarely achieved in patients who are on ibrutinib, a drug that offers significant clinical benefit in PFS and survival in CLL patients [66]. So, there is consensus that while MRD- U is generally a favorable outcome for patients but its exact use case scenario in clinical practice is yet to be determined. As of now the potential use of MRD status in CLL patients is in the context of clinical trials, as a surrogate for PFS depending on the type of treatment used and possibly as a replacement for clinical and radiographic response assessments in the future.

7. Richter's transformation

Maurice Richter initially described the transformation of CLL into an more aggressive form of lymphoma and since then this has been recognized as Richter's Transformation (RT) [67]. In most cases RT consists of transformation of CLL into Diffuse Large B Cell Lymphoma (DLBCL), however other aggressive lymphomas have been reported. As of now the reported incidence of RT in the era of novel agents is not very different from the incidence of RT in the chemoimmunotherapy era [68, 69] with incidence rates varying from 3–20% among various studies. RT is suspected when there is rapid clinical deterioration, worsening discordant lymphadenopathy to new onset cytopenia. However, its presentation can be varied. When RT is suspected a comprehensive evaluation with a PET/CT, image guided biopsy as well as a bone marrow biopsy is required. SUV of greater than 10 can distinguish RT form CLL with high sensitivity (91%) and specificity (95%) [70]. However, this has been disputed in the setting of novel agents and thus a concern for RT necessitates a biopsy of the index lesion preferably. RT primarily arises in the background of TP53 disruption and complex karyotype. MYC activation and CDKN2A/B likely play an important role in RT. Clonally related RT patients (>80% of RT DLBCL) respond very poorly to traditional chemotherapy for DLBCL, whereas clonally unrelated DLBCL RT patients respond to traditional chemotherapy just as de novo DLBCL. Thus, determination of clonal evolution is important but difficult to determine [71].Trials performed prior to the use of novel agents used R-CHOP or similar

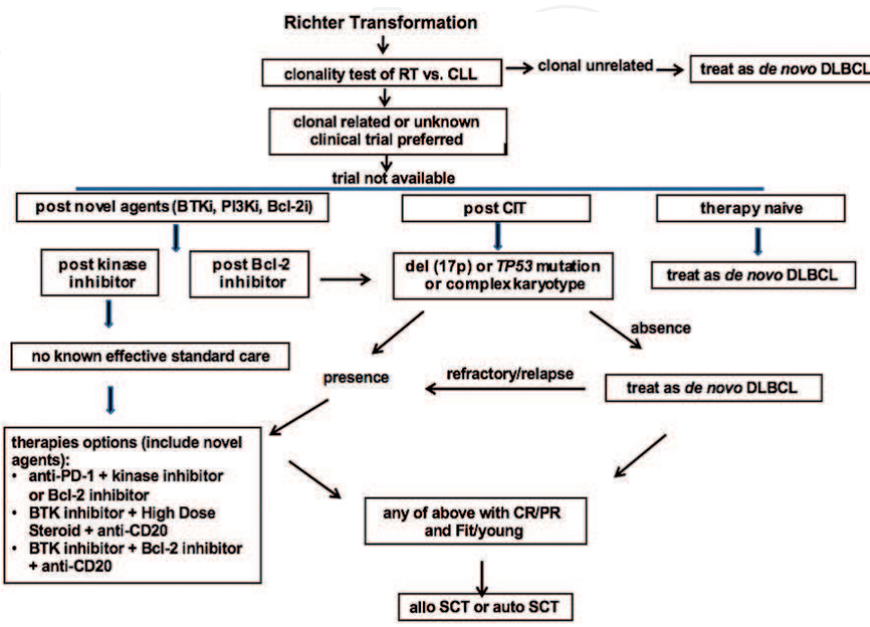

Figure 3.
Richter transformation. Adapted by ASH education handbook [73].

regimens as the standard therapy to treat RT. Fit patients who achieve a complete response or good partial response achieve benefit from a post induction strategy involving stem cell transplant [72]. Novel combinations, PDL-1 blockade and CAR-T or bispecific antibodies are being currently investigated as potential treatment options [72]. **Figure 3** below shows a suggested treatment approach algorithm for suspected patients with RT.

8. Hypogammaglobulinemia and autoimmune hemolytic anemia (AIHA)

8.1 CLL and hypogammaglobulinemia

Hypogammaglobulinemia is the most predominant inherent immune defect in CLL patients, with subtypes IgG3 and IgG4 particularly affected. Hypogammaglobulinemia becomes more pronounced with longer disease duration and advanced-stage disease. There is generally no reversal in this defect, even with response to therapy. However, in one report, ibrutinib therapy resulted in partial reconstitution of humoral immunity, with an increase in IgA levels [73]. The most common site of infection in CLL patients is the respiratory tract, which may be related to serum IgA and IgG4 deficiencies and possibly to mucosal immune defects. The majority of patients with CLL will develop hypogammaglobulinemia at some point in the course of their disease. The use of prophylactic intravenous immunoglobulin (IVIG) to restore IgG levels is controversial. For most patients with CLL, prophylactic IVIG is **not** recommended. For patients with CLL who have had recurrent infections requiring intravenous (IV) antibiotics or hospitalization and who also have a serum IgG <500 mg/dL, it is reasonable to administer IVIG. The usual dose is 200–400 mg/kg by IV infusion, given at three- to four-week intervals. The goal is to maintain the trough serum IgG in treated patients above 500–700 mg/dL as a general guideline. If there is a substantial decrease in the incidence of infections, treatment at gradually extended intervals may be considered. There is no good endpoint for when such therapy can be discontinued. The randomized trials of prophylactic IVIG found that patients who receive IVIG have a decreased incidence of minor and moderate, but not major, bacterial infections. However, IVIG does not appear to increase quality of life or survival [74]. Potential toxicities related to IVIG include anaphylaxis, fever, chills, "flu-like" symptoms, and headache. Another important aspect of IVIG therapy is that it replaces neither IgM nor IgA.

8.2 CLL and AIHA

CLL is frequently associated with autoimmune phenomena, the most common being autoimmune hemolytic anemia (AIHA) [75]. Up to 33% of CLL cases have a positive direct antiglobulin test (DAT) during the course of disease, but overt AIHA occurs much less frequently. In a report of 1203 patients with CLL consecutive cases reported from a single institution, 52 (4.3%) cases of AIHA were observed, 19 at the time of diagnosis [76]. The prevalence of AIHA in patients with CLL have been reported in the range of 4–10%. It increases with disease stage. The autoantibodies that cause AIHA can be produced by nonmalignant B cells or, less commonly, by the malignant CLL clone itself [77, 78]. In practice, AIHA may occur in patients with no other requirement for treatment, or in patients in whom chemotherapy treatment is imminent or already started. Factors associated with an increased risk of development of AIHA at diagnosis included a high white blood count, older age, and male sex. AIHA alone was not itself associated with poor prognosis. The diagnosis of

AIHA is usually based on the presence of an isolated fall in hemoglobin associated with a positive DAT, increased reticulocytes, and serum bilirubin. There have been no controlled trials of treatment for AIHA in CLL and the treatment approach is based on personal and institutional experience. In general, AIHA is responsive to CLL treatment, but if there is no indication to treat CLL, AIHA should be treated as a separate entity with steroids and other immune suppressants, the details of which is beyond the scope of this chapter. There has been controversy whether some chemotherapy agents, particularly purine analogs, induce or worsen AIHA. In a trial comparing outcomes of treatments using chlorambucil, fludarabine, or fludarabine in combination with cyclophosphamide, a positive DAT was found in 14%, and AIHA occurred in 10% of patients [75]. AIHA occurred more often in patients treated with chlorambucil than fludarabine, and occurred least frequently in patients receiving the combination of fludarabine and cyclophosphamide. For patients requiring therapy, a positive DAT test had poor prognostic significance, even in the absence of AIHA. The results suggest that the most successful treatment of AIHA in patients requiring chemotherapy treatment is the treatment associated with the best response rate.

9. Future directions

In summary, there has been a significant change in how we manage patients in CLL over the last 5 years. We have shifted away from chemoimmunotherapy towards novel agents such as BTK, PIK3, and BCL-2 inhibitors, which are not only more efficacious but are also safer and better tolerated. New prognostic models are being developed, and it appears that MRD directed therapy will become the norm in the future. Many clinical trials are looking at various combinations of novel therapies, with a defined period of treatment based on MRD analysis, to enable patients to have a period of treatment-free remission instead of continuous therapy.

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