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LEUKEMIA (A AGUAYO, SECTION EDITOR)

How to Choose the Best Treatment and Testing for Chronic Lymphocytic Leukemia in the Tsunami of New Treatment Options

Cecilia C. S. Yeung [1,2,3] · Mazyar Shadman [1,3,4]

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Abstract

Purpose of Review Treatment of chronic lymphocytic leukemia (CLL) has undergone a major shift since introduction of multiple targeted agents. B cell receptor inhibitors that target either bruton tyrosine kinase (ibrutinib) or phosphatidylinositol 3-kinases (idelalisib and duvelisib) and BCL-2 inhibitor venetoclax have become the mainstay of treatment.

Recent Findings Newer generations of monoclonal antibodies targeting CD20 (obinutuzumab and ofatumumab) are commonly used with novel drugs or chemotherapy agents and result in improved efficacy. At the same time, chemoimmunotherapy remains a reasonable option for selected patients. Therefore, with variety of reasonable options, choice of treatment in first-line or relapsed setting has become more challenging. Better understanding of the molecular and cytogenetics data for each patient is critical to improve management of patients with CLL.

Summary Herein, we review our approach to diagnosis and treatment of CLL in the era of novel therapeutic agents.

Keywords Karyotype · FISH · Microarray · Targeted mutation testing by NGS · Prognosis · B cell lymphoma, PLL, CLL · FCR, BTK, BCL2, PI3Kδ

Introduction

Overview of CLL Diagnosis

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world to affect adult patients with a SEER quote incidence of approximately 5 in 100,000 people in western countries (WHO 2016) [1]. For the remainder of this review, small lymphocytic lymphoma, which is considered by the WHO to be the same disease as CLL with the exception of documented nodal, splenic, or extramedullary sites and cases with less than 5×10^9 circulating abnormal clonal B cells, will also be referred to as CLL [2]. While most patients are generally considered to have a good prognosis, better understanding of the molecular and cytogenetics data as well as a barrage of novel therapy have enabled improved management of patients with CLL. Current standard of care for patients with CLL must include assessment of known prognostic markers and molecular markers which may guide treatment with targeted therapies.

The diagnosis of CLL has remained largely unchanged and are made in the setting of lymphocytosis with immunophenotypically aberrant lymphocytes. However, multicolor flow cytometry allowed identification of a small subset of patients without lymphocytosis but show a persistent B cell clone in their peripheral blood. Studies showed that most of these patients will not develop CLL [3, 4] and in the 2008 WHO, a provisional diagnosis of monoclonal B cell lymphocytosis (MBL) with uncertain significance was made. Refinement of the MBL definition showed that division between a low-count MBL (below 0.5×10^9) and a high-count MBL (above 0.5×10^9) was clinically important as the former almost never progresses to CLL whereas the latter has a report progress risk of 1–2% [5]. This was further clarified in 2015 when additional data showed that people with monoclonal lymphocytosis greater than 11×10^9/L, 11q deletion, and

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✉ Cecilia C. S. Yeung
cyeung@fredhutch.org

[1] Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, G71910, Seattle, WA 98109, USA

[2] Department of Pathology, University of Washington, Seattle, WA, USA

[3] Seattle Cancer Care Alliance, Seattle, WA, USA

[4] Department of Medicine, University of Washington, Seattle, WA, USA

elevated B2M had comparatively worse progression-free survival than people with lower monoclonal lymphocyte counts and respective counterparts [6].

Prognostic Factors of CLL

Largely, current prognostic indicators in CLL are based on recurrent molecular and cytogenetic aberrations. The known cytogenetic markers in CLL as listed in Table 1 are proven to impact prognosis [7]. Although different subtypes carry unique characteristics and confer different prognoses, on average, 5- and 10-year relative survival rates for patients with NHL are 67% and 55% respectively [8, 9].

Approximately 5% of patients with CLL will progress to forms with larger size and higher proliferation rates. The classical Richter's transformation is used to describe a CLL that has transformed into Diffuse large B cell Lymphoma (DLBCL), which occurs in 2–8%. Although rare (occurring in less than 1%), some Richter's will transform into a Hodgkin-like lymphoma. In the setting of a DLBCL, Richter's transformation that also have an immunoglobulin variable region heavy chain (IgVH) unmutated status are considered to be highly aggressive with a survival of less than 1 year [10, 11]. In comparison, Richter's DLBCL which have retained their IGHV-mutated status typically have a prognosis that is more similar to de novo DLBCL. Morphologic variations can be seen in Richter's transformation from CLL ranging from most commonly a DLBCL to Hodgkin's lymphoma. Clonal evolution also notes recurrent molecular aberrations such as TP53, CDKN2a, MYC, and NOTCH1 which are seen in Richter's transformation of CLL [10]. Cases of CLL which show an increased proliferative index by Ki67 immunohistochemistry staining have also been associated with a worst prognosis as compared to typical CLL. These patients typically have an intermediate prognosis between those with standard CLL and those with classic Richter's transformation.

Prognostic Significance of B-PLL

Prolymphocytes are defined as medium-sized lymphocytes with round nuclei, which show enlarged nuclear size, with moderate condensed nuclear chromatin (comparatively finer chromatin quality than CLL but not nearly as fine as a lymphoblast), and a prominent nucleolus that is called prolymphocytic leukemia. By definition, B-PLL should have a minimum of 55% circulating prolymphocytes in the peripheral blood. B-PLL are not CLL. Historically, it was thought that B-PLL are related to CLL due to the similarity in presenting lymphocytosis in the peripheral blood and the fact that CLL may show varying amounts of circulating prolymphocytes. However, in the past decade, gene expression studies have shown that B-PLL and CLL have different gene signatures and thus they are now considered different entities [12, 13]. Distinction between B-PLL and CLL is important as B-PLL do not respond well to standard CLL therapy and the significance of IGV mutation status, deletion in 17p, as well as ZAP70 expression in B-PLL is not as clearly understood as in CLL [14].

Molecular Markers and Prognosis

In next-generation sequencing (NGS) (P53 mutations, BTK, PLCG2, BCL2, BAX, etc.), IGHV status is linked with the type of genomic aberration identified, with significantly increased 13q deletions seen in patients with mutated IGHV and a higher proportion of patients with 17q and 11q deletions demonstrating unmutated IGHV. It is therefore not surprising that patients with mutated IGHV also demonstrate better prognosis. Other prognostic markers that have been shown to be relevant include increased expression of ZAP70, CD38, or CD49d conferring an adverse outcome [15, 16]. Three epigenetic subtypes of CLL are recognized to show prognostic

Table 1 Common genomic aberrations in CLL

Genomic aberration	Frequency	Impact
Deletions in 13q14	50–60%	Good prognosis
Deletions in 14q32.33	12–15%	Good prognosis
Trisomy 12	15–25%	Intermediate prognosis
Deletions in 11q22 (ATM)	10–25%	Adverse prognosis
Deletion in 17p13 (TP53)	5–10%	Adverse prognosis
Recurrent balanced translocations	Rare	Adverse prognosis
Deletions in 6q	Rare	Intermediate prognosis
Deletion of 9p21	Rare	Unknown
Deletion of 10q23	Rare	Unknown
Total or partial trisomies of chromosomes 3, 8, 18, or 19	Rare	Unknown
Duplications in 2p24	Rare	Unknown

significance and include naïve-like cases which are associated with worse prognosis and memory-like cases which are associated with the best prognosis [17, 18].

Deletion of 17p or TP53 mutations are seen in approximately 25% of CLL patients [7] and a small subset of patients without abnormalities in del17p may still show a TP53 mutation [19]. These patients should be identified as soon as possible after diagnosis as CLL with TP53 mutation has been shown to have poorer outcomes with traditional management scheme [20] but can be chemosensitive to regimens with ibrutinib, venetoclax, and idelalisib [21].

Clinical Management of CLL Is Reliant on Molecular Markers

Historical approaches to risk stratification in CLL are based primarily on Rai and Binet system, which are both based on CBC data and extent of organ involvement [22]. More recently, a third prognostic system, the CLL international prognostic index, was published and includes the following parameters: TP53 deletion and/or mutation (collectively called TP53 dysfunction), IGHV mutational status, serum b2-microglobulin, clinical stage, and age. In the large Germany and Poland cohort of over 3400 patients, these parameters identified four risk groups with significantly different OS at 5 years [$P < .001$; C-statistic, c 5 0.723]. This prognostic index was later validated by additional external independent groups in patients treated with chemoimmunotherapy. Brander et al. looked at the utility of CLL-IPI model in 326 patients treated with ibrutinib in the frontline setting. In their study, the CLL-IPI did not predict the response to ibrutinib although only less than 25% of patients had all CLL-IPI variables available [23]. Clearly, novel prognostic models are needed in the era of targeted therapy. One example is the model developed by the group at National Institute of Health (NIH) and includes TP53 aberration, Rai stage, and beta-2-microglobulin or relapsed/refractory status [24]. While this model provides important predictive information about response to ibrutinib, it does not include variables like complex karyotype which is known to be an adverse predictive factor in patients treated with ibrutinib [25].

Current Therapy for CLL

Recent advances introduced a panel of novel agents for use in the management of patients with CLL. Selection of first-line agents are now chosen based on algorithms that take prognostic markers into consideration. A list of novel agents is provided in Table 2.

Treatments

In Fig. 1, we have outlined our recommended treatment algorithm based on the currently available novel therapies and the corresponding prognostic markers.

Watch and wait—close monitoring without treatment is still recommended for asymptomatic patients. It is the current practice to follow the consensus guidelines published by International Workshop on Chronic Lymphocytic Leukemia (iwCLL) and only offer treatment to patients who show signs of cytopenia or progressive and significant lymphadenopathy and organomegaly [2]. Given the introduction of novel agents for CLL, there are randomized studies investigating the role of early intervention for high-risk patients based on molecular/cytogenetic profile [33, 34].

First-Line Treatment

Patients With Evidence of TP53 Aberration (Mutation or Deletion) In the absence of a functional P53 gene, there is no role for chemoimmunotherapy. Patients with del17p or mutated P53 have poor clinical responses to CIT but remain at risk for complications from it [35]. Ibrutinib is considered standard of care for these patients. Study conducted at the NIH showed 74% 5-year progression-free survival (PFS) in treatment-naïve patients with del17p who were treated with ibrutinib [36]. Even in previously treated patients, ibrutinib has shown promising results with median PFS of 26 months (PCYC-1102/1103 study follow-up) [28•], 30-month PFS of 55% (RESONATE follow-up) [37], and 5-year PFS of 19% (NCI study) [36]. Venetoclax was initially approved for del17p CLL patients based on overall response rate of 80% (CR 8%) in the M13-982 study which included del17p CLL patients after one prior line of treatment. In that study, venetoclax was given as monotherapy until progression or intolerance [32]. The long-term follow-up showed a median PFS of 27 months [38]. PFS was longer in patients who achieved an MRD-negative state. One third of patients treated on the MURANO study (see below) had del17p and had a 3-year PFS for these patients that was 70% [31•]. Lastly, the real-world experience with novel agents indicates a median PFS of 15 months for del17p CLL patients treated with venetoclax [39]. Of note, 82% of these patients were previously exposed to ibrutinib. Both idelalisib and duvelisib have shown efficacy for CLL patients with del17p or P53 mutation. Combination therapy with idelalisib and ofatumumab produced more than 15 months median PFS in patients with del17p or P53 mutation [40]. Similarly, median PFS was 12.7 months with duvelisib monotherapy for patients with P53 aberration [30•].

In patients with TP53 aberration, ibrutinib is our first treatment choice. An important factor in deciding the right sequence

Table 2 Currently approved oral targeted agents for CLL

Drug	Category	Mechanism of action	Important side effects	Setting	References
Ibrutinib	BCRi	BTKi	Arthralgia, atrial fibrillation, hypertension, bleeding (rare)	First-line and previously treated	[26, 27, 28•]
Idelalisib	BCRi	PI3Ki (delta)	Transaminitis, colitis/diarrhea, pneumonia/pneumonitis, infections	Previously treated	[29]
Duvelisib	BCRi	PI3Ki (delta and gamma)	Colitis/diarrhea; pneumonia/pneumonitis	Previously treated	[30•]
Venetoclax	Pro-apoptotic agent	Bcl-2	TLS, neutropenia	Previously treated	[31•, 32]

CMV cytomegalovirus, *BCRi* B cell receptor inhibitor, *BTKi* bruton tyrosine kinase inhibitor, *PI3Ki* phosphatidylinositol 3-kinase inhibitor, *PJP Pneumocystis jirovecii* pneumonia, *TLS* tumor lysis syndrome

of treatment is knowledge about efficacy of each drug in patients who progress on other novel agents. Venetoclax is established to be the treatment of choice after ibrutinib failure based on a clinical trial that showed ~70% response rate in patients who received venetoclax after ibrutinib [41]. Data is limited about use of ibrutinib after venetoclax failure [42]. For this reason and until there is more information about the efficacy of ibrutinib after venetoclax failure, we recommend ibrutinib as first-line treatment. Patients who show disease progression after one of the novel agents should be considered for cellular therapy approaches like chimeric antigen receptor (CAR-T) therapy of allogeneic hematopoietic cell transplant (allo-HCT) [43, 44] (please see below).

Patients Without Evidence of P53 Aberration (Mutation or Deletion) These patients have variety of treatment options, but the optimal treatment should be decided based on patient and disease factors. In general, and based on 3 recently published/presented randomized trials, ibrutinib is considered a reasonable option for any patient in the first-line setting:

ECOG1912 Study In this study, young (≤ 70) and fit (ECOG performance score 0–2 and CrCL > 40) patients were randomized between ibrutinib and rituximab or standard fludarabine, cyclophosphamide, and rituximab (FCR) regimen. Overall, there was PFS and overall survival (OS) benefit in favor of ibrutinib and rituximab. It should be noted that there was no

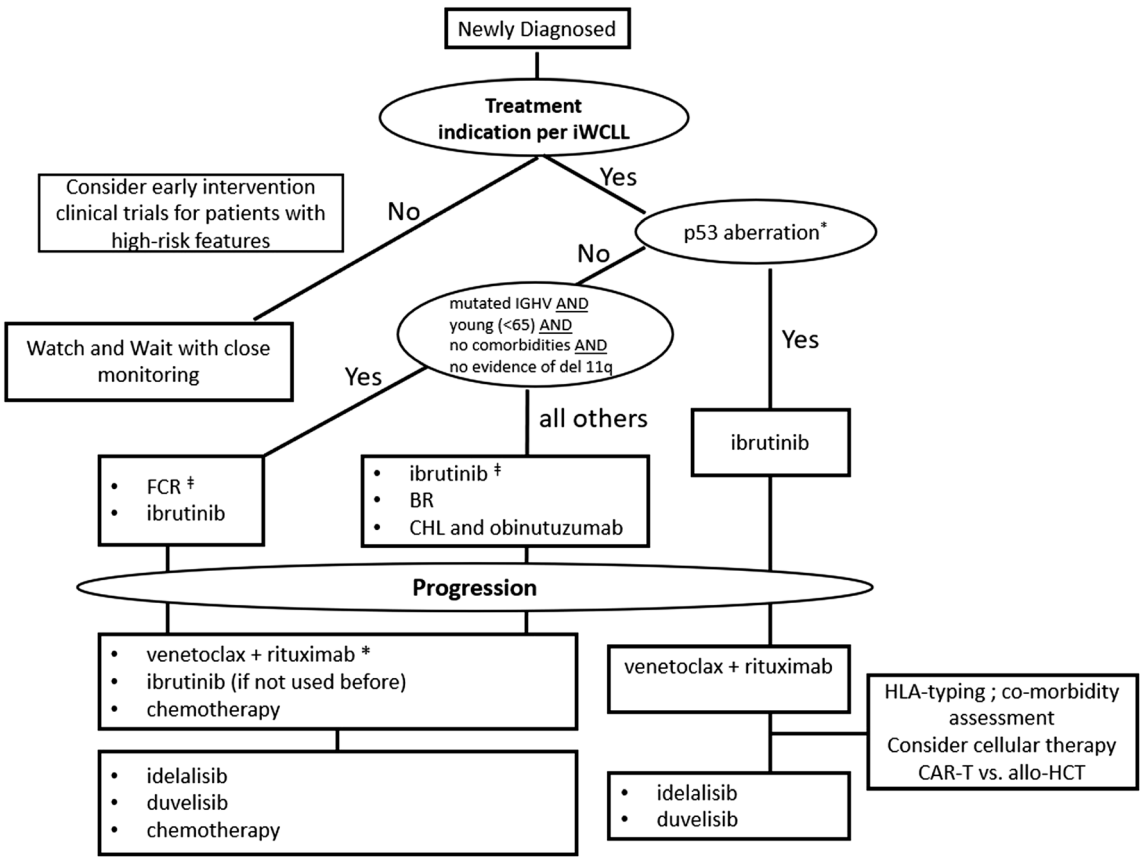

Fig. 1 Suggested algorithm for CLL treatment. *del17p or P53 mutation. ǂPreferred regimen

statistical difference in PFS between the 2 arms in patients with a mutated IGHV [45]. While this study establishes ibrutinib as treatment of choice in patients with an unmutated IGHV gene, it does not provide enough evidence to support its use in patients with mutated IGHV. These patients can still benefit from FCR with long remissions based on the data from the MD Anderson Cancer Center [46].

A041202 Study This study was designed for older patients (≥ 65) and had 3 arms: (1) bendamustine and rituximab (BR); (2) ibrutinib monotherapy; and (3) ibrutinib and rituximab. There are 3 major findings from this study. First, both IB and IB + R showed significant PFS benefit compared to BR with HR 0.39 (95% CI 0.26–0.58) and HR 0.28 (95% CI 0.25–0.59), respectively. Second, there was no difference in clinical outcomes between the IB and IB + R arms. Third, with the current follow-up, there was no OS difference between the 3 arms. It was concerning that 9 ibrutinib-treated patients died for "unexpected/unexplained" reasons [47].

iLLUMINATE Study The iLLUMINATE study was designed for older patients (≥ 65 years) or ones with comorbidities with either a cumulative Illness Rating Score of more than 6 or a creatinine clearance < 70 mL/min. This study compared chlorambucil and obinutuzumab which is one of the standard regimens for this population with combination of ibrutinib and obinutuzumab. The ibrutinib and obinutuzumab arm was superior for PFS [HR 0.23 (95% CI 0.15–0.37)] and 35% of patients on this treatment had no detectable minimal residual disease (MRD) in the bone marrow or peripheral blood. There was no OS benefit with the current follow-up [48]. Without an ibrutinib monotherapy arm, it is not clear from this study if addition of obinutuzumab to ibrutinib is necessary. Extrapolating from the A041202 study where there was no benefit with addition of rituximab, one could advocate for use of ibrutinib as a single agent. On the other hand, knowing the superiority of obinutuzumab over rituximab in CLL [49], such extrapolation may not be justified.

Conclusions from the frontline studies and treatment recommendations are as follows:

- Ibrutinib is considered standard for patients at any age with or without comorbidities. Patients need to be counseled about the indefinite duration of treatment and associated side effects from this treatment. Given the significance of some of these adverse events (atrial fibrillation, hypertension, infections, and less commonly bleeding), treatment with CIT may be reasonable for some patients especially those with a mutated IGHV gene.
- CIT with FCR still seems to be a reasonable option for young (< 65) patients without P53 abnormality and with a mutated IGHV in the absence of comorbidities. This is supported by data from the MD Anderson Cancer Center and German CLL group showing long remissions from the FCR regimen in this setting. Patients need to be aware of risk of secondary myeloid malignancies which is associated with FCR [46, 50].
- Use of FCR is not recommended in patients with an unmutated IGHV given the poor clinical responses which does not justify accepting the 5% risk of myelodysplastic syndrome or acute myeloid leukemia with this regimen.
- In the absence of an OS benefit in A041202 and iLLUMINATE studies, use of BR or obinutuzumab and chlorambucil combination can be considered in situations where IB is not desired or feasible. One example is the patient preference for a fixed treatment duration.

Treatments in the Relapsed Setting

Ibrutinib: In RESONATE study, ibrutinib showed survival benefit when compared with ofatumumab leading to its FDA approval for relapsed CLL. There is now robust clinical data generated from clinical trials and real-world experience supporting efficacy of ibrutinib in relapsed CLL [26, 28•, 51, 52]. Treatment with ibrutinib as a "chemo-free" and "infusion-free" option is appealing for physicians and patients. Adverse events, however, could be significant in some patients leading to drug discontinuation [52]. Some common side effects include joint/bone pain, muscle cramps, hypertension, and atrial fibrillation. Bleeding is a less common but potentially serious side effect especially if used concurrently with anti-platelets or anti-coagulants [53]. Acalabrutinib is a second-generation BTK inhibitors with less off-target effects and is associated with lower rate of adverse events [54]. Acalabrutinib is currently approved for Mantle cell lymphoma but has shown efficacy in CLL [55, 56]. While waiting for the results of registration studies that may lead to FDA approval for CLL, acalabrutinib could be considered in ibrutinib-intolerant patients [57].

Idelalisib and duvelisib are inhibitors of phosphatidylinositol 3-kinases. Idelalisib is a selective PI3Kδ inhibitor and duvelisib inhibits PI3K-δ,γ [29, 30•]. By inhibiting PI3Kδ, idelalisib inhibits proliferation, chemotaxis, motility, adhesion, and B cell survival and promotes apoptosis in cell lines derived from B cell malignancies [58]. Both drugs are approved for treatment of CLL patients in the relapsed setting. Combination of idelalisib and rituximab was superior to rituximab monotherapy in previously treated patients [29]. Duvelisib was compared to ofatumumab and showed PFS and OS benefit [30•]. Despite clinical efficacy, use of PI3K inhibitors is associated with immune-mediated adverse events like transaminitis, colitis, and pneumonitis [59]. Also, with some reports indicating higher risk for certain infections [60], most experts recommend prophylaxis against *Pneumocystis*

jirovecii pneumonia (PJP) and close monitoring for cytomegalovirus (CMV) reactivation [61]. It should be noted that the immune-related side effects seem to be more common if idelalisib is used in previously untreated patients, and for this reason, these agents should not routinely be used in the first-line setting [62, 63].

One of the main disadvantages of B cell receptor inhibitors (BCRi) like ibrutinib, acalabrutinib, idelalisib, and duvelisib is indefinite duration of treatment. This is a more significant issue for younger patients especially in the first-line setting who can in theory remain on treatment for decades. Given the fact that these agents do not provide deep remissions, a fixed duration of treatment is not a feasible option. Unlike BCRi drugs, venetoclax induces deep molecular remissions and provides the opportunity of having a chemo-free options with fixed treatment duration.

Venetoclax is an oral B cell lymphoma 2 (BCL2) inhibitor which induces apoptosis [64]. In the MURANO clinical trial, venetoclax in combination with rituximab (Ven-R) was shown to have superior progression-free survival and overall survival rate in patients with CLL, leading to Food and Drug Administration approval [31•]. In this study, venetoclax was given for a fixed duration of 2 years along with rituximab which was only continued for 6 months [31•]. Ven-R-treated patients had a high rate of MRD negativity on peripheral blood (62% less than 10^{-4}). More importantly, with 9.9 months follow-up after completion of venetoclax treatment, only 12% of patients developed disease progression and depth of remission at the end of 2-year was a predictor of PFS in this study [65]. Major safety concern with venetoclax is related to tumor lysis syndrome (TLS). The drug should be started at a much lower dose (20 mg) than the target dose (400 mg). A dose escalation ramp-up needs to be followed as detailed in the package insert to minimize the TLS risk [31•, 57].

Recommendation for Treatment of Patients With Relapsed Disease

With the introduction of novel agents, there is limited role for CIT in the relapsed setting. Ven-R and ibrutinib are both reasonable first choice options in relapsed patients. Fixed treatment duration is an attractive feature of the Ven-R regimen. First month of venetoclax requires frequent clinic visit and possibly inpatient hospitalization to mitigate the TLS risk but the drug seems to be well tolerated beyond the initial ramp-up period. On the other hand, with longer track record of ibrutinib, there is more confidence about the safety profile. As mentioned above, there is data indicating efficacy of venetoclax in patients who progress on ibrutinib but experience is very limited for reverse order [41, 42]. In other words, it is not clear what percentage of patients who progress on venetoclax would respond to ibrutinib. While awaiting those data, some advocate using ibrutinib before venetoclax. Idelalisib and duvelisib are reasonable options but are rarely used before ibrutinib or venetoclax mainly because of safety and tolerability reasons.

Cellular Therapy for CLL

In the pre-novel agents era, allogenic hematopoietic cell transplant (allo-HCT) used to be the treatment of choice for patients with high-risk disease defined as harboring del17p or with fludarabine-refractory disease. Despite being potentially curative in ~ 40% of patients, allo-HCT is associated with high rates of morbidity and mortality in patients with medical comorbidities. Role of allo-HCT is now less prominent with the advent of novel agents. Appropriate patient selection using the hematopoietic cell transplantation (HCT)-specific comorbidity index is critical to lower the non-relapse mortality rate. Practice guidelines by the American Society of Blood and Marrow Transplantation (ASBMT), the International Workshop on CLL (iwCLL), the European Research Initiative on CLL (ERIC), and the European Society for Blood and Marrow Transplantation (EBMT) recommend allo-HCT for high-risk CLL patients with refractory disease to at least one of the novel agents while still responding to either BCR inhibitors or venetoclax [2, 43, 44].

Chimeric antigen receptor T cell (CAR-T) therapy targeting CD19 has shown promising efficacy in very high-risk CLL patients. Fred Hutch investigators reported their experience treating high-risk CLL patients (79% ibrutinib refractory, 25% venetoclax refractory, 17% prior allo-HCT, 67% complex karyotype, and 58% del17p). Impressive overall and complete responses (69% and 25%, respectively) were reported by iwCLL criteria. Using the Lugano criteria, 64% of patients achieved a PET-negative CR [66]. Recent studies show improved efficacy with concurrent use of ibrutinib with CAR-T cells [67].

In our practice, we start conversation about cellular therapy when patients show evidence of disease progression on one of the novel agents (see Fig. 1). While continuing treatment with another targeted agent preferably on a clinical trial, we initiate HLA typing and try to optimize patient's comorbidities. If available, we utilize CAR-T therapy before allo-HCT. Data suggests that long-term clinical remissions are only seen in patients who achieve a deep molecular remission in the bone marrow after CAR-T [66]. For this reason, in patients with evidence of disease (even at the MRD range) after CAR-T, a strong consideration to allo-HCT should be given if medically eligible.

Future Directions

An ideal treatment strategy would be using a "chemo-free" regimen with limited toxicity and fixed duration of treatment.

This seems to be a feasible goal considering the impressive efficacy of BTK inhibitors, venetoclax, and monoclonal anti-CD20 antibodies. Many groups have shown high rates of complete remissions without detectable minimal residual disease by combining venetoclax and ibrutinib with or without an anti-CD20 antibody [68, 69]. While promising, these single-arm studies will not provide enough evidence to support use of these combinations. A critical question is the outcome of patients who progress on a regimen that contains our best available options for CLL (BTK inhibitors and venetoclax). Also, long-term efficacy and toxicity of these regimens need to be tested against monotherapy with each of these novel drugs. Ongoing intergroup studies (EA9161 and A041702) are designed to compare the efficacy of triplet therapy with ibrutinib + venetoclax + obinutuzumab vs. ibrutinib and obinutuzumab in younger and older patients, respectively [70, 71]. More importantly, the field needs similar studies with venetoclax (± anti-CD20 antibodies) in the control arm.

Compliance with Ethical Standards

Conflict of Interest Cecilia C.S. Yeung has received research funding from Gilead for a study on idelalisib colitis. Mazyar Shadman has received research funding from MustangBio, Celgene, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, Acerta Pharma, and Merck, and has received compensation for service as a consultant from AbbVie, Genentech, Sound Biologics, Verastem Oncology, ADC Therapeutics, and Atara Biotherapeutics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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