Risk-Adapted Treatment Strategies for Chronic Lymphocytic Leukemia

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2017.8.7.18

Abstract

Chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia among elderly patients. The disease can behave quite heterogeneously, as certain CLL patients will experience an indolent course, whereas others endure an aggressive course with poor outcomes. Several prognostic indicators exist to stratify CLL patients into risk groups aimed at predicting disease course and outcomes to treatment modalities. Patients with high-risk disease features such as deletion 17p (del[17p]) and/or tumor suppressor gene (*TP53*) mutations or early relapse following fludarabine-based therapy once had limited therapeutic options, with only allogeneic stem cell transplantation (alloSCT) considered a curative option. The advent of novel oral targeted agents inhibiting key proteins in signaling pathways important for CLL survival and proliferation has shown improved outcomes, in particular for high-risk patients and in the relapsed or refractory setting. Optimal selection and sequencing of these treatments can pose challenges as new data emerge on disease-based factors with patient outcomes. Although several ongoing clinical trials are investigating the use of combination therapy with new oral targeted agents, this article will review only currently approved treatment options for first-line and relapsed or refractory CLL patients based on risk stratification with an emphasis on the sequencing of therapies.

J Adv Pract Oncol 2017;8:87–96

Chronic lymphocytic leukemia (CLL) is the second most common type of leukemia in the United States, with an estimated 18,960 new cases and 4,660 deaths during 2016 (Siegel, Miller, & Jemal, 2016). This incurable malignancy is the most frequently diagnosed cancer among elderly individuals aged 65 to 74, with a median age at presentation of 71 (Siegel et al., 2016). The disease is characterized by the clonal proliferation and accumulation of mature B-cell lymphocytes with a specific immunophenotype as diagnosed by flow cytometry from peripheral blood, bone marrow, or lymphoid tissue (Hallek et al., 2008). Therapy is not indicated unless patients experience B symptoms impairing quality of life or have bulky or progressive

lymphadenopathy, splenomegaly, or progressive cytopenias (Hallek et al., 2008).

Although CLL is classically considered an indolent B-cell lymphoproliferative disorder, the disease course can behave quite heterogeneously, largely due to the diversity of genetic and molecular characteristics that interface with the microenvironment and key signaling pathways leading to prolonged cell survival (Burger, 2011; Rodriguez-Vicente, Diaz, & Hernandez-Rivas, 2013). These genetic and molecular attributes are among the most important predictors of prognosis and in some cases determine treatment (Hallek, 2015). Over the past decade, insights into the disease biology have led to the development and approval of newer agents that have improved the outcomes of patients with CLL, including those of high-risk patients (Furman et al., 2014; O'Brien et al., 2014a, 2014b, 2016a; Stilgenbauer et al., 2016).

PROGNOSTIC ASSESSMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA

Staging Systems

Staging and a prognostic assessment of patients with CLL at diagnosis are essential for appropriate monitoring, prediction of disease progression risk, and overall survival (Hallek et al., 2008; Shanafelt, Byrd, Call, Zent, & Kay, 2006). Staging of CLL for both patient care and clinical trials is based upon either the Rai or Binet system; these systems were developed over 45 years ago and are still utilized in clinical practice (Binet et al., 1981; Rai et al., 1975; Rai, 1987). Both staging systems rely on standard laboratory parameters of complete blood cell counts and a physical exam for splenomegaly and/or hepatomegaly to stratify patients into three hierarchical risk categories. However, these staging systems are unable to predict individual patient outcomes.

Newer Prognostic Factors

In addition to staging, a comprehensive assessment includes fluorescence in situ hybridization (FISH) testing for the presence or absence of del(13q), trisomy 12, del(11q), or del(17p); immunoglobulin heavy-chain variable region gene (*IgHV*) mutation status; serum beta2-microglobulin (β_2M); CD38 expression and zeta-chain–associated protein 70 (ZAP-70) expression (Hallek et al., 2008). Unmutated *IgHV*, β_2M ≥ 3.5 mg/L, and overexpression of CD38 and/or ZAP-70 are associated with an unfavorable risk with a shorter overall survival and time to first treatment (Parikh & Shanafelt, 2016; Stilgenbauer, Bullinger, Lichter, & Dohner, 2002).

Genomic Aberrations

Increasing evidence has shown that certain chromosomal abnormalities have a significant impact on the prognosis of CLL, with implications for therapeutic decision-making (Dohner et al., 2000; Hallek et al., 2008). Chromosomal deletions have been identified in 82% of CLL patients as detected by a FISH test, with the most frequent being del(13q; 55%), del(11q; 18%), trisomy 12 (6%), del(17p; 7%) and del(6q; 6%; Dohner et al., 2000). This pivotal study paved the way for the accepted use of FISH analysis as the gold standard for the genetic characterization and prognostic assessment of newly diagnosed and relapsed or refractory patients with CLL (Dohner et al., 2000; Van Dyke et al., 2015).

Patients carrying del(13q) as their sole abnormality or normal cytogenetics have a median survival of 133 and 111 months, respectively, and may experience a relatively benign course (Dohner et al., 2000; Van Dyke et al., 2015). In contrast, those carrying del(17p) or del(11q) carry a worse prognosis, with a median survival of 32 and 79 months, respectively (Dohner et al., 2000; Van Dyke et al., 2015). Unmutated *IgHV* has been shown to correlate more frequently with del(11q) and del(17p; Gladstone, Blackford, Cho, Swinnen, & Kasamon, 2012). Deletions in the long arm of chromosome 11 are associated with shortened overall survival (OS), rapid disease progression, and bulky lymphadenopathy (Dohner et al., 1997; Tam et al., 2008). The inferior prognosis of patients harboring del(17p) is related to the tumor suppressor gene (*TP53*), which, when mutated, confers higher-risk disease with little benefit from chemoimmunotherapy regimens (Tam et al., 2008; Zenz et al., 2008, 2010). Therefore, both FISH testing and sequencing for *TP53* mutations are of paramount importance prior to the initiation of any line of therapy to avoid unnecessary exposure to toxicities from a therapy with limited expected response.

RISK-ADAPTED TREATMENT STRATEGIES

Chronic lymphocytic leukemia remains an incurable but highly treatable disease. The indication for CLL treatment relies upon meeting the criteria for therapy, as defined by the International Workshop on CLL. Patients with lower-risk disease do not require treatment at the time of diagnosis (Hallek et al., 2008). Risk-adapted treatment is critical to the selection of the best available therapy, with consideration of both disease attributes and the overall health of the patient. Allogeneic stem cell transplantation (alloSCT) is considered the only potentially curative therapy, but it is not an option for many patients due to age, comorbidities, and the lack of a suitable donor (Mewawalla & Nathan, 2014). Clinical trials should always be considered for patients with higher-risk disease (Barrientos, 2016). All patients should be evaluated for frailty. Figure 1 shows currently approved options for first-line CLL therapy.

FIRST-LINE THERAPY

Chronic Lymphocytic Leukemia Patients Without del(17p) and/or *TP53* Mutations

Chemoimmunotherapy using a fludarabine-based regimen and an anti-CD20 antibody is the current therapeutic standard for fit CLL patients without del(17p) and/or *TP53* mutations. Fludarabine, cyclophosphamide, and rituximab (Rituxan; FCR) is the recommended regimen based on results of the FCR300 study showing efficacy (overall response rate [ORR] of 95%, complete response (CR) of

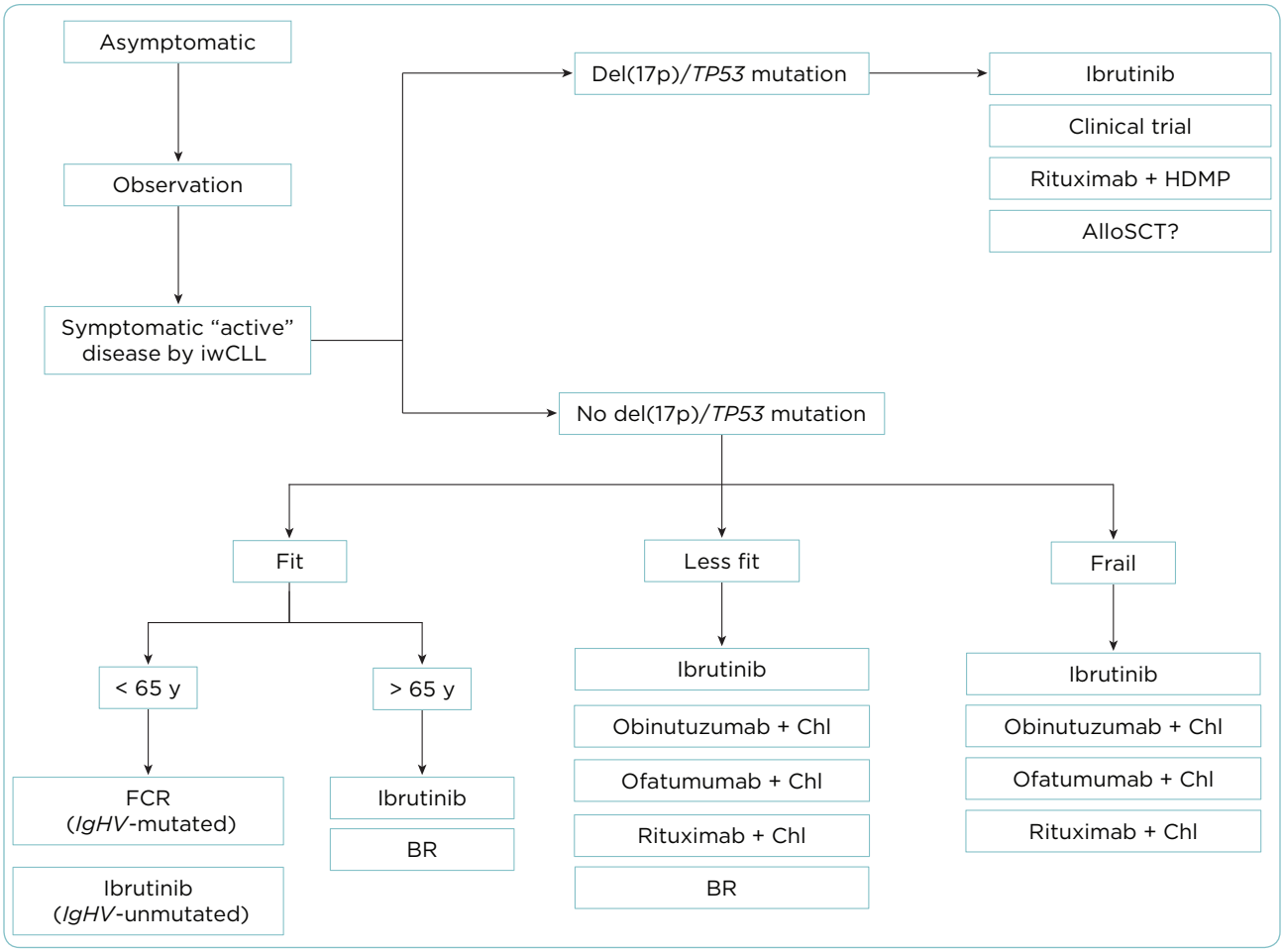

Figure 1. Front-line treatment algorithm for chronic lymphocytic leukemia. iwCLL = International Workshop on Chronic Lymphocytic Leukemia; Chl = chlorambucil; HDMP = high-dose methylprednisolone; alloSCT = allogeneic stem cell transplant; FCR = fludarabine, cyclophosphamide, and rituximab; IgHV = immunoglobulin heavy-chain variable region gene; BR = bendamustine and rituximab.

72%, and median progression-free survival [PFS] of 6 years; Tam et al., 2008).

These results led to a larger phase III trial, CLL8, by the German CLL Study Group. In the CLL8 trial, 817 treatment-naive patients (median age of 61 years) with good fitness were randomized to receive either six cycles of FCR or fludarabine and cyclophosphamide (FC). Compared with the FC group, FCR was superior at inducing a higher ORR (92.8% vs. 85.4%), PFS at 3 years (65% vs. 45%), and OS at 3 years (87% vs. 83%). Grade ≥ 3 neutropenia was more frequent with FCR (34%) than FC (21%). After 5.9 years of follow-up, FCR continued to show superior PFS (56.8 months) as compared with FC (32.9 months), with OS not reached for FCR and an OS of 86 months for FC.

Retrospective analysis of treatment-naive CLL patients receiving first-line FCR defined a subgroup of low-risk patients with mutated *IgHV* and without del(11q) or del(17p) and who sustained a durable remission with an OS rate of 81.2% at 5 years (Rossi, Terzi-di-Bergamo, De Paoli, Cerri, & Ghilardi, 2015). At 12.8 years of follow-up, PFS was superior for CLL patients with mutated *IgHV* (79.8%) as compared with unmutated *IgHV* (8.7%; Thompson et al., 2016). These studies support the use of FCR in the first line in young and fit or elderly and fit patients with mutated *IgHV* in the absence of del(11q) or del(17p), given the prolonged PFS.

Bendamustine and rituximab (BR) is an alternative option for patients with comorbidities or for those who are less fit. A total of 564 treatment-naive CLL patients with a median age of 62, a Cumulative Illness Rating Scale (CIRS) score ≤ 6, and no del(17p) mutation (Extermann, Overcash, Lyman, Parr, & Balducci, 1998; Eichhorst et al., 2014) were enrolled in the CLL10 study. Patients were randomized to receive either FCR or BR.

The rate of CR was higher for FCR (40.7%) vs. BR (31.5%). Fludarabine, cyclophosphamide, and rituximab showed a superior PFS of 55.2 months compared with 41.7 months for BR. Severe infections were more frequent with FCR in the older patients (48.4% vs. 26.8%) compared with those seen in patients on BR. The CLL10 trial validated FCR as the standard of care for young, fit patients without del(17p) given the higher rates of CR, longer PFS, and minimal residual disease (MRD) negativity. Bendamustine and rituximab represents an alternative for less fit, elderly patients at a higher risk for therapy-related toxicities.

The CLL11 phase III trial investigated the use of chlorambucil in combination with obinutuzumab, a humanized type II glycoengineered anti-CD20 monoclonal antibody, in frail and treatment-naive CLL patients with increased comorbidities (CIRS baseline of 8) and a median age of 73 years (Goede et al., 2013). A total of 781 patients were randomized to receive chlorambucil monotherapy or obinutuzumab plus chlorambucil or rituximab plus chlorambucil.

Patients treated with combination therapy achieved an increased PFS (median of 26.7 months for obinutuzumab plus chlorambucil vs. 16.3 months for rituximab plus chlorambucil vs. 11.1 months for chlorambucil monotherapy). Obinutuzumab plus chlorambucil was superior to rituximab plus chlorambucil in achieving CR (20.7% vs. 7%), PFS (26.7 months vs. 16.3 months), and MRD in peripheral blood (37.7% vs. 3.3%) and bone marrow (19.5% vs. 2.6%). Neutropenia and infusion-related reactions were more prevalent in the obinutuzumab plus chlorambucil arm than in the rituximab plus chlorambucil arm.

The phase III COMPLEMENT 1 trial examined the use of another anti-CD20 monoclonal antibody, ofatumumab, in combination with chlorambucil (Hillmen et al., 2015). Ofatumumab is a fully humanized type I glycoengineered monoclonal antibody that has greater binding affinity to a CD20 epitope with enhanced complement-dependent cytotoxicity (CDC) than rituximab in CLL (Dyer, 2012; Mossner, Brunker, & Moser, 2010). In this trial, 447 patients considered inappropriate for fludarabine-based therapy due to age (> 65 years) and/or comorbid conditions (≥ 2) were randomized to receive chlorambucil monotherapy or ofatumumab plus chlorambucil. The combination of ofatumumab plus chlorambucil produced a higher ORR (82% vs. 69%) and CR (14% vs. 1%) than chlorambucil monotherapy. At a median follow-up of 28.9 months, ofatumumab plus chlorambucil–receiving patients had a superior PFS of 22.4 months as compared with 13.1 months for those who received chlorambucil monotherapy. Grade ≥ 3 adverse events were experienced by 50% of patients receiving ofatumumab plus chlorambucil and 43% receiving

chlorambucil monotherapy, with the most common being neutropenia (26% ofatumumab plus chlorambucil vs. 14% chlorambucil). A higher incidence of grade ≥ 3 infusion-related reactions (10%) occurred in the combination arm.

Chronic Lymphocytic Leukemia Patients With del(17p) and/or *TP53* Mutations

Ibrutinib is an oral, small-molecule inhibitor that covalently binds to Bruton's tyrosine kinase (BTK) downstream of the B-cell receptor (BCR), thus abrogating B-cell survival and proliferation signals (Davids & Brown, 2014). Ibrutinib is the only oral targeted agent that has been US Food and Drug Administration (FDA) approved and incorporated into the treatment algorithm for the first-line treatment of patients with or without del(17p) and/or *TP53* mutations based on high response rates, acceptable toxicity, and sustained remission rates (Burger et al., 2015; Byrd et al., 2014, 2015).

Ibrutinib initially received first-line approval for CLL patients carrying del(17p) based on the results of the RESONATE trial (Byrd et al., 2014). In this phase III trial, 391 patients with relapsed or refractory CLL were randomly assigned to receive ibrutinib or ofatumumab. Approximately 57% of these patients were deemed high risk, carrying del(17p) or del(11q).

At a median follow-up of 9.4 months, the median duration of PFS for ibrutinib had not been reached compared with 8.1 months with ofatumumab. Among patients with CLL carrying del(17p), 83% were without disease progression at 6 months compared with 49% of those receiving ofatumumab. Ibrutinib led to superior OS (90%) as compared with ofatumumab (81%) at 12 months. The ORR was higher for those receiving ibrutinib than ofatumumab (42.6% vs. 4.1%).

Adverse events ≥ grade 3 were higher for patients receiving ibrutinib than for those receiving ofatumumab, including diarrhea (4% vs. 2%) and atrial fibrillation (3% vs. 0%). Bleeding events of any grade were more common in the ibrutinib arm (44%) than in the ofatumumab arm (12%), consisting mainly of petechiae and ecchymoses. Grade 3 infections were similar between the ibrutinib (24%) and ofatumumab (22%) arms.

Subsequently, the phase III RESONATE-2 trial by Burger et al. (2015) led to the expanded first-line approval of ibrutinib in the treatment of all patients with CLL. In this phase III trial, 269 treatment-naive CLL patients with a median age of 73 were randomized to receive either ibrutinib or chlorambucil with the primary endpoint of PFS. Patients carrying del(17p) were excluded from this trial.

Ibrutinib resulted in a longer PFS than did chlorambucil (median not reached vs. 18.9 months), with an 84% reduction in the relative risk of death and a 91% reduction in disease progression. The ORR was higher with ibrutinib than with chlorambucil (86% vs. 35%). Adverse events of any grade occurring in > 20% of patients were diarrhea, musculoskeletal pain, rash, nausea, vomiting, fatigue, anemia, and neutropenia. Four patients in the ibrutinib arm experienced a grade 3 hemorrhage and one had a grade 4 hemorrhage. The use of ibrutinib in the first-line setting for young, fit patients without del(17p) and/or *TP53* mutation is debatable, as such therapy is currently considered lifelong with chronic exposure to potential toxicities.

THERAPEUTIC OPTIONS FOR RELAPSED OR REFRACTORY CLL

The decision-making for therapy in the relapsed or refractory setting is similar to indications for treatment in the first line, as one should take into account a patient's physical fitness, comorbidities, duration of remission, response to prior therapy, and new prognostic findings. If the duration of remission exceeds 24 to 36 months, then repeating first-line treatment may be a reasonable option (Hallek, 2015). In the second line, repeating FCR or BR is reasonable for select patients, provided they tolerated the prior regimen and relapsed without new identification of del(17p) and/or *TP53* mutations or a history of unmutated *IgHV*.

The choice of therapy becomes challenging if relapse occurs early, such as with refractory CLL, defined as treatment failure or relapse within 6 months of prior therapy, presence of del(17p), and/or *TP53* mutations or a complex karyotype. Patients who relapse within 24 months after receiving a fludarabine-based regimen have shortened OS and are deemed as having high-risk disease (Zenz et al., 2012). In such cases, chemoimmuno-

therapy has not been shown to result in a significant response. Rather, therapeutic options should include a targeted agent such as ibrutinib, idelalisib, or venetoclax, given the improved outcomes in patients where chemoimmunotherapy has not produced a sustained response (Barrientos, 2016). Figure 2 depicts the currently approved options for CLL therapy in the relapsed or refractory setting. Clinical trials should always be considered when appropriate.

Oral Targeted Therapy in Relapsed or Refractory CLL With or Without del(17p) and/or *TP53* Mutations

Several B-cell signal transduction pathways have been shown to play an integral role in the pathogenesis of CLL through the BCR and mitochondrial apoptosis-induced channel (MAC; Marini, Samanas, & Perissinotti, 2016; Woyach, Johnson, & Byrd, 2012). Such studies have led to the recent approval of three oral targeted agents. As previously discussed, ibrutinib is the only oral targeted agent approved for both first-line and relapsed or refractory CLL regardless of high-risk features. Idelalisib inhibits phosphatidylinositol 3-kinase delta (PI3Kδ), which, like BTK, is important for BCR-mediated CLL cell survival and proliferation (Woyach et al., 2012). Venetoclax inhibits the prosurvival B-cell lymphoma 2 (Bcl-2) protein, which, when overexpressed, inhibits apoptosis through the MAC pathway (Marini et al., 2016).

The advent of these oral targeted therapies has transformed treatment approaches for CLL, as they are improving outcomes in patients with relapsed or high-risk disease, where therapeutic options are limited (Furman, et al., 2014; Shar-

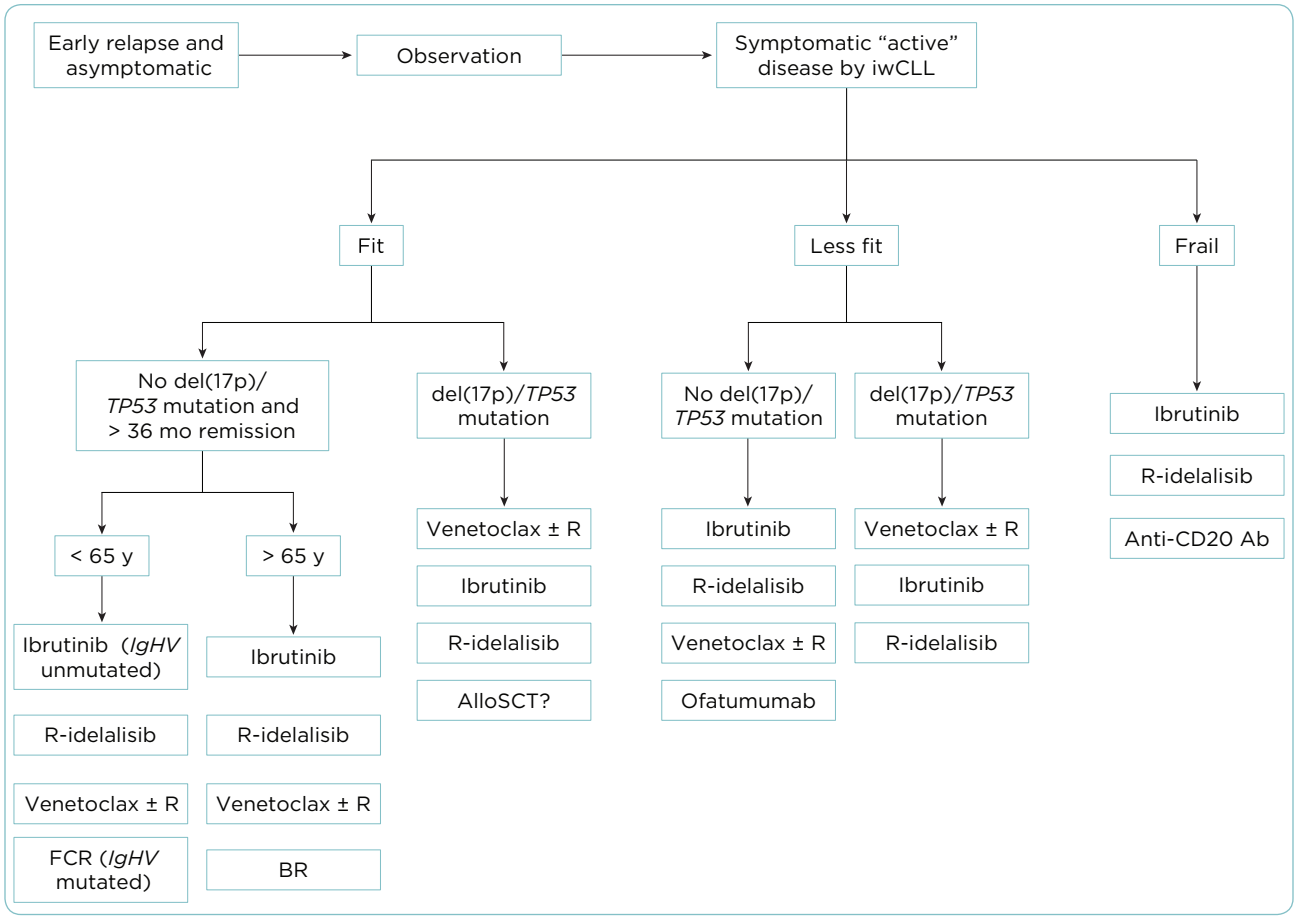

Figure 2. Relapsed or refractory chronic lymphocytic leukemia treatment algorithm. iwCLL = International Workshop on Chronic Lymphocytic Leukemia; R-idelalisib = idelalisib and rituximab; FCR = fludarabine, cyclophosphamide, and rituximab; IgHV = immunoglobulin heavy-chain variable region gene; BR = bendamustine and rituximab; alloSCT = allogeneic stem cell transplant; Ab = antibody.

man, et al., 2014). Idelalisib is an oral inhibitor of PI3Kδ that has been FDA approved to be given in combination with rituximab for relapsed CLL (Furman et al., 2014). PI3Kδ mediates signaling pathways transduced from the BCR, culminating in B-cell proliferation, survival, adhesion, homing, and growth (Lannutti et al., 2011). In a phase III trial, 220 relapsed CLL patients, deemed inappropriate for chemotherapy due to a CIRS > 6 and a median age of 71 years, were randomized to receive idelalisib plus rituximab or placebo plus rituximab (Furman et al., 2014). Approximately 80% of the patients had unmutated *IgHV* and 40% had del(17p) or *TP53* mutations. The combination arm produced superior ORR (81% vs. 13%) and 12-month OS rates (92% vs. 80%) when compared with placebo plus rituximab. The median duration of PFS was 5.5 months with placebo plus rituximab and not reached for the combination arm at the time of analysis. This effect was also favorable in a subgroup analysis for those with unmutated *IgHV*, del(17p), or *TP53* mutations. Pneumonia, febrile neutropenia, pyrexia, diarrhea, and alanine aminotransferase/aspartate aminotransferase elevations were the most frequent adverse events in the combination arm.

Venetoclax is an oral agent approved for second-line therapy in CLL patients with del(17p) that induces a rapid reduction in disease burden (Roberts et al., 2016). Venetoclax is administered in weekly escalating doses until the final prescribed daily dosing due to the risk of tumor lysis from the distinct mechanism of action.

In a phase I trial, venetoclax demonstrated an ORR of 80% and a CR rate of 20% in heavily pretreated relapsed or refractory CLL patients (Roberts et al., 2016). Approximately 89% of enrolled patients had poor prognostic features, including resistance to fludarabine, del(17p), del(11q), or unmutated *IgHV*. The phase II trial leading to the approval of venetoclax selectively enrolled 107 relapsed or refractory CLL patients with del(17p), resulting in an ORR of 79.4% and a CR rate of 7.5% (Stilgenbauer et al., 2016). Of the patients who achieved a CR, 37.5% achieved MRD– status, whereas 3% achieved MRD– status in the intent-to-treat population. The most common grade ≥ 3 adverse events were neutropenia (40%), infection (20%), anemia (18%), thrombocytopenia (15%), and autoimmune hemolytic anemia (7%; Stilgenbauer et al., 2016).

SEQUENCING OF ORAL TARGETED THERAPIES

Although oral targeted therapies have induced high response rates and improved PFS in high-risk CLL patients, features such as del(17p) and/or *TP53* mutations retain their unfavorable prognostic impact in regard to the duration of response as compared with that in patients without these indicators (Burger et al., 2014; Furman et al., 2014; O'Brien et al., 2014b; Sharman et al., 2014). Moreover, acquired resistance mutations in *BTK* and 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-2 (*PLCγ2*) genes have been identified in relapsing CLL patients, conferring a loss of response to ibrutinib (Woyach et al., 2014). Retrospective analyses show poor survival after ibrutinib discontinuation due to Richter's transformation (RT) or CLL progression, with many patients having high-risk features of unmutated *IgHV*, del(17p), and a complex karyotype (Jain, Keating, & Wierda, 2015; Mato et al., 2016). Pretreated patients without del(17p) receiving ibrutinib as an earlier line of therapy as opposed to after more than two or three lines are less likely to discontinue treatment for disease progression (O'Brien et al., 2016b).

In practice, the distinct toxicity profiles of these agents are considered when selecting an oral therapy in the relapsed or refractory setting. A retrospective multicenter study was conducted to examine outcomes in 178 CLL patients who had discontinued either ibrutinib or idelalisib after a median time on therapy of 5 months (Mato et al., 2016). Most of these patients had adverse features of del(17p; 34%), *TP53* mutations (27%), del(11q; 33%), and a complex karyotype (29%). The most common reasons for discontinuation of ibrutinib and idelalisib were toxicity (51%), CLL progression (29%), and RT (8%). Atrial fibrillation (20%) and infection (12%) were the most common reasons for discontinuing ibrutinib, whereas pneumonitis (33%) and colitis (28%) were the most common reasons for discontinuing idelalisib.

Progression-free survival and OS were not impacted by initial kinase inhibitor choice; however, RT resulted in a median PFS of 6 months. The

ORR to idelalisib in patients who discontinued ibrutinib was 28%, with a median time on therapy of 4 months. Conversely, with a median time on therapy of 7.5 months, the ORR to ibrutinib in patients who discontinued idelalisib was 64%. At the time of this study, venetoclax was under investigation as part of clinical trials and demonstrated an ORR of 76%, with incomplete knowledge of the preceding targeted agent being either ibrutinib or idelalisib. Based on these studies, switching to an alternative kinase inhibitor or venetoclax is recommended for patients whose disease progresses or who experience adverse events.

SUMMARY

Advancements in our understanding of the impact prognostic factors play in the disease course of CLL and patient outcomes have led to the concept of risk-adapted treatment. Patients with significant comorbidities, high-risk prognostic factors, and relapsed or refractory CLL once had limited treatment options with poorer outcomes. The FDA approval of the glycoengineered anti-CD20 monoclonal antibodies ofatumumab and obinutuzumab has proven to be both efficacious and tolerable in elderly CLL patients with comorbidities precluding them from traditional chemoimmunotherapy. Moreover, the approval of ibrutinib, idelalisib, and venetoclax has led to improved patient outcomes in high-risk and relapsed or refractory CLL patients. As such, oncology providers must be aware that the optimal application of these agents requires consideration of the risk profile of the patient, including disease risk and the overall health of the patient. However, despite these advances, relevant questions remain unanswered as to the optimal timing and sequencing of novel targeted agents. As such, data continue to accumulate on the optimization of treatment regimens for CLL.

Disclosure

Dr. Nodzon has served as a consultant for Ariad and Gilead; has served on speakers bureaus for Ariad, Bristol-Myers Squibb, Genentech, Gilead, Novartis, and Pfizer; and has received payment for the development of educational presentations for Genentech/AbbVie. Dr. Pinilla-Ibarz has received consulting fees or honoraria from AbbVie, Gilead, Janssen, Pharmacyclics, and Roche.

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