Management of Chronic Lymphocytic Leukemia

Stephan Stilgenbauer, MD, Richard R. Furman, MD, and Clive S. Zent, MD

OVERVIEW

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is usually diagnosed in asymptomatic patients with early-stage disease. The standard management approach is careful observation, irrespective of risk factors unless patients meet the International Workshop on CLL (IWCLL) criteria for “active disease,” which requires treatment. The initial standard therapy for most patients combines an anti-CD20 antibody (such as rituximab, ofatumumab, or obinutuzumab) with chemotherapy (fludarabine/cyclophosphamide [FC], bendamustine, or chlorambucil) depending on multiple factors including the physical fitness of the patient. However, patients with very high-risk CLL because of a 17p13 deletion (17p-) with or without mutation of TP53 (17p-/TP53mut) have poor responses to chemoimmunotherapy and require alternative treatment regimens containing B-cell receptor (BCR) signaling pathway inhibitors. The BCR signaling pathway inhibitors (ibrutinib targeting Bruton’s tyrosine kinase [BTK] and idelalisib targeting phosphatidyl-inositol 3-kinase delta [PI3K-delta], respectively) are currently approved for the treatment of relapsed/refractory CLL and all patients with 17p- (ibrutinib), and in combination with rituximab for relapsed/refractory patients (idelalisib). These agents offer great efficacy, even in chemotherapy refractory CLL, with increased tolerability, safety, and survival. Ongoing studies aim to determine the best therapy combinations with the goal of achieving long-term disease control and the possibility of developing a curative regimen for some patients. CLL is associated with a wide range of infectious, autoimmune, and malignant complications. These complications result in considerable morbidity and mortality that can be minimized by early detection and aggressive management. This active monitoring requires ongoing patient education, provider vigilance, and a team approach to patient care.

Chronic lymphocytic leukemia/small lymphocytic lymphoma is the most prevalent lymphoid malignancy in many parts of the world, and approximately 90% of patients are diagnosed with asymptomatic, early-intermediate stage (Rai 0-I, Binet A) disease.1-3 Many of these patients have indolent disease and could have a normal life expectancy, whereas others have rapid disease progression and poor outcome. There is no proven survival benefit from early therapy in patients with CLL.4-5 There are now multiple prognostic factors that can be used to predict the risk of disease progression including serum thymidine kinase (TK) and beta-2-microglobulin (β2MG) levels, genomic aberrations assessed by fluorescence in situ hybridization (FISH), ZAP70, CD38, and CD49 expression, somatic hypermutation of the immunoglobulin heavy chain variable region genes (IGHV), and mutations of other genes, most prominently TP53.6-7 Despite multiple published studies of these prognostic factors in early-stage CLL, none have been prospectively validated.8-14 Moreover, there is currently no evidence that early, risk factor–guided intervention with chemoimmunotherapy can alter the natural course of early-stage CLL.4-5 Therefore, “watch and wait” remains the standard of care for patients with early-stage, asymptomatic CLL. The intervals of monitoring can be adjusted to a patient’s risk profile, that is, with 3-monthly follow-up for patients with high-risk markers such as 17p- with or without TP53mut, unmutated IGHV, 11q22.3 deletion (11q-), and high β2MG or TK serum levels.

INITIAL MANAGEMENT OF CLL

Early-Stage Asymptomatic Patients

A small proportion of patients with early-stage CLL (approximately 3% to 5%) have 17p-/TP53mut,15 which predicts a very high risk of disease progression16-21 based on data from chemoimmunotherapy studies in patients who required treatment (discussed later). However, a small proportion of early-stage patients with 17p-/TP53mut CLL do not have early disease progression,15,22 and 17p-/TP53mut at diagnosis in a patient who does not have active disease1 is not an indication for treatment. However, these patients deserve a more extensive prognostic work-up and closer monitoring, including the discussion of allogeneic stem cell transplantation (ASCT) as an option in young/fıt patients when their disease progresses and treatment is indicated. In summary, outside of clinical trials, the decision to start therapy requires the presence of active disease and is not modified by the presence of any high-risk marker. Prognostic markers can, however, be very helpful in counseling patients and planning patient follow-up.

From Ulm University, Ulm, Germany; Weill Cornell Medical College, New York, NY; University of Rochester, Rochester, NY.

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Corresponding author: Clive S. Zent, MD, Wilmot Cancer Institute, University of Rochester Medical Center, 601 Elmwood Ave., Box 704, Rochester, NY 14642; email: clive_zent@urmc.rochester.edu.

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Up-Front Management of Advanced Stage, Symptomatic Patients with an Indication for Treatment

Conventional chemoimmunotherapy regimens. The current up-front standard of care in physically fit patients with CLL who require treatment based on IWCLL criteria is fludarabine, cyclophosphamide, and rituximab (FCR; Fig. 1). This is based on high response rates (40% to 50% complete response [CRI]), prolonged median progression-free survival (PFS), and, notably, median overall survival (OS) compared with FC. However, many patients with CLL cannot tolerate FCR because of age (e.g., age > 65 to 70), decreased fitness (e.g., Cumulative Illness Rating Scale [CIRS] score > 6) and decreased renal function (e.g., creatinine clearance < 30 to 50 mL/min). In these patients, recent trials have suggested that other regimens could be more tolerable. The German CLL Study Group (GCLLSG) CLL10 study compared FCR versus bendamustine/rituximab (BR) among fit (CIRS ≤ 6, creatinine clearance ≥ 70 mL/min) patients without 17p-, and showed that overall BR was inferior to FCR in terms of response rate and PFS. However, FCR was associated with markedly increased toxicity without substantially better outcomes in patients over age 65, suggesting that BR is a reasonable alternative treatment for this population. There are now new monoclonal antibody–based treatment options for patients who are not considered fit for FCR-type treatment. Ofatumumab in combination with bendamustine or chlorambucil was licensed based on the randomized, phase III COMPLEMENT-1 trial that compared chlorambucil with ofatumumab/chlorambucil and showed substantially higher efficacy with only moderately increased toxicity for the combination therapy. The phase III CLL11 trial compared chlorambucil, rituximab/chlorambucil, and obinutuzumab/chlorambucil in a three-arm design. Obinutuzumab/chlorambucil showed higher efficacy compared with both chlorambucil and rituximab/chlorambucil with an acceptable safety profile, which led to the approval of obinutuzumab/chlorambucil for the up-front treatment of patients with CLL who are less fit. Therefore, the combination of anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) and chemotherapy (FC, bendamustine, or chlorambucil) is the standard up-front treatment for the vast majority of patients with CLL.

Initial therapy of patients with 17p-/TP53mut. Patients with 17p-/TP53mut CLL have markedly inferior outcomes with both chemotherapy and chemoimmunotherapy. Patients in the subset of patients with 17p- CLL enrolled in the randomized CLL8 study that compared FC with FCR, FCR was superior in terms of overall response rate (ORR, 68% for FCR vs. 34% for FC; p = 0.03) and PFS (median 11.3 months for FCR vs. 6.5 months for FC; p = 0.02), but there was no difference in complete remission rates (CRR, 5% for FCR vs. 0% for FC) or 3-year OS (38% for FCR vs. 37% for FC). TP53mut and 17p- were the two markers that had the strongest independent effect on PFS and OS in a multivariable analysis after FC and FCR treatment. These unacceptable outcome data were clearly inferior to all other disease subgroups. In the British CLL4 trial, TP53 mutation was identified as an adverse prognostic marker after treatment with chlorambucil, fludarabine, and FC. These findings of inferior response and poor prognosis are supported by the reported results for 17p- patients undergoing initial treatment of active CLL in studies conducted by MD Anderson Cancer Center/ Mayo Clinic, the Spanish Group for CLL, and the Memorial Sloan Kettering Cancer Center which showed that only about 25% of patients with 17p- CLL achieve remissions of 3 years or longer after treatment with purine analog–containing chemoimmunotherapy. There is limited data on bendamustine containing chemoimmunotherapy for the first-line treatment of patients CLL with 17p-. The GCLLSG CLL2M phase II study of front-line BR enrolled only eight patients with 17p- CLL, of which three responded; all responses were partial, and the median PFS was only 7.9 months. Therefore, BR is likely inferior to FCR as initial therapy in 17p- CLL. In the relapsed/refractory setting, both FCR and BR were unsatisfactory, with response rates of 35% and 7%, respectively, and median PFS of 5 months and 7 months, respectively.

The value of using other recurrently mutated genes in the definition of high-risk disease and the treatment of patients with CLL is less well defined. There is data from heteroge-

KEY POINTS

- Careful observation for disease progression and complications, together with appropriate preventative interventions, remains the standard of care for patients with early-stage, asymptomatic, chronic lymphocytic leukemia. Patients with very high-risk chronic lymphocytic leukemia should not receive treatment until they meet standard criteria for progressive disease.
- The most critical determinants of treatment choice are the presence of 17p-/TP53mut, physical fitness/age, and duration of prior response in patients who have received previous treatment. In addition, 17p-/TP53mut analysis should be repeated before initiation of therapy.
- The combination of anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) and chemotherapy (FC, bendamustine, or chlorambucil) is the standard up-front treatment for the majority of patients with chronic lymphocytic leukemia, with the specific choice of agents mostly determined by fitness of the patient. Based on the dramatic efficacy and favorable toxicity profile of the BCR and BCL2 inhibitors compared with historic chemoimmunotherapy regimens, these agents are the preferred treatment approach for very high-risk chronic lymphocytic leukemia (17p-/TP53mut and early relapse).
- Ongoing and future clinical trials are essential to further improve treatment efficacy, determine treatment duration, and eventually develop curative therapy.
- The role of allogeneic stem cell transplant in the management of chronic lymphocytic leukemia requires careful and early discussion in patients who are very high-risk.
neous cohorts outside clinical trials that mutation of genes such as \textit{NOTCH1}, \textit{SF3B1}, and \textit{BIRC3} could improve the prognostic accuracy of genomic analysis.\textsuperscript{20} However, data from the U.K. CLL4 and GCLLSG CLL8 clinical trials have only partly confirmed the independent prognostic role of these gene mutations and their effect was less pronounced.

Optimal therapy for patients with CLL requires evaluation of disease biology, patient fitness, and treatment history. (A) Initial treatment of patients with CLL requires determination that they meet the International Workshop on CLL (IWCLL) criteria for active disease. These patients should then be clinically evaluated for fitness, and those considered fit for treatment then require FISH analysis for 17p13 deletion (17p-) and gene sequencing for mutations in TP53 considered to be dysfunctional (TP53mut). (B) In patients with relapsed/refractory CLL, the response to previous treatment should also be considered when determining the treatment of choice. Patients who previously responded to chemoimmunotherapy with a response duration of 2 years or longer (late relapse) can be considered for retreatment with a chemoimmunotherapy regimen. In contrast, patients with a response duration of less than 2 years should be considered to have early relapse and should be treated with nonchemotherapy regimens.

Abbreviations: CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; Alem, alemtuzumab; BR, bendamustine/rituximab; Clb, chlorambucil; CR, complete response; FCR, fludarabine/cyclophosphamide/rituximab; Ibr, ibrutinib; Idela, idelalisib; Obi, obinutuzumab; Ofa, ofatumumab; PD, progressive disease; PR, partial response; SD, stable disease.

than 17p-/TP53mut. An interesting finding from the GCLLSG CLL8 clinical trial was that patients with CLL and NOTCH1 mutations had a reduced benefit from the addition of rituximab to FC. Additional biologic markers associated with inferior treatment response include unmutated IGHV, 11q-, increased expression of CD38, ZAP70, and CD49, and high serum levels of β2MG and TK. Nevertheless, these markers do not define a subgroup of patients with CLL who require a different standard therapeutic approach. There are ongoing efforts by an international consortium trying to integrate biologic and clinical variables into a universal risk score to predict outcome in all patients with CLL (CLL-IPI consortium, see corresponding international consortium trying to integrate biologic and standard therapeutic approach. There are ongoing efforts by an international consortium trying to integrate biologic and clinical variables into a universal risk score to predict outcome in all patients with CLL (CLL-IPI consortium, see corresponding 2015 ASCO Annual Meeting abstract). This model uses five independent predictors for OS (age, clinical stage, 17p- and/or TP53mut, IGHV status, and β2MG) in a weighted grading to define four different CLL subgroups with significantly different OS rates at 5-years (93.2%, 79.4%, 63.6%, and 23.3%; p < 0.001). This system could be an improvement on risk stratification based on staging and single parameters alone, but is limited by data from trials based on chemoimmunotherapy rather than the novel agents discussed below.

In summary, conventional chemoimmunotherapy combining an anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) and chemotherapy (FC, bendamustine, or chlorambucil) is the standard of care in front-line CLL treatment, except for the subgroup with 17p-/TP53mut CLL.

Alemtuzumab-based regimens. Alemtuzumab is a humanized anti-CD52 monoclonal antibody effective against refractory CLL cells irrespective of 17p-/TP53mut. However, in patients with 17p-/TP53mut relapsed/refractory CLL, alemtuzumab monotherapy achieves only a modest ORR of 39% to 60% and CRR of 0% to 20%, and median remission durations are short (6 to 8 months). The addition of high-dose corticosteroids to alemtuzumab for the treatment of patients with CLL with 17p- was tested in two studies. The U.K. CLL206 study administered alemtuzumab and methylprednisolone to 39 patients. The German/French CLL208 study treated 131 patients with fludarabine-refractory or 17p- CLL (front-line use in 42 patients with 17p-, 28 with relapsed 17p- disease) with alemtuzumab and dexamethasone followed by ASCT or maintenance alemtuzumab. Among patients with 17p- CLL who received front-line therapy, ORR from the two studies were encouraging at 88% to 97%. In the CLL206 study, the CRR was very high at 65%, but remissions were only moderately durable with a median PFS of 18 months. In contrast, remissions in the CLL208 study were more durable with a median 33 months, with the key difference being the use of postinduction therapies. The overall result (considering both front-line and patients whose disease relapsed) from CLL208 showed that ASCT was superior to maintenance alemtuzumab as postinduction therapy, with approximately 50% of transplanted patients remaining free of disease beyond 3 years. As a result of the inferior risk/benefit ratio of alemtuzumab compared with novel agents (see below) and the withdrawal of alemtuzumab from the market, these regimens have a limited role in the current management of CLL. However, the results of these studies provide a historic benchmark to compare efficacy data from phase II trials of novel agents in 17p-/TP53mut CLL.

The role of ASCT. There is unequivocal evidence that reduced intensity conditioning (RIC) ASCT is effective therapy in CLL, and can result in prolonged disease-free survival even for patients with advanced, chemotherapy-refractory disease. Patients with CLL with 17p-/TP53mut have shown equivalent outcomes in these studies with approximately 40% to 50% of patients achieving sustained long-term remission and possibly cure, although the substantial morbidity and about 20% mortality rate restricts the use of this therapy. Factors associated with inferior outcomes included more than three prior treatment regimens, advanced clinical stage, and refractory disease at the time of RIC ASCT. Thus, RIC ASCT should be considered earlier in the course of CLL when therapeutic options for remission induction still exist, and is preferably performed in patients with low disease burden. In the chemoimmunotherapy era, consolidation with RIC ASCT would have been considered for all fit patients with CLL with early (within 24 to 36 months) relapsed or refractory disease, as well as 17p-/TP53mut as a component of initial treatment. The availability of more effective therapy for relapsed/refractory CLL has altered this strategy as detailed in a recent ERIC/EBMT consensus paper, which concluded that there are now few indications for RIC ASCT in the initial therapy of patients with CLL. Even in early relapse and for patients with 17p-/TP53mut CLL, there is no universal indication for RIC ASCT and a careful consideration of the risk profile must be performed including genetics (17p-/TP53mut, 11q-), age, comorbidities, and degree of donor matching. To facilitate this, immediate referral of patients with early relapse and/or undergoing initial therapy for 17p-/TP53mut CLL to a transplant center for evaluation and counseling is recommended.

Novel Agents Targeting BCR Signaling and BCL2 in the Management of 17p-/TP53mut CLL

The two major classes of novel agents with substantial activity across all genomic subgroups of CLL are the BCR signaling inhibitors and the BCL2 antagonists. These drugs are orally bioavailable and show dramatic efficacy and favorable tolerability compared with chemoimmunotherapy (see Relapsed/Refractory CLL below). In contrast to chemotherapy, these drugs are not genotoxic and are therefore active in patients with p53 dysregulation (i.e., 17p-/TP53mut). Over 200 patients with relapsed/refractory CLL with 17p-/TP53mut have been treated with ibrutinib monotherapy across three clinical trials with excellent results compared with historic controls treated with chemoimmunotherapy. Over 80% of these patients achieved objective responses (including partial response with persistent lymphocytosis) with 12-month PFS of approximately 80% and projected 24-month PFS of approximately 50% to 60%. However, CRs were rare (<5%), and in one study patients with 17p- CLL had a substantial increase in relapse rates com-
pared with patients without 17p- CLL. In addition, the efficacy of idelalisib/rituximab appeared to not be impacted by 17p-/TP53mut in a retrospective subgroup analysis, suggesting that this regimen is another treatment option for this subgroup.

Whereas the BCR antagonists very rarely achieve CR in the relapsed/refractory setting, the results may be different when these drugs are used as front-line therapy. For example, two CRs were recorded in the four treatment-naïve patients with 17p- CLL enrolled in the ibrutinib/rituximab study, and in a study of front-line idelalisib and rituximab, ORR and CRR of 100% and 33%, respectively, were reported in nine patients with 17p- CLL. Prospective studies of these agents in the front-line setting are currently underway. Notably, both the U.S. Food and Drug Administration (FDA) and European Medicines Agency have granted approval of ibrutinib and the European Medicine Agency has approved idelalisib/rituximab for the up-front treatment of patients with 17p-/TP53mut, clearly underlining the dramatically superior efficacy of these agents in these patients. However, there are data that suggest that resistance to novel agents may be related to genomic instability of the CLL clone, resulting in either development of diffuse large B-cell lymphoma (DLBCL; Richter transformation) or acquired resistance to ibrutinib (see below). These observations suggest that patients with 17p-/TP53mut CLL, which is associated with a high degree of genomic instability, could still benefit from ASCT.

The antiapoptotic members of the BCL2 family are targeted by BH3-mimetics (ABT-737, ABT-263, and ABT-199). The current drug in clinical development for CLL is venetoclax (ABT-199, GDC-0199), which is a specific inhibitor of BCL2 and does not cause BCLXL inhibition–related thrombocytopenia. The results of venetoclax in CLL have been presented in abstract form. Both as single-agent and in combination with rituximab, venetoclax achieved high response rates of approximately 80%, and importantly—and differently from the results of BCR antagonists—complete remission rates of approximately 25% were reported even in the relapsed/refractory 17p- setting. A number of patients have become negative for minimal residual disease (MRD) following venetoclax (with or without rituximab) therapy, and five have discontinued venetoclax in remission without recurrent disease at early follow-up. A pivotal phase II study of venetoclax in 17p- CLL (front-line and relapsed/refractory) is currently underway.

**MANAGEMENT OF RELASED/REFRACTORY CLL**

**BCR Inhibitors**

The importance of the BCR pathway in the pathogenesis of CLL is exemplified by the use of stereotypic immunoglobulin variable regions, biased VH gene family usage, prognostic implications of mutational status, and the profound clinical efficacy of the BCR pathway inhibitors in CLL (reviewed in Jones and Stevenson). As a result of their novel mechanisms of action, BCR antagonists have required a re-evaluation of several key aspects of our management practices in CLL. First, the initial lymphocytosis seen with these agents would be considered progressive disease based on the standard IWCLL criteria. This lymphocytosis likely results from the inhibition of several adhesion molecule pathways, including CXCR4/5, and could contribute to the efficacy of these agents. Fortunately, the lymphocytosis is usually accompanied by a very rapid decrease in lymphadenopathy, and improvement in cytopenias and symptoms. As a result, the IWCLL criteria have been revised by a group sponsored by the Lymphoma Research Foundation to exclude use of lymphocytosis as the sole indicator of progression in patients who are receiving treatment with a BCR antagonist. This new response category has been termed “PR with lymphocytosis.”

Second, maximal response is often measured shortly after the completion of therapy. The German CLL Study Group validated the prognostic effect of measuring MRD 2 months after completion of cycle six in the CLL8 study. For the BCR signaling pathway inhibitors, responses evolved over time and treatment is often ongoing. Patients receiving treatment typically move from stable disease (or partial response with lymphocytosis) to partial response when the lymphocytosis resolves, to CR. Although we know the median time to response to treatment, the median time to CR has not yet been determined because half of the population has not yet achieved CR or had progressive disease. In addition, although we can assume that negative MRD studies will predict for an excellent outcome, the presence of MRD can no longer be seen as indicative of a poor response. Thus, comparison of responses to therapy with BCR signaling inhibitors to chemoimmunotherapy in clinical trials should not use the previously used conventional endpoints of partial response, CR, and MRD status, but should rather focus on PFS and OS.

The third issue to re-evaluate is the role of prognostic markers. Although the prognostic markers commonly used in clinical practice (CD38, ZAP70, IGHV mutation status, and interphase FISH) retain their predictive value for time to treatment, they do not predict response to treatment with BCR antagonists. It is also worth noting that in the first publication of the phase II data on ibrutinib therapy in CLL, patients with mutated IGHV were reported to have poorer responses. However, analysis at a later time point showed no difference in response rates based on IGHV mutation status. The initial difference could have been because the CLL cells in patients with unmutated IGHV were more dependent on BCR signaling, and therefore more sensitive to its inhibition. With regard to possible predictors of resistance developing to ibrutinib, complex karyotype and a “mutator phenotype” might predict for the development of resistance. Resistance to ibrutinib has been shown to occur because of a single base pair mutation resulting in a cysteine-to-serine change at amino acid 481 in BTK that alters the ibrutinib binding site, or gain-of-function mutations in the PLCγ2 gene that overcome the inhibition of BTK. These data alter the role of use of prognostic factors in treatment planning for patients with CLL. Important considerations include the role of ASCT and the ability to avoid DNA-damaging drugs that
could be associated with the increased risk of secondary myeloid neoplasms\textsuperscript{61} and other second malignancies (see below).

**Ibrutinib therapy.** Ibrutinib was the first BCR pathway inhibitor approved for treatment in CLL. The phase I study demonstrated a wide therapeutic window, with all patients who were treated with doses of ibrutinib greater than 2.5 mg/kg demonstrating complete inhibition of BTK at 4 hours. Two subsequent phase II studies used a fixed dose of ibrutinib of 420 mg/day. Patients with relapsed/refractory CLL study who received ibrutinib experienced a 90% ORR. Response was durable and the median PFS had not been reached at a median follow-up of 35.2 months, with an estimated PFS of 69% at 30 months.\textsuperscript{41,59} In the study of initial therapy of previously untreated CLL patients with progressive disease over the age of 65, the ORR including partial response with lymphocytosis was 84%, with an estimated PFS of 96% at 30 months. Of the 31 patients enrolled in this study, three discontinued treatment for adverse events, two patients withdrew consent, and one patient demonstrated progressive disease in the form of a Richter transformation that was diagnosed at month 8.

Overall, treatment with ibrutinib was well tolerated, with the most common adverse events reported being transient diarrhea (58%), fatigue (28%), infections (32%), and bleeding (61%). The diarrhea appeared to be transient with a median duration of 20 days and was only severe (\textgeq grade 3) in 6% of patients. Diarrhea was controllable in most patients with anti-motility agents and only led to treatment discontinuation in one patient, and ibrutinib dose reductions in two patients. The frequency of severe infections was considerably higher in patients with relapsed/refractory disease compared with previously untreated patients (51% vs. 13%). In addition, the frequency of severe infections was highest in the first year of treatment and then decreased in subsequent years for both relapsed/refractory (36%, 32%, and 24%) and previously untreated (10%, 8%, and 4%) disease. Long-term ibrutinib therapy did not appear to increase the risk of infection in these patients.\textsuperscript{41,59,62} Bleeding was reported in 61% of CLL patients treated with ibrutinib and was severe in 8% with one death. Bleeding resulted in treatment discontinuation in three patients. In these studies, 58% of patients were receiving anti-platelet agents and 22% were receiving anticoagulants.\textsuperscript{41,59,62}

An obvious shortcoming in when evaluating phase II data is the lack of a control population to assess what would be the expected adverse events in the population being studied. When ibrutinib was compared to ofatumumab in the RESONATE study, several important findings related to adverse events were noted. First, fatigue was seen in equal numbers in both arms (28% ibrutinib vs. 30% ofatumumab). Second, severe infections were seen in similar numbers in both arms (24% ibrutinib vs. 22% ofatumumab). Third, atrial fibrillation, an adverse event not previously attributed to ibrutinib in phase II trials, was found to occur more frequently in patients treated with ibrutinib compared with ofatumumab (4% ibrutinib vs. 1% ofatumumab). Whether atrial fibrillation is associated with ibrutinib treatment will require subsequent phase III trials to ascertain, but for now, clinicians might consider cardiac risks when making treatment decisions.

Data for ibrutinib in patients with 17p- CLL are derived from three studies.\textsuperscript{46,49,63,64} In the pivotal RESONATE study, 127 of the 391 patients had 17p-. The overall response rate, excluding partial response with lymphocytosis, was 47.6% with ibrutinib, compared with 4.7% with ofatumumab. The median PFS for ibrutinib was not reached compared with 5.8 months for ofatumumab. In patients who received ibrutinib, 83% with 17p- were progression-free at 6 months. There was no difference in response rate or PFS based on the presence or absence of 17p-.\textsuperscript{46} An NIH phase II study of 51 patients with TP53 aberrations demonstrated a 97% response rate in previously untreated patients, with a 91% PFS at 24 months (35 patients), and an 80% response rate in previously treated patients, with an 80% PFS at 24 months (16 patients). The third study, RESONATE-17, involved 144 patients with CLL with 17p- whose disease had relapsed or was refractory to one prior therapy. The overall response rate was 82.6%, with a PFS at 12 months of 79.3%. Progressive disease occurred in 20 patients (13.9%), including Richter transformation in 11 patients, seven of which occurred within the first 24 weeks of treatment.\textsuperscript{49,64} These data suggest that treatment of patients with relapsed/refractory CLL and 17p-/TP53mut using ibrutinib results in better outcomes than that achieved with any previously used therapies.

**Idelalisib therapy.** Idelalisib, which targets PI3K-delta, demonstrated excellent efficacy and tolerability in patients with relapsed/refractory CLL. Across its phase I/II studies, idelalisib used as a single agent resulted in a 72% response rate with a median PFS of 15.8 months\textsuperscript{65} in a high- to very high-risk relapsed/refractory CLL population (70% treatment-refractory, 24% 17p-/TP53mut). Severe adverse events included diarrhea/colitis (5.6%), transaminitis (1.9%), and pneumonia (20.4%).

Idelalisib’s pivotal phase III study was conducted in a heavily pretreated population of patients considered unlikely to benefit from chemotherapy because of a previous response duration of less than 2 years who had additional comorbidities (persistent myelosuppression or creatinine clearance < 60 mL/min).\textsuperscript{42} Two-hundred and twenty patients were randomly assigned to receive rituximab/placebo or rituximab/idelalisib (150 mg twice daily). The patient population had a median CIRS score of eight, median creatinine clearance of 64.5 mL/min, and 43.5% had 17p-. The study met its primary endpoint at the first interim analysis with an 85% reduction in the risk of progression or death between the two arms (median PFS, 5.5 months for placebo vs. not reached for idelalisib) and a substantial improvement in OS (survival at 12 months of 80% for placebo vs. 92% for idelalisib). A subsequent update after the second interim analysis demonstrated a 12-month PFS for the idelalisib/rituximab arm of 66% compared with 13% for the placebo/rituximab arm.\textsuperscript{47} PFS and response rates were not affected by prognostic factors, including deletion 17p-/TP53mut, ZAP70 expression, or IGHV mutational status. Severe adverse events occurred in
40% compared with 35% of patients for idelalisib or placebo, respectively. Severe adverse events of note for idelalisib compared with placebo included diarrhea (19% vs. 14%), pneumonia (6% vs 8%), and transaminitis (35% vs. 19%). The risk of rituximab infusion reactions decreased with idelalisib compared with placebo (15% vs. 28%).

**BCR inhibitor therapy.** The studies detailed above have clearly demonstrated the effectiveness of ibrutinib and idelalisib as treatments for CLL patients. The FDA approvals for these agents reflects the populations studied in the clinical trials; ibrutinib has been approved for the initial therapy of CLL in patients with 17p- and for all patients with relapsed/refractory disease, and idelalisib has been approved for use in combination with rituximab for patients who are considered candidates for treatment with single-agent rituximab. Choice of the best BCR antagonists for an individual patient should currently be based on the toxicity profiles of ibrutinib and idelalisib. For ibrutinib, the risks of bleeding, diarrhea, atrial fibrillation, and drug interactions affecting CYP3A4 are the most worrisome. Idelalisib can cause liver injury, inflammatory colitis, and pneumonitis, and should be avoided in patients with hepatic dysfunction or autoimmune diseases.

The optimal duration of therapy with BCR has not yet been determined. Because these therapies are effective and relatively well tolerated, it could be reasonable to continue treatment. However, we do not yet know the long-term effects of continuing therapy and conversely have little data on the mechanisms of resistance and how development of resistance may be affected by stopping treatment. Studies are currently underway looking at discontinuing therapy once patients reach MRD negativity. Until the data from these studies are available, it is prudent to continue patients on therapy indefinitely.

**Complications of CLL**

Acquired immune defects occur early in the course of CLL and increase the risk of infection and autoimmune disease. Defective immune surveillance could also contribute to the increased risk of second malignancy. In addition, clonal evolution can cause transformation to DLBCL.

**Infections**

Patients with CLL have a high risk of serious infection, which causes considerable morbidity and mortality. Defective nonmalignant B-cell function impairs humoral responses to antigens, and although absolute T-cell counts are usually increased, CD4/CD8 ratios are reversed with decreased T-cell receptor repertoire, and impaired T-cell function. Monocyte, dendritic, and natural killer cell dysfunction, decreased serum complement levels, and bone marrow failure-associated neutropenia result in defective innate immunity. Immune dysfunction is further impaired by chemotherapy and monoclonal antibody therapy.

**Clinical.** Impaired humoral immunity increases the risk of bacterial infections by encapsulated organisms (e.g., *Streptococcus pneumoniae* and *Staphylococcus aureus*) in all stages of CLL. T-cell defects increase the risk of herpesvirus reactivations. The clinical consequences include shingles (frequently complicated by postherpetic neuralgia), disseminated varicella zoster, herpes simplex infections (including lymphadenitis), and cytomegalovirus-induced disease. The risk of herpesvirus reactivation is increased by treatment with lymphotoxic drugs (e.g., purine analogs, corticosteroids, and alemtuzumab) that can cause prolonged T-cell lymphopenia. Patients with advanced-stage CLL and those undergoing immunosuppressive therapy or ASCT are at high risk of contracting fungal and atypical bacterial infections. Major concerns are *Pneumocystis jiroveci* pneumonia, cryptococcal meningitis, and systemic histoplasma, *Aspergillus*, *Nocardia*, and atypical *Mycobacteria* infections.

**Prevention.** Active monitoring and treatment of patients with CLL can decrease the risk of serious infections and their complications. Patient education is essential and should emphasize the need for immediate medical evaluation of systemic infections and fevers at 38.5°C or higher. Vaccination efficacy is suboptimal in patients with CLL. Pneumococcal vaccine responses are improved by the use of the conjugated 13-valent vaccine, and additional use of the 23-valent polysaccharide pneumococcal vaccine, as well as the influenza vaccine, could be of value, especially in patients with early-stage CLL. Live vaccines (e.g., shingles and yellow fever) are contraindicated.

There are limited data on the efficacy of the use of prophylactic antimicrobial therapy in CLL. *Pneumocystis* and herpesvirus prophylaxis is commonly used during and for 3 to 6 months after treatment with purine analog–containing chemoinmunotherapy, alemtuzumab, and high-dose corticosteroids. Prophylactic antiviral therapy can decrease the risk of recurrent varicella zoster and herpes simplex infection in patients with recurrent infections.

Intravenous immunoglobulin (IVIG) can normalize serum IgG levels and decrease the risk of infections but has not been shown to improve survival. IVIG therapy can cause serious toxicities and is time consuming and expensive. Use should probably be limited to patients with recurrent major infections (two or more in 6 months).

Effective management of established infections in patients with CLL requires a vigorous effort to determine the cause of infection with a high index of suspicion for encapsulated bacteria, atypical, and opportunistic infections. Therapy planning should assume that all CLL patients are immunocompromised.

**Hematologic Autoimmune Disease**

Patients with CLL have an approximate 5% to 10% lifetime risk of hematologic autoimmune complications, but CLL-related nonhematologic autoimmune complications are rare. In most (> 90%) patients with CLL and autoimmune cytopenia, loss of immune self-tolerance results in the produc-
tion by nonmalignant B cells of pathologic high affinity polyclonal IgG antibodies directed against blood cell antigens. Self-reactive monoclonal antibody production by CLL cells (usually IgM) causes less than 10% of autoimmune hemolytic anemia (AIHA) in patients with CLL. Pure red blood cell aplasia (PRCA) can be mediated by either pathologic autoantibodies or T-cell dysfunction. Autoimmune cytopenias can occur at any time in the course of CLL and are the cause of approximately 15% to 20% of noniatrogenic cytopenias in patients with CLL. Onset can be acute or insidious. Patients with CLL should not be classified as advanced-stage disease because of their autoimmune cytopenia.

**AIHA: clinical.** AIHA is the most common autoimmune complication of CLL and is characterized by reticulocytosis in the absence of bleeding, elevated lactate dehydrogenase and indirect bilirubin, and a positive direct antiglobulin test (DAT). DAT tests detecting red blood cell (RBC)–bound anti-RBC IgG antibodies and the complement degradation product C3 are positive in over 90% of patients with CLL and AIHA. However, approximately 15% to 20% of all patients with CLL have a positive DAT during the course of their disease and only about 35% of these patients develop AIHA. The diagnosis of AIHA thus requires definitive evidence of hemolysis. Patients with CLL with both AIHA and CLL-related bone marrow failure (complex AIHA) often do not have a reticulocytosis. These patients require a diagnostic bone marrow biopsy to ensure an accurate diagnosis of the cause of their cytopenia and thus appropriate treatment.

**AIHA: management.** Patients with AIHA and adequate erythropoiesis (simple AIHA) usually respond to immunosuppression with corticosteroids. More rapid responses can be obtained with IVIG. However, responses are not usually sustained when immunosuppression is decreased and patients frequently require long-term immunosuppression or additional treatment such as anti-CD20 monoclonal antibodies. Patients with both AIHA- and CLL-related bone marrow failure require therapy that treats both their CLL and autoimmune complication. Purine analogs should be used with caution because myelosuppression can exacerbate the anemia and the risk that monotherapy can precipitate autoimmune complications of CLL. Combination therapies including alkylating agents (cyclophosphamide or bendamustine), corticosteroids, and anti-CD20 monoclonal antibodies are usually effective. There is preliminary data that therapy with B cell receptor pathway inhibitors could be effective. Splenectomy is of limited value.

**ITP: clinical.** Patients with CLL with cytopenia caused by progressive bone marrow failure usually develop anemia followed by thrombocytopenia. Patients with CLL who have thrombocytopenia without anemia should be evaluated for etiologies other than bone marrow failure including increased platelet sequestration. Those with insidious onset thrombocytopenia and platelet counts greater than 50 x 10⁹/L should be evaluated for hypersplenism. Acute onset (< 2 weeks) or more severe thrombocytopenia (platelet counts < 50 x 10⁹/L) in patients with CLL is more likely to be caused by ITP, which still remains a diagnosis of exclusion. Antiplatelet antibodies have low specificity and sensitivity and are of limited diagnostic value. The diagnosis of ITP thus requires a bone marrow biopsy to exclude other potential etiologies and demonstrate adequate megakaryocytopenia.

**ITP: management.** Patients with stable ITP without bleeding complications and platelet counts above approximately 20 to 30 x 10⁹/L should be carefully observed and educated, but do not require treatment. Patients with CLL and ITP without evidence of bone marrow failure should be treated with immunosuppression with the addition of thrombopoietin agonists if required. Splenectomy is less effective compared with primary ITP. Patients with both ITP and bone marrow failure can be treated with the same regimens used to manage complex AIHA except that BTK inhibitors (e.g., ibrutinib) that affect platelet function and increase the risk of bleeding should be avoided.

**PRCA: clinical.** PRCA usually presents as progressive anemia with a very low absolute reticulocyte count and no evidence of hemolysis. Definitive diagnosis requires a bone marrow study. The differential diagnosis includes parvovirus and other viral infections. Clinical testing for pathologic antibodies or T cells is not routinely available.

**PRCA: management.** PRCA responds slowly to immunosuppression (e.g., prednisone and cyclosporine) because of the lag time to restoration of erythropoiesis. Long-term immunosuppression (e.g., low dose cyclosporine) is frequently required to maintain adequate hematopoietic levels. Autoimmune neutropenia. This is a rare and poorly understood condition which should be considered in the differential diagnosis of patients with isolated neutropenia of uncertain etiology.

**Nonhematologic Autoimmune Disease**

Patients with CLL have an increased risk of autoimmune acquired angioedema, paraneoplastic pemphigus, and glomerulonephritis. A clinically important consequence of immune dysregulation in CLL is exaggerated cutaneous arthropod bite reactions. These can be complicated by cellulitis and systemic infections.

**Hematologic Second Malignancies**

**Lymphoid malignancies.** Patients with CLL have an increased risk of second lymphoid malignancies. The highest risk is for DLBCL (approximately 0.5% per year). DLBCL can occur at any time in the course of CLL and is more frequent in patients with NOTCH1 mutations and 17p-/TP53mut. The most common etiology of DLBCL (about 80%) is clonal transformation of a CLL cell and these patients have a poor prognosis.
prognosis.91 In contrast, approximately 20% of patients with CLL have clonally-unrelated DLBCL, which has a considerably better prognosis.91 This clinically important distinction between clonally-related and -unrelated DLBCL can be made by VDJ rearrangement analysis of CLL and DLBCL cells.91 Patients with CLL are also at an increased risk of developing Hodgkin lymphoma and other B-cell malignancies.

There is no standard of care for second lymphomas in patients with CLL. Patients with nonclonal DLBCL should be treated as having de novo disease.

Nonhematologic Second Malignancies

Skin cancer. Patients with CLL have a markedly increased risk of skin malignancies. Squamous cell carcinoma and basal cell carcinoma rates are increased by approximately 5- to 10-fold and these malignancies are more likely to be locally aggressive and metastatic.74,92-94 Melanoma is also more common and aggressive with poorer outcome.88,92,93,95

Patients require education on avoidance of ultraviolet radiation and should be evaluated by a dermatologist at diagnosis and then at least annually. Patients and families need to be educated on how to conduct monthly skin inspections.

Other malignancies. Noncutaneous second malignancies are a major cause of morbidity and mortality in patients with CLL.88,92,96,97 Patients should be encouraged to avoid smoking and excessive alcohol use, and to undergo routine preventative screening.

Disclosures of Potential Conflicts of Interest

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