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Choosing first line therapy for chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL) exhibits a highly variable natural history, but the addition of genomic risk stratification to traditional clinical staging systems has begun to explain the heterogeneous clinical course. Overall response to treatment has significantly improved over the past three decades, and for the first time, a survival benefit has been demonstrated with the use of monoclonal antibodies in combination with cytotoxic chemotherapy. Newer therapeutic strategies have abrogated the adverse prognosis associated with some higher-risk features, but other genetic subgroups remain at high risk for rapid disease progression and early mortality. Patients at advanced age or with significant co morbidity constitute a large proportion of the CLL population and present unique clinical challenges. This review will discuss the evolution of contemporary therapeutic approaches to the initial treatment of CLL and highlight the ways in which risk-adapted therapeutic strategies are improving clinical outcomes.

Keywords

chronic lymphocytic leukemia; risk stratification; chemo immunotherapy; fludarabine; cyclophosphamide; rituximab; chlorambucil; bendamustine; alemtuzumab; pentostatin

Introduction

Chronic lymphocytic leukemia (CLL) remains the most common hematologic malignancy in the Western world, representing 30% of leukemias.[1] The median age at the time of diagnosis is 72 years old; less than 10% of patients are under 60 years old. [2,3] The age-adjusted incidence rate is 4.2 per 100,000, with CLL occurring more often in Caucasians than in other ethnic groups and more often in men than in women. CLL is generally considered an indolent disease. However, the disease demonstrates a heterogeneous course. While many patients have slowly progressive disease, a subset of patients will experience more aggressive disease marked by rapid progression to requiring treatment. The recent introduction of new chemotherapeutic agents, the advent of biologic agents and combinations, as well as the identification of prognostic markers, have led to better risk-

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adapted treatments and, in turn, longer remissions. Unfortunately, CLL remains an incurable disease outside the hematopoietic stem cell transplant setting.[4] This article outlines the diagnosis, staging, and front-line treatment for patients with CLL, highlighting the application of newer therapeutic approaches.

The World Health Organization describes CLL as a leukemic, lymphocytic lymphoma, distinguishable from small lymphocytic lymphoma (SLL) by only its leukemic appearance. The diagnosis of CLL requires the presence of at least 5,000 B lymphocytes/μL, and the clonality of these cells must be confirmed by peripheral blood immunophenotyping. CLL cells express CD5, CD19, CD20, and CD23. The expression of surface immunoglobulin, CD20, and CD79b is typically low compared with normal B cells. Morphologically, CLL cells are small, mature appearing lymphocytes with a dense nucleus. Smudge cells are a characteristic finding on a peripheral blood smear. Patients who are found to have a clonal B cell population with fewer than 5,000 lymphocytes/μL in the absence of lymphadenopathy or organomegaly are classified as having monoclonal B-lymphocytosis, which progresses to CLL at a rate of 1–2% per year.[5]

Risk Stratification

There are 2 widely used staging systems in CLL: the Rai and Binet systems.[6,7] The Rai system has been modified to reduce the number of prognostic subgroups from the original 5 to a more clinically relevant 3, similar to the Binet scheme (Table 1). In addition to staging, genetic risk stratification should be done at diagnosis. Interphase cytogenetics, as determined by fluorescent in-situ hybridization (FISH), give important prognostic information and may influence therapeutic decisions. Del(13q14) is the most common abnormality, and when occurring in isolation conveys a favorable prognosis. In contrast, patients with del(11q23) or del(17p13) abnormalities – which result in the loss of the *ATM* and *TP53* tumor suppressor genes, respectively -- often have more aggressive disease, require earlier treatment, and experience inferior survival with standard therapies.[8] So poor is the prognosis associated with del17p13 (median survival of only 32 months beyond diagnosis) that these patients should be referred for investigational therapies followed by consideration for reduced-intensity allogeneic stem cell transplant in first remission if appropriate.[9]

In addition to FISH, mutational status of the immunoglobulin heavy chain variable region genes (IGVH genes) confers important prognostic information. CLL patients with IGVH genes which have not undergone somatic hyper mutation (“unmutated”) demonstrate inferior survival compared to those with the IGVH mutated phenotype.[10] Patients with unmutated IGVH are also prone to developing clonal evolution, or the acquisition of additional karyotypic abnormalities on metaphase cytogenetics, which likely accounts for refractory disease at relapse.[11] Because IGVH testing is quite expensive and not universally available in community practice, expression of ZAP70 and/or CD38 as measured by either flow cytometry or immunohistochemistry, which strongly correlates with unmutated IGVH, has been explored with similar intent but has yet to enter routine clinical practice.[12,13] Serum markers such as CD23, thymidine kinase, and β2-microglobulin may also predict survival and have been utilized for risk stratification in several large clinical

trials. [14–17] Bone marrow biopsy is typically not done at diagnosis in the absence of cytopenias, although it is recommended prior to starting treatment.[18]

When to Treat

In contradistinction to many other forms of leukemia, many patients with CLL are initially observed following diagnosis. To date there has been no demonstrable survival benefit when treatment is initiated for early stage, asymptomatic CLL. Two randomized trials enrolled patients with untreated Binet stage A CLL to receive treatment with the oral alkylating agent chlorambucil (with/without prednisone) or standard of care observation. Treatment failed to impart a survival benefit, although the use of chlorambucil did slow disease progression.[19] A meta-analysis of 6 studies evaluating the effect of early treatment with chlorambucil further confirmed these findings.[20] A more recently published study evaluating single-agent treatment with the anti-CD20 monoclonal antibody rituximab in early stage patients with higher risk disease (β2-microglobulin ≥ 2) demonstrated that this is approach is safe, but further studies are needed to demonstrate whether early treatment with newer therapies can impact morbidity or mortality.[21] Early intervention remains an appealing prospect for CLL with high-risk genomic features. Combination monoclonal antibody treatment in such patients appears feasible but has not yet been shown to alter the natural history of high-risk disease.[22] The German CLL Study Group (GCLLSG) CLL7 trial randomizes recently diagnosed (<1 year) high-risk patients (as determined by FISH, IGVH mutation status, serum thymidine kinase, and lymphocyte doubling time) to receive combination chemo immunotherapy versus standard-of-care observation. Accrual is ongoing. A similar study in the United States (CALGB 10501) was designed to assess the benefits of treatment with fludarabine and rituximab among patients deemed high-risk on the basis of unmutated IGVH, but the trial closed early secondary to poor enrollment.

Because the decision to initiate therapy for CLL is often a subjective one, the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) has developed guidelines to assist physicians in choosing the optimal time to begin treatment. The IWCLL recommends that therapy be initiated for Binet stage C or Rai high-risk disease, as well as for those with active or “progressive” disease (Table 2). While ostensibly defined to standardize inclusion criteria for clinical trials, the IWCLL’s definition of progressive CLL is likewise useful in routine clinical decision-making. The guidelines characterize progressive CLL as meeting one or more of the following criteria: evidence of progressive marrow failure, manifested by the development or worsening of anemia or thrombocytopenia; massive (at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly; massive (at least 10 cm in the longest dimension) or progressive or symptomatic lymphadenopathy; progressive lymphocytosis with an increase of more than 50% over a 2-month period or a doubling time of less than 6 months; autoimmune anemia and/or thrombocytopenia that is poorly responsive to steroids or other standard therapy; or the development of constitutional symptoms, including a greater than 10% weight loss within 6 months, significant fatigue, fevers higher than 100.5° over a 2-week period without other evidence of infection, or night sweats for more than 1 month without other evidence of infection. In patients with initial lymphocyte counts under 30,000/μL, lymphocyte doubling time should not be used as a single indicator for initiating treatment, and in this situation, other factors which can

contribute to lymphocytosis should be excluded. The absolute lymphocyte count should not be used as the sole indicator for treatment.[18]

Chemotherapeutic Approaches

Single-Agent Alkylators

For many years, chlorambucil has been the mainstay of treatment for CLL. In 1977 Sawitsky *et al* published a randomized study comparing chlorambucil given daily or intermittently with prednisone to prednisone alone in previously untreated patients with Rai stage III and IV CLL. While there was no statistically significant survival benefit in any of the treatment arms, there were overall response advantages with chlorambucil (55% for intermittent, 40% for daily) compared with prednisone alone (6%).[23] Chlorambucil continues to play a role in the treatment of elderly or otherwise infirm patients who would not tolerate more intensive purine-analog-based chemotherapy. The CLL5 trial from the German CLL Study Group (GCLLSG) evaluated fludarabine versus chlorambucil in patients over the age of 65. While fludarabine treatment resulted in higher response rates, with a 72% overall response rate (ORR) versus 51% for chlorambucil ($p=0.003$) and a 7% complete response (CR) versus 0% for chlorambucil ($p=0.011$), there was no statistically significant difference in progression-free survival. Toxicity was significantly higher among fludarabine-treated patients, as well as a non-significant trend toward worse overall survival in that arm, suggesting that chlorambucil still has a role in the front-line therapy of CLL.[24] Other alkylators such as cyclophosphamide have been evaluated, typically in combination (CVP: cyclophosphamide, vincristine, and prednisone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone), but have failed to demonstrate superiority.[25,26]

Bendamustine is a bifunctional chemotherapeutic agent with both alkylating and purine analog-like properties which has been used extensively for the treatment of lymphoma in Europe for more than 30 years. Its utility in CLL has only recently been systematically evaluated. Following demonstration of safety and efficacy with the use of single-agent bendamustine in heavily pretreated patients with relapsed CLL, a randomized phase III study comparing bendamustine with chlorambucil was conducted.[27] Thirty-one percent of patients treated with bendamustine had a CR, compared with 2% of patients treated with chlorambucil ($p<0.0001$). The median duration of remission with bendamustine was 21.8 months, compared with 8.0 months following chlorambucil.[28] Bendamustine was approved by the United States Food and Drug Administration (FDA) for use in previously untreated CLL on the strength of this study. These data were recently updated at a median observation time of 54 months; the median overall survival in the chlorambucil group was 78.8 months but was not yet reached in the bendamustine arm. Importantly, quality of life scores for physical, social, emotional, cognitive function, and global health status were not different in the 2 arms, further supporting the initial observation of only modestly increased toxicity with bendamustine.[29]

Purine Nucleoside Analogs and Combinations

Building on promising early clinical study results, the purine analog fludarabine was evaluated in previously untreated CLL patients with 33% of patients achieving a CR, 39%

achieving a nodular partial remission (nPR), and 6% demonstrating a partial response (PR), for an overall response rate of 79%.[30] Longer follow-up demonstrated a 63 month median survival following treatment with fludarabine, with a median time-to-progression of 31 months among responders. Many patients responded to rechallenge with fludarabine when treated after relapse.[31] A phase III study comparing fludarabine with chlorambucil as primary therapy demonstrated improved overall response and progression-free survival (PFS), with 73% ORR and 20 month median PFS for fludarabine compared with 37% and 14 months respectively for chlorambucil. There was no statistically significant difference in overall survival.[32] Fludarabine was subsequently combined with cyclophosphamide in an effort to build upon this success. Among previously untreated patients with CLL treated with the combination on a phase II study, all of them had a response, with 47% CR and 53% PR.[33] When FC was compared with fludarabine alone in a phase III study of untreated younger patients, the combination resulted in a higher response rate (24% CR, 94% ORR) compared with fludarabine (7% CR, 90% ORR, $p<0.001$), as well as a significantly longer median PFS (48 versus 20 months, $p=0.001$), but no difference in overall survival was seen.[34] A further important observation from this study, as well as a second large randomized trial comparing fludarabine to combination FC, was the finding that the addition of the alkylator appeared to abrogate the adverse prognosis associated with presence of del(11q23).[35,36] However, while fludarabine-based chemotherapy significantly improved the proportion and duration of responses, there remained no demonstrable improvement in overall survival.

Pentostatin is a nucleoside analog that was initially thought to be too toxic for use when administered daily, but it was demonstrated to be safe when given in weekly or biweekly doses of 4 mg/m^2. A phase II study performed by the Cancer and Leukemia Group B (CALGB) evaluating its effectiveness in untreated or minimally treated patients with CLL yielded a 46% ORR. Most patients tolerated treatment well, but life-threatening bacterial infections occurred in 36% of patients, and opportunistic infections occurred in 26%.[37] Much of the subsequent development of pentostatin has focused on its utility in combination treatment strategies.

Immunotherapy

Rituximab

Rituximab was the first therapeutic antibody approved for the treatment of any malignancy. The drug is a chimeric murine/human antibody directed against the CD20 antigen. CD20 is expressed relatively selectively on B cells from the pre-B cell stage until post-germinal cells differentiate to become plasma cells.[38] While the pivotal phase III study of rituximab in non-Hodgkin lymphomas (NHL) demonstrated promising clinical activity overall, the response among the 33 patients with SLL was less impressive, with only 12% of patients achieving a PR.[39] Two trials performed by our group and the MD Anderson Cancer Center (MDACC) administered either thrice-weekly doses or higher weekly doses of rituximab to relapsed CLL patients with improved response, predominantly in the blood and nodal compartments. [40,41] These two studies established a role for single-agent rituximab in relapsed disease and encouraged further evaluation of single-agent rituximab in

previously untreated CLL and in combination strategies with chemotherapy.[42] Treatment of 44 previously untreated, symptomatic patients with weekly rituximab yielded a 51% and 4% ORR and CR rate respectively after 4 weeks. An additional 4 week course of rituximab given every 6 months for up to 4 cycles to the 28 patients with stable or responsive disease did modestly increase the ORR to 58%, but the proportion of complete responders improved to only 9%. Median PFS was 19 months.[42]

Alemtuzumab

Alemtuzumab is a recombinant DNA-derived humanized IgG_1 kappa monoclonal antibody targeted against the cell surface antigen CD52. CD52 is expressed on all B and T lymphocytes at most stages of differentiation, as well as on granulocytes, monocytes, macrophages, eosinophils, natural killer cells and dendritic cells.[43,44] It is also expressed on tumor cells, including T-cell prolymphocytic leukemia (T-PLL), CLL, hairy cell leukemia, NHL, and acute lymphoblastic leukemia.[45] Alemtuzumab was initially approved on the basis of the CAM 211 study in which 93 patients with CLL relapsed or refractory following treatment with fludarabine and an alkylating agent were treated with a one-week dose escalation followed by 30 mg three times weekly for an additional 11 weeks.[46] The ORR was 33% (2% CR, 31% PR) with a median response duration of 8.7 months. Cytopenias and infections resulting from profound cellular immune suppression were the most common adverse events noted. Opportunistic infections, including reactivation of herpes viruses including cytomegalovirus (CMV) were noted. Prophylaxis against opportunistic infections, together with monitoring for CMV reactivation, is highly recommended during and after treatment with alemtuzumab. The addition of valganciclovir 450 mg orally twice daily has been demonstrated to provide effective prophylaxis against CMV reactivation but can exacerbate disease- or treatment-related cytopenias.[47]

Treatment with alemtuzumab showed significant activity in several pilot studies in previously untreated CLL.[48,49] On the strength of these results, a phase III study evaluating IV alemtuzumab versus chlorambucil in untreated CLL patients was performed.[50] Alemtuzumab-treated patients had a significantly superior response rate compared to chlorambucil (ORR 83% versus 56%, CR rate 24% versus 2%). Median time to next treatment (23.3 versus 14.7 months) and PFS (14.6 versus 11.7 months) both favored alemtuzumab. Significantly, patients with del(17p13) had better responses with alemtuzumab treatment compared with chlorambucil. At the time of publication, the median overall survival had not been reached in either arm; at a median follow-up of 24.6 months, 84% of the patients in each arm were alive at the data cutoff or the last follow-up date. No differences in terms of grade 3–4 hematologic toxicities were noticed between the two arms, but 19.7% of patients receiving alemtuzumab and only 4.1% of chlorambucil-treated patients experienced drug-related adverse events leading to discontinuation of treatment. Importantly, 52% of patients treated with alemtuzumab developed a positive CMV PCR result compared with 7.5% of the patients treated with chlorambucil.

Chemo immunotherapy

Notwithstanding the clinical benefit accruing to treatment with chemotherapy alone, recent studies incorporating monoclonal antibodies with chemotherapy, so-called chemo

immunotherapy, have reported not only improved response rates but significantly longer survival (Table 3). And while prior therapies consistently demonstrated improved PFS, more recently developed chemo immunotherapy combinations have for the first time resulted in significant improvements in overall survival.

Fludarabine and Rituximab Containing Combinations

A phase II study performed by the German CLL Study Group (GCLLSG) combining fludarabine and rituximab (FR) in both refractory and previously untreated patients resulted in an ORR of 87% with a subset achieving complete response.[51] CCALGB phase II study 9712 evaluated the FR combination with the antibody given either concurrently or sequentially. Patients in the concurrent arm experienced more severe hematologic and infusion-related toxicity, but the OR was 90% with a CR rate of 47% compared with an ORR of 78% and CR rate of 28% in the sequential arm.[52] A retrospective comparison to results from a similarly-designed CALGB study evaluating, in part, fludarabine alone demonstrated improved progression free survival (PFS) and overall survival (OS) with chemo immunotherapy.[53,54] Long-term follow-up data recently presented shows no increased risk of treatment-related acute myeloid leukemia (AML), which has been noted following treatment with alkylating agents.[54] An Italian phase II study of sequential FR confirmed good response rates, with 78% of patients achieving a CR, but only patients who had stable disease (SD) or better following treatment with fludarabine remained on the study to receive rituximab. [55]

The addition of rituximab to fludarabine and cyclophosphamide (FCR) has been extensively explored. A study of 300 previously untreated patients from the MDACC reported an OR of 95% with 72% of patients achieving a CR, 10% an nPR, and 13% a PR.[56] The six-year OS and PFS were 77% and 51%, respectively.[56] Toxicity included predominately cytopenias and infection. Eight patients subsequently developed treatment-related myelodysplasia, which has not been observed in patients treated without alkylators. Interestingly, patients with del(11q23) appeared to benefit from FCR, again confirming that fludarabine and alkylator combinations can overcome the adverse prognosis observed in fludarabine-monotherapy studies.[57] However, patients with IGHV unmutated disease and del(17p13) continued to demonstrate inferior survival following FCR.[56,58]

The landmark phase III CLL8 study from the GCLLSG, confirmed improved response rates and demonstrates improved overall survival with FCR when compared to treatment with fludarabine and cyclophosphamide alone.[59] Data from this study was recently published at a median observation time of 37 months. Patients were aged 30–81 years with a median age of 61. Forty-four of the 408 patients receiving chemo immunotherapy were over the age of 70. Both the ORR (95% versus 88%) and CR rate (52% versus 27%) significantly favored the three-drug combination. The median PFS for patients receiving FCR was 51.8 months versus 32.8 months for patients receiving FC, and FCR was likewise associated with a significant improvement in overall survival at 3 years, 87.2% versus 82.5% (HR =0.66, p=0.01). Rituximab did not appear to lead to more infectious complications, and more deaths actually occurred in the FC arm (10 in the FC arm versus 8 in the FCR arm).[59] Patients with del(17p13) were again noted to have particularly poor outcome, and a trend

towards shorter overall survival in patients with unmutated IGHV status was observed. Patients with del(11q23) again appeared to benefit from the addition of cyclophosphamide, with response rates approaching that of patients without this abnormality.[35] The inclusion of cyclophosphamide in this regimen is clearly important for patients with del(11q23) but remains of less certain utility for patients with more favorable genomic risk factors. An ongoing randomized study phase III study in the U.S. (CALGB 10404) examines this important question.

In an effort to improve upon the outcomes with the FCR combination, investigators at the MDACC increased the rituximab dose to three infusions per cycle (FCR3). Sixty-five patients were treated with this regimen, which failed to show any benefit when compared with historical controls.[60] Additionally, efforts to mitigate the toxicity of FCR to allow its use in elderly patients have been undertaken. In the FCR-lite regimen, the daily doses of fludarabine and cyclophosphamide were decreased by 20% and 40% respectively, and rituximab was administered every 2 weeks. The median age of patients enrolled on this study was 58 years, with a range of 36 to 85 years, including 7 patients over the age of 70. After 6 cycles, maintenance rituximab was given once every 3 months until relapse. High response rates were again seen, with 100% ORR and 77% CR. All 7 patients over the age of 70 had a response, with 4 CRs and 3PRs. Less grade 3 and 4 neutropenia was observed compared with conventionally-dosed FCR.[61]

Other Rituximab-based Chemo immunotherapy Combinations

Pentostatin is a nucleoside analog that may be less myelotoxic than fludarabine but still active in CLL. Studies have been done substituting pentostatin for fludarabine in both relapsed and untreated CLL.[62] The combination of pentostatin, cyclophosphamide, and rituximab (PCR) resulted in an ORR of 75% with a CR rate of 25% in patients with relapsed disease. Subsequent study of the same regimen for previously untreated disease produced an ORR of 91% and CR rate of 41%. The major toxicities, myelosuppresion and infections, were similar in both cohorts.[63] Importantly, the reported toxicities, as well as the fraction of patients completing all planned therapy, was similar in patient both above and below the age of 70. As noted with both the FC and FCR combinations, patients with del(11q23) demonstrated similar response rates and PFS as those without this karyotypic abnormality.[63] A small cohort of previously untreated patients has also been treated with a combination of pentostatin and rituximab without cyclophosphamide, albeit at a higher dose of pentostatin (4 versus 2 mg/m^2/dose). The ORR was 76% but the CR rate only 9%. The PFS was likewise shorter than observed after PCR. Toxicity, however, was favorable: only 12% experienced grade 3 hematologic events and 15% experienced grade 3 or higher non-hematologic toxicity.[64]

Given its significant single-agent activity, bendamustine has inevitably drawn interest in combination. Following its approval, pilot studies combining this agent with rituximab have been reported in previously untreated patients, where a 90% ORR and 33% CR rate were observed.[65] Toxicity, chiefly myelosuppression and infection, compared favorably with other commonly used chemotherapy and rituximab combinations. While patients with del(17p13) abnormalities fared poorly, patients with the del(11q23) abnormality

demonstrated response rates and survival comparable to the group as a whole. A randomized phase III study of the GCLLSG comparing bendamustine and rituximab to FCR in previously untreated patients is currently ongoing.

Alemtuzumab Combination Strategies

Notable for its activity in genomic high-risk disease, alemtuzumab has been incorporated into several fludarabine-based combination therapies with the aim of further enhancing efficacy, particularly for higher risk patients (reviewed in [67]). These studies have, in general, demonstrated feasibility, but it remains uncertain whether the addition of alemtuzumab significantly improves outcomes. Building on the FCR backbone, the MDACC group initially developed the CFAR (cyclophosphamide, fludarabine, alemtuzumab, and rituximab) regimen for relapsed disease.[68] A more recent trial evaluated CFAR in previously untreated patients with high-risk disease, including patients with del(17p13) or beta-2-microglobulin higher than twice the upper level of normal. The 92% ORR and 70% CR rate were comparable to that reported for FCR. But while an encouraging 52% of patients with del(17p13) attained CR, the median time to progression of only 18 months compared poorly to the 38 months observed among all evaluable patients. [69] A French group has also conducted a randomized study comparing the FCR regimen to a comparable chemotherapy backbone substituting alemtuzumab for rituximab (FC-Cam). [70] While the study was discontinued early after an unexpected excess of deaths in the FC-Cam arm, FCR appeared to likewise outperform with respect to efficacy. ORR and CR rates in the FCR group (91% and 74%) were significantly higher than those reported for FC-Cam treated patients (85% and 58%). The CLL2L trial from the GCLLSG evaluated FC-Cam in patients with relapsed or genetic high-risk CLL. The ORR was 68% with 22% CR, 11% CRu, and 35% PR, independent of FISH status. Twelve of 56 patients died during or within 6 months following their final chemotherapy, 5 deaths of which were attributed to therapy. [71] The combination of alemtuzumab and rituximab, omitting cytotoxic agents altogether, has also been evaluated by several groups with improved response versus the single agents, but the clinical benefit remains unclear.[22,72,73] The phase II NCRN CLL207 trial evaluated the use of alemtuzumab consolidation in patients with MRD-positive marrow after treatment. Patients received 30 mg subcutaneous injections 3 times a week for 6 weeks; patients with MRD-negative marrow or those without an appropriate response stopped therapy. Those with at least one log reduction in MRD continued therapy. Patients received prophylaxis with co-trimoxazole and acyclovir and had weekly CMV monitoring. Thirty-six percent of patients experienced a significant adverse event, with 2 treatment related deaths (EBV lymphoproliferative disorder and para influenza infection). Positive CMV titers were detected in 21 patients, all of whom were treated successfully. Of the 38 patients who received at least 8 weeks of alemtuzumab, 33 were MRD-negative at the end of treatment, and 15 remained MRD-negative at 6 months following treatment.[74] Until further phase III studies comparing these or other alemtuzumab-containing combinations to present treatment standards have demonstrated superiority -- and perhaps equally as important, confirmed safety -- they cannot be recommended for routine clinical use outside of the investigational setting.

Ofatumumab

Ofatumumab, a second-generation, fully-humanized anti-CD20 monoclonal antibody was approved on the basis of a pivotal phase II trial in which the single-agent produced objective responses of up to 50% in patients with bulky and/or alemtuzumab and fludarabine-refractory disease. Encouraged by the enhanced single-agent activity versus rituximab, even when the latter is administered on more dose-intensive schedules, the drug has been studied in substitution for rituximab in the O-FC (ofatumumab, fludarabine, and cyclophosphamide) regimen. Patients were randomized to receive one of two doses of ofatumumab (500 and 1000 mg/m^2) in combination with standard-dose FC. Overall response rates were (73–77%) were similar in both groups, but the observed CR rate was greater in the higher-dose ofatumumab arm (50 versus 32%). Toxicity was in keeping with that reported for FCR, but the regimen as a whole does not immediately appear to offer a significant advantage versus FCR.[66]

Maintenance and Consolidation Strategies

Similar to other indolent lymphoid malignancies, all patients with CLL will ultimately relapse following initial therapy; therefore, consolidation and/or maintenance strategies to prolong the treatment-free interval are appealing. The use of maintenance rituximab, for instance, has become the standard of care in follicular non-Hodgkin's lymphoma, where large, controlled trials have demonstrated that the treatment is associated with a significant improvement in PFS as compared to observation.[75] No similar such trials have yet been completed to determine whether a comparable benefit is derived in CLL/SLL. A phase II study of 75 previously untreated patients evaluated the efficacy of rituximab maintenance following treatment with 6 cycles of fludarabine.[76] All patients received 4 weekly doses of 375 mg/m^2 rituximab following therapy, and those with minimal residual disease (MRD) then went on to consolidation with 4 monthly cycles of 375 mg/m^2 rituximab followed by 12 monthly cycles of 150 mg/m^2. MRD-positive patients in CR or PR receiving consolidation had a longer PFS than the patients not receiving consolidation (87% versus 32% at 5 years). A randomized study evaluating maintenance rituximab is now underway by the Polish CLL group. Until the results from this study are available, maintenance rituximab should only be undertaken as part of a clinical trial.

The use of alemtuzumab as consolidation has also been evaluated (reviewed in[67]). O'Brien and colleagues administered alemtuzumab 10 or 30 mg IV three times weekly to CLL patients with residual disease after their most recent therapy, resulting in an OR of 46%.[77] Eleven of the 29 patients treated with 30 mg (38%) achieved a MRD-negative marrow. Infections occurred in 37% of patients, including CMV reactivation. Three patients developed Epstein-Barr virus-positive large B cell lymphoma. The GCLLSG performed a phase III trial where patients responding to fludarabine-based induction therapy were randomized to receive IV alemtuzumab 30 mg 3 times weekly for a maximum of 12 weeks, or observation.[78] This study closed prematurely closed because of severe infections in the alemtuzumab arm. However, in the small number of patients treated (N=21), alemtuzumab consolidation appeared to improve both the quality of response as well as the duration of progression free survival.[79] The CALGB has performed two studies administering

alemtuzumab after fludarabine or fludarabine and rituximab.[80] Both studies demonstrated improved response with alemtuzumab, but reactivation of CMV and unacceptable infectious toxicities were noted, most notably deaths from infection among patients already in CR at the end of induction chemo immunotherapy.[80,81] A community-based clinical trial administering alemtuzumab after fludarabine and rituximab also demonstrated problematic infectious toxicity with combined chemo immunotherapy.[82] As a result, consolidation with alemtuzumab should only be undertaken in the context of a clinical trial.

Lenalidomide, a second-generation immunomodulatory agent with activity in both previously untreated and relapsed CLL, has recently been employed in the consolidation setting. A phase II study enrolled 44 patients to receive lenalidomide consolidation following induction with PCR for 6 cycles. Response improved in 21% of patients treated with consolidation, which was generally well-tolerated. Twelve-month freedom from retreatment (97%) compared favorably with historical PCR data, but the results have yet to fully mature.[83] The randomized frontline study of the North American intergroup (CALGB 10404) is also designed to explore the benefit of lenalidomide consolidation after fludarabine-based chemo immunotherapy.

Special Situations

Elderly/Infirm patients

Given that the median age at diagnosis of CLL is 72 years, efforts have been made to identify treatment regimens that are relatively non-toxic and easily administered to a patient population unable to tolerate more intensive cytotoxic therapy. The results of the GCLLSG CLL5 trial discussed above are telling: notwithstanding improved response, fludarabine proved no better than chlorambucil with respect to PFS and showed a near-significant trend toward worse overall survival.[84] As a result of that and other studies, single-agent chlorambucil remains a *de facto* standard of care for the initial treatment of elderly patients. Other studies, such as the FCR-lite and PCR studies already discussed, have shown that selected elderly patients may benefit from reduced-intensity chemo immunotherapies, particularly when supported with colony stimulating factors and antimicrobial prophylaxis. More recently, further studies specifically targeting the elderly population have explored chlorambucil or high-dose methylprednisolone in combination with rituximab. A cohort of 100 patients with a median age of 70.5 was treated with chlorambucil given daily for 7 days of a 4-week cycle with rituximab given on the first day of the first 6 cycles. Responding patients then continued single-agent chlorambucil for 6 additional cycles. The interim intention-to-treat analysis yielded an ORR of 82% -- 16% higher than a historical control population treated with chlorambucil alone -- but grade 3 or 4 neutropenia was still seen in 39% of patients.[85] In a separate study, the combination was given for 8 cycles followed by randomization of responding patients to maintenance rituximab every 2 months for 2 years versus observation. The study demonstrated an ORR of 81.4% with a CR in 16.7% and a CRi in 3.7%. Grade 3 neutropenia was seen in 16.7% of patients. The median age in this study was also 70.5 years.[86] Rituximab in combination with high-dose methylprednisolone (1 gm/m^2) has also been studied in elderly, untreated patients. An ORR of 96% with a CR rate of 32% was reported, with 2 of 28 patients achieving a minimal

residual disease (MRD) negative bone marrow result. Responses were similar when stratified based on high-risk features, including elevated ZAP-70 and CD38 expression, unmutated IGHV, unfavorable cytogenetics, and bulky lymphadenopathy.[87]

High Risk Patients

Patients with high genomic risk CLL, particularly those with del(17p13) where the median survival beyond diagnosis is only 32 months, tend to have more aggressive disease that progresses more quickly to require treatment, responds less well to treatment, and relapses sooner after initial therapy than CLL without these features.[8] Response to standard treatment with chemo immunotherapy is poor, and these patients should ideally be treated on a clinical trial. Younger, fit patients who have del(17p13) CLL are candidates for reduced-intensity allogeneic stem cell transplant first remission, as this modality appears to mitigate its adverse prognostic effect associated with the loss of *TP53*.[88] Much of what we know about treating high-risk disease has been learned in large clinical trials enrolling a heterogeneous patient population. More recently, therapies such as the CFAR regimen discussed above have been developed to specifically target this difficult to treat subgroup. Preliminary data from the GCLLSG CLL20 trial was recently presented. Patients with previously untreated del(17p13) or relapsed, fludarabine-refractory CLL were induced with a combination of alemtuzumab and dexamethasone given with growth factor support. Consolidation with either alemtuzumab given every 2 weeks or, for eligible patients, reduced-intensity allogeneic stem cell transplant followed. Sixty patients were evaluable for response with a median follow-up of 11 months. The ORR in previously untreated del17p13 patients was 96% with a CR rate of 24%. Fifty-two percent of patients had CMV reactivations, all of which were successfully treated.[89]

Expert Commentary

Fludarabine-based chemo immunotherapy with the fludarabine and rituximab or fludarabine, cyclophosphamide and rituximab combinations has emerged as the standard of care for the initial therapy of CLL among patients eligible for aggressive treatment. Such therapies are not only associated with unprecedented response rates in excess of 90% in well-controlled trials, but they are the first therapies for this disease to demonstrate both a progression-free and overall survival benefit. However, while these regimens are generally well tolerated, toxicity remains prohibitively significant for many patients with comorbid medical illness or at advanced age. In these populations, lower intensity approaches, such as single-agent alkylating agents (i.e. chlorambucil, bendamustine) or immunotherapy (i.e. rituximab) have been shown to produce more favorable outcomes. Ongoing trials will help to establish whether the addition or substitution of newer agents such as bendamustine (for fludarabine and cyclophosphamide) or of atumumab (for rituximab) can result in improved clinical outcomes or reduced toxicity. Notwithstanding the appeal of consolidation or maintenance therapies in a disease where all patients will ultimately relapse, the clinical benefit of such approaches remains to be determined. Given the unexpected toxicity reported in some consolidation trials, continuation therapy cannot be recommended outside the context of a clinical trial.

Genetic risk-stratification studies performed prior to commencing treatment have become essential in the selection of initial therapy. Patients with high-risk genetic abnormalities as detected by interphase FISH may benefit from specific therapies, such as the incorporation of an alkylating agent when treating cases positive for del(11q23). In the case of del(17p13) CLL, outcomes with most extant therapies are sufficiently poor that such patients should first be considered for investigational therapies, as well as reduced intensity conditioning allogeneic stem cell transplantation in first remission. Current and planned clinical trials now routinely incorporate genetic risk stratification, and the expected refinement of risk-adapted therapeutic approaches may not only improve outcomes for high-risk patients (such as the benefit of cyclophosphamide for del(11q23) CLL) but also limit toxicity (such as the increased risk for secondary malignancies in cyclophosphamide-treated patients) among patient subgroups not clearly benefiting. Other studies will also establish whether early initiation of treatment, prior to the patients' meeting commonly accepted indications, can alter the natural history of high-risk disease.

Five-year View

Chemo immunotherapy represents a significant advance in the treatment for CLL, and much of what will be learned over the next several years will build upon this backbone. Already, genetic risk stratification has helped refine the application of this important modality and improved the outcome of many patients with formerly poor prognosis disease. The emergence of uniquely efficacious cytotoxic agents (e.g. bendamustine) and more potent monoclonal antibodies (e.g. ofatumumab, GA-101) makes this an especially exciting era in the treatment of CLL, and outcomes from chemo immunotherapy are expected to improve as the results of ongoing clinical trials become available. Received wisdom based on now-dated clinical data dictates that there is no benefit to initiating therapy early in the course of asymptomatic disease, but ongoing studies applying therapies with unprecedented efficacy in that setting may alter such longstanding truisms.

Most exciting, however, are the ways in which new insights into the pathogenesis of the disease now impacting novel therapies for relapsed disease may potentially transform initial treatment. Signaling through the B-cell receptor likely represents a key event initiating, promoting and maintaining the CLL clone. Novel kinase inhibitors targeting signaling pathways downstream from the B-cell receptor, such as the spleen tyrosine kinase (Syk) (fostamatinib), phosphatidylinositol-3-delta (PI3δ) (CAL-101), and Bruton's tyrosine kinases (PCI 32765), have shown great promise in treating highly refractory disease, often with oral bioavailability and relatively modest toxicity. Several of these agents may further act by disrupting the interaction of CLL cells and their microenvironment, which is one likely mechanism of action accounting for the efficacy of the immunomodulatory agent lenalidomide in this disease. Lenalidomide has shown promising clinical activity in previously untreated disease, where it is associated not only with objective responses but also symptomatic improvement and restoration of immune impairment, a significant source of morbidity for CLL patients. Ongoing studies have already begun to explore the utility of these agents in treating treatment-naïve patients from special populations, where extant therapies result in suboptimal outcomes. Results of these studies are eagerly awaited and

may prove the beginning of a new era in which traditional cytotoxic agents are held in reserve.

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Key Issues

- Notwithstanding recent therapeutic advances, CLL remains an incurable disease, and treatment should only be initiated for symptomatic or progressive disease.
- Genetic risk stratification studies performed prior to starting treatment for CLL should inform the selection of initial therapy.
- Fludarabine- and rituximab-based chemo immunotherapy results in the highest response rates yet reported for CLL. Further, several large, controlled trials have now shown that such regimens convey a survival benefit in the frontline setting and should therefore constitute the standard of care for younger, fit patients.
- Incorporation of an alkylating agent (such as cyclophosphamide) into initial therapy may abrogate the adverse risk associated with deletion of chromosome 11q23.
- The optimal therapy for patients with del(17p13) CLL remains to be determined. Such patients should be referred for clinical trial where available, and eligible patients should be considered for reduced intensity allogeneic stem cell transplant in first remission.
- Older patients and those with comorbid medical illnesses present unique therapeutic challenges. Except for selected cases, more aggressive therapies do not convey the same therapeutic advantages for older patients. Lower intensity approaches, such as single-agent alkylating agents, or investigational therapies merit first consideration in this population.
- The role of consolidation or maintenance treatment with agents such as rituximab or alemtuzumab has not yet been established and should only be undertaken in the context of a clinical trial.
- Ongoing studies will help better refine risk-adapted treatment strategies using currently available agents, as well as establish the role for emerging therapies such as newer monoclonal antibodies, immunomodulatory agents, and protein kinase inhibitors.

Table 1

Clinical Staging Systems Used in Chronic Lymphocytic Leukemia (CLL)

Rai Staging System			**Binet Staging System**	
Risk Group	Stage	Definition	Stage	Definition
Low Risk	0	Lymphocytosis with leukemia cells in the blood or marrow	A	Hemoglobin ≥ 10g/dL, platelets ≥ 100,000/μL, and lymphadenopathy in up to 2 sites
Intermediate Risk	1	Lymphocytosis with lymphadenopathy at any site	B	Hemoglobin ≥ 10g/dL, platelets ≥ 100,000/μL, and lymphadenopathy in 3 or more sites*
	2	Lymphocytosis with organomegaly, with or without lymphadenopathy		
High Risk	3	Disease-related anemia	C	All patients who have hemoglobin < 10g/dL or platelets < 100,000/μL, regardless of lymphadenopathy
	4	Disease-related thrombocytopenia		

*Sites considered (bilateral involvement counts as one site): 1. Head and neck, including Waldeyer's ring; 2. Axillae; 3. Groin; 4. Palpable spleen; 5. Palpable liver

Table 2

Indications for Initiating Therapy in Previously Untreated CLL[18]

- Evidence of progressive marrow failure: development/worsening anemia or thrombocytopenia
- Massive (i.e. >6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (i.e., >10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of >50% over a 2-month period, or lymphocyte doubling time of less than 6 months
- Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy
- A minimum of any one of the following disease-related symptoms must be present:
  - Unintentional weight loss of >10% within the previous 6 months
  - Significant fatigue (i.e. ECOG performance status 2 or worse)
  - Fevers >100.5°F for 2 or more weeks without evidence of infection
  - Night sweats for >1 month without evidence of infection

Table 3

Chemo immunotherapy for Previously Untreated CLL

Regimen	Trial	N	ORR (%)	CR (%)	PFS (months)
FCR	MDACC[90,91]	300	95	72	80
	GCLLSG CLL8[59]	408	95	44	52
FR	CALGB 9712[52,53]	51	90	47	42
PCR	Mayo-Ohio State[63]	64	91	41	34
BR	GCLLSG CLL2M[92]	119	90	33	NR

ORR = overall response rate; CR = complete response; PFS = progression-free survival; F = fludarabine; P = pentostatin; B = bendamustine; C = cyclophosphamide; R = rituximab; NR = not reported; N = number treated with regimen of interest

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