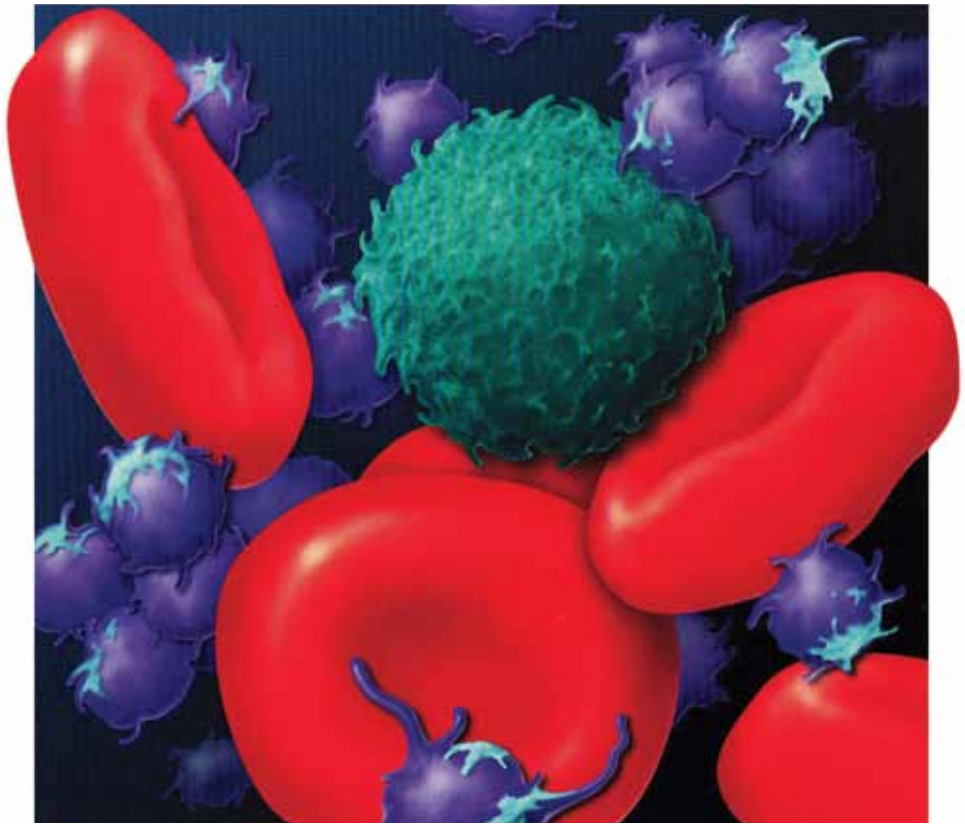
HOSPITAL PHYSICIAN®

Volume 7, Part 2 May 2012

HEMATOLOGY
Board Review Manual



Chronic Lymphocytic Leukemia

HOSPITAL PHYSICIAN®

HEMATOLOGY BOARD REVIEW MANUAL

STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Hematology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Internal Medicine.

Chronic Lymphocytic Leukemia

Series Editor:
Eric D. Jacobsen, MD
Instructor in Medicine, Harvard Medical School; Attending Physician, Dana-Farber Cancer Institute, Boston, MA

Contributors:
Kami J. Maddocks, MD
Assistant Professor of Internal Medicine, Division of Hematology, The Ohio State University, Columbus, OH

Samantha M. Jaglowski, MD
Assistant Professor of Internal Medicine, Division of Hematology, The Ohio State University, Columbus, OH

Table of Contents

Chronic Lymphocytic Leukemia

Kami J. Maddocks, MD, and Samantha M. Jaglowski, MD

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common hematologic malignancy in the Western world, representing 30% of leukemias.[1] The median age at diagnosis is 72 years, and fewer than 10% of patients are under 60. CLL occurs more frequently in Caucasians than in other ethnic groups and more often in men than in women. The age-adjusted incidence rate is 4.2 per 100,000 population.[2,3] Although CLL is generally considered indolent, it is a heterogeneous disease, and while many patients have slowly progressive disease, a proportion of patients have disease that will have a more aggressive course, requiring treatment soon after diagnosis. Over the past 3 decades, increasing knowledge about the mechanism of CLL and the introduction of new chemotherapeutic and biologic agents has led to better treatments, improved risk stratification, and more durable remissions. Despite these advances in treatment, CLL remains incurable outside the setting of hematopoietic stem cell transplant.[4]

DIAGNOSIS AND RISK STRATIFICATION

The diagnosis of CLL requires the presence of at least 5000 B lymphocytes/µL, and peripheral blood immunophenotyping must be performed to confirm their clonality. CLL cells express CD5, CD19, CD20, and CD23, with low expression of surface immunoglobulin, CD20, and CD79b, compared with normal B cells. CLL cells are small, mature-appearing lymphocytes with a dense nucleus, and smudge cells are a characteristic finding on a peripheral blood smear. Monoclonal B lymphocytosis comprises a population of patients who have a clonal B-cell population with fewer than 5000 lymphocytes/µL in the absence of lymphadenopathy or organomegaly. This progresses to CLL at a rate of 1% to 2% per year.[5]

The Rai and Binet systems are the 2 commonly used staging systems in CLL.[6,7] The Rai system, which originally had 5 subgroups, has been modified to 3, similar to the Binet scheme (**Table 1**). Genetic risk stratification should be done at diagnosis and prior to each new therapy, and can add important prognostic information to that obtained by traditional staging. Interphase cytogenetics, as determined by fluorescent in-situ hybridization (FISH), not only provides prognostic information, but may also influence therapeutic decisions. Del(13q14) is the most common abnormality and conveys a favorable prognosis when occurring in isolation. In contrast, patients with del(11q23) or del(17p13) abnormalities, resulting in the loss of the tumor suppressor genes *ATM* and *TP53*, respectively, frequently have more aggressive disease, progress to requiring treatment faster, and experience inferior progression-free and overall survival with standard therapies.[8] While patients with del(13q14) have a median survival of 133 months beyond diagnosis, patients with del(17p13) have a median survival of only 32 months beyond diagnosis.[9]

In addition to FISH, important prognostic information is conferred by the mutational status of the immunoglobulin heavy chain variable region (IGVH) genes. CLL patients with IGVH genes which have not undergone somatic hypermutation ("unmutated") have inferior survival compared to those with mutated IGVH genes.[10] Patients with unmutated IGVH are prone to acquiring additional karyotypic abnormalities on metaphase cytogenetics, a process known as "clonal evolution."[11] IGVH testing is not universally available, so expression of ZAP-70 and/or CD38 as measured by either flow cytometry or immunohistochemistry is often used as a surrogate marker.[12,13] Serum markers such as CD23, thymidine kinase, and β2-microglobulin may have prognostic value and have been evaluated in several large clinical trials.[14–17] While bone marrow biopsy is recommended prior to starting therapy, it is typically not done at diagnosis in the absence of cytopenias.[18]

TREATMENT

WHEN TO TREAT

Contrary to other forms of leukemia, many patients with CLL are initially observed following diagnosis.

Table 1. Clinical Staging Systems Used in Chronic Lymphocytic Leukemia

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 ≥10 g/dL, platelets ≥100,000/μL, and lymphadenopathy in up to 2 sites
Intermediate Risk	I	Lymphocytosis with lymphadenopathy at any site	B	Hemoglobin ≥10 g/dL, platelets ≥100,000/μL, and lymphadenopathy in 3 or more sites*
	II	Lymphocytosis with organomegaly, with or without lymphadenopathy		
High Risk	III	Disease-related anemia	C	All patients who have hemoglobin <10 g/dL or platelets <100,000/μL, regardless of lymphadenopathy
	IV	Disease-related thrombocytopenia		

*Sites considered (bilateral involvement counts as 1 site): (1) head and neck, including Waldeyer's ring; (2) axillae; (3) groin; (4) palpable spleen; (5) palpable liver.

Adapted with permission from Jaglowski S, Jones JA. Choosing first-line therapy for chronic lymphocytic leukemia. Expert Rev Anticancer Ther 2011;11:1379–90.

To date, no demonstrable survival benefit has been observed when treatment is initiated for early-stage, asymptomatic CLL. While early use of chlorambucil with or without prednisone can slow disease progression, 2 trials randomly assigning patients with untreated Binet stage A CLL to receive treatment with chlorambucil versus observation, which is the standard of care, failed to demonstrate a survival benefit with early treatment.[19] This was confirmed by a meta-analysis of 6 studies evaluating the effect of early treatment with chlorambucil.[20] According to a recently published study, treating early-stage patients with higher-risk disease (β2-microglobulin level ≥2 mg/dL) with single-agent rituximab, an anti-CD20 monoclonal antibody, is safe, but further studies are needed to demonstrate whether this can impact survival.[21] The ongoing German CLL Study Group (GCLLSG) CLL7 trial is randomly assigning recently diagnosed high-risk patients (determined by FISH, IGVH mutation status, serum thymidine kinase, and lymphocyte doubling time) to receive combination chemoimmunotherapy versus observation. Accrual is ongoing. CALGB-10501 in the United States was designed to assess the benefits of early treatment with fludarabine and rituximab among patients with unmutated IGVH, but the trial closed early secondary to poor enrollment.

The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) has developed guidelines to help determine the appropriate time to start treatment. The IWCLL recommends that therapy be initiated for Binet stage C or Rai high-risk disease, as well as for patients with active or "progressive" disease (**Table 2**). Progressive CLL is defined as meeting 1 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 lymphocyte doubling time of less than 6 months
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to steroids or other standard therapy
- Development of constitutional symptoms, including a greater than 10% weight loss within 6 months, significant fatigue, fevers higher than 100.5°F over a 2-week period without other evidence of infection, or night sweats for more than 1 month without other evidence of infection.

For patients with initial lymphocyte counts under 30,000/μL, the lymphocyte doubling time should not be used as a single indicator for initiating treatment, and 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]

FRONT-LINE TREATMENT

Chlorambucil

Chlorambucil was the mainstay of treatment for CLL for many years. In 1977, a randomized study comparing chlorambucil, given daily or intermittently,

Table 2. Indications for Initiating Therapy in Previously Untreated Chronic Lymphocytic Leukemia

Evidence of progressive marrow failure: development/worsening anemia or thrombocytopenia
Massive (ie, >6 cm below the left costal margin) or progressive or symptomatic splenomegaly
Massive nodes (ie, >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
Presence of a minimum of any one of the following disease-related symptoms:
Unintentional weight loss of >10% within the previous 6 months
Significant fatigue (ie, Eastern Cooperative Oncology Group [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

Adapted from Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446–56.

and prednisone to prednisone alone in previously untreated patients with Rai stage III and IV CLL was published. Responses were superior with chlorambucil compared with prednisone alone (55% for intermittent chlorambucil, 40% for daily chlorambucil, and 6% for prednisone), but there was no statistically significant survival benefit in any of the treatment arms.[22] The CLL5 trial from the GCLLSG evaluated fludarabine versus chlorambucil in patients over the age of 65. While treatment with fludarabine resulted in higher response rates, with a 72% overall response rate (ORR) versus 51% for chlorambucil (P = 0.003) and 7% complete response (CR) versus 0% for chlorambucil (P = 0.011), there was no statistically significant difference in progression-free survival (PFS). Toxicity was significantly higher among patients who received fludarabine, and there was a nonsignificant trend toward worse overall survival (OS) in that arm, suggesting that chlorambucil still has a role in the front-line therapy of CLL for elderly or otherwise infirm patients who cannot tolerate more intensive therapy.[23]

Fludarabine

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 ORR of 79%.[24] On longer follow-up, a 63-month median survival following treatment with fludarabine was observed, with a median time-to-progression of 31 months among responders, and many patients responded to rechallenge with fludarabine when treated after relapse.[25] When compared with chlorambucil as front-line therapy in a phase III study, fludarabine was found to result in improved overall response and PFS, with 73% ORR and 20-month median PFS for fludarabine compared with 37% and 14 months, respectively, for chlorambucil. However, there was no statistically significant difference in OS.[26] In an attempt to improve upon these results, fludarabine was combined with cyclophosphamide. Among previously untreated patients with CLL treated with the combination in a phase II study, there was a 100% response rate, with 47% CR and 53% PR.[27] The combination versus fludarabine in previously untreated younger patients resulted in a higher response rate (24% CR and 94% ORR versus 7% CR and 90% ORR, P < 0.001), as well as a significantly longer median PFS (48 versus 20 months, P = 0.001), but again, no difference in OS was seen.[28] An important observation from this study, as well as from another randomized trial comparing fludarabine with combination fludarabine/cyclophosphamide, was the finding that the addition of cyclophosphamide appeared to abrogate the adverse prognosis associated with presence of del(11q23).[29,30]

Rituximab

Rituximab, a chimeric murine/human antibody directed against the CD20 antigen, was the first therapeutic antibody approved. CD20 is expressed relatively selectively on B cells from the pre-B-cell stage until postgerminal cells differentiate to become plasma cells.[31] The phase III study of rituximab in non-Hodgkin lymphomas (NHL) demonstrated promising clinical activity overall, but the response among the 33 patients with small lymphocytic lymphoma (SLL) was less impressive, with only 12% of patients achieving a PR.[32] In trials performed by Ohio State University and the MD Anderson

Cancer Center (MDACC), rituximab was administered at either thrice-weekly doses or higher weekly doses to relapsed CLL patients, with improved response,[33,34] establishing a role for single-agent rituximab in relapsed disease and encouraging further evaluation of the antibody, particularly in combination with conventional cytotoxic chemotherapies.[35]

The GCLLSG performed a phase II study combining fludarabine and rituximab (FR) in both refractory and previously untreated patients, resulting in an ORR of 87% with a subset achieving CR.[36] CALGB-9712, another phase II study, evaluated the FR combination in the upfront setting with the antibody given either concurrently or sequentially following fludarabine. While patients in the concurrent arm experienced more severe hematologic and infusion-related toxicity, the ORR was 90% with a CR rate of 47% compared with an ORR of 78% and CR rate of 28% in the sequential arm.[37] A retrospective comparison to a similarly designed CALGB study evaluating, in part, fludarabine alone demonstrated improved PFS and OS with chemoimmunotherapy compared to chemotherapy alone.[38,39]

Fludarabine/Cyclophosphamide/Rituximab Combination

The combination of fludarabine, cyclophosphamide, and rituximab (FCR) has been extensively explored. The combination resulted in an ORR of 95% in a phase II study of 300 previously untreated patients from the MDACC, with 72% of patients achieving a CR, 10% an nPR, and 13% a PR.[40] The 6-year OS and PFS were 77% and 51%, respectively.[40] Toxicity was mainly cytopenias and infection. Eight patients subsequently developed treatment-related myelodysplasia. Patients with del(11q23) appeared to benefit from FCR, with response rates approaching those of patients without that particular abnormality, again confirming that fludarabine and alkylator combinations may overcome the adverse prognosis observed in fludarabine-monotherapy studies.[41] However, patients with IGHV unmutated disease and del(17p13) had inferior survival following FCR.[40,42]

The phase III CLL8 study from the GCLLSG confirmed improved response rates and, for the first time, prospectively demonstrated improved OS with FCR when compared to treatment with fludarabine and cyclophosphamide (FC) combination.[43] Patients were aged 30 to 81 years with a median age of 61. Forty-four of the 408 patients receiving chemoimmunotherapy were over the age of 70. Both the ORR (95% versus 88%) and CR rate (52% versus 27%) significantly favored FCR. At a median observation time of 37 months, 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 OS at 3 years, 87.2% versus 82.5% (hazard ratio = 0.66, $P = 0.01$). Rituximab did not appear to lead to more infectious complications, and more deaths occurred in the FC arm (10 in the FC arm versus 8 in the FCR arm).[43] As with previous studies, patients with del(17p13) had a particularly poor outcome, and there was a trend towards shorter OS in patients with unmutated IGHV. Patients with del(11q23) again appeared to benefit from the addition of cyclophosphamide, with response rates approaching those of patients without del(11q23).[29] An ongoing randomized phase III study in the United States (CALGB-10404) is comparing FCR to FR in order to determine the importance of cyclophosphamide for patients who do not have del(11q23).

Pentostatin

Pentostatin is another nucleoside analog that has activity in CLL and may be less myelotoxic than fludarabine. Studies substituting pentostatin for fludarabine have been performed in both relapsed and untreated CLL.[44] 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 and an ORR of 91% and CR rate of 41% in patients with previously untreated disease. The major toxicities, myelosuppression and infections, were similar in both cohorts.[45] The reported toxicities, as well as the fraction of patients completing therapy, was similar in patients above and below the age of 70. As noted with both FC and FCR, patients with del(11q23) demonstrated similar response rates and PFS as those without this abnormality.[45]

Bendamustine

Bendamustine is a bifunctional chemotherapeutic agent with both alkylator and purine analog–like properties. Following demonstration of safety and efficacy with the use of single-agent bendamustine in heavily pretreated patients with relapsed CLL,[46] a randomized phase III study comparing bendamustine with chlorambucil in previously untreated patients demonstrated that 31% 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.[47] Bendamustine was approved by the U.S. Food and Drug Administration (FDA) for use in previously untreated CLL

on the basis of this study. Following its approval, pilot studies combining this agent with rituximab have been performed in previously untreated patients, where a 90% ORR and 33% CR rate were observed.[48] Toxicity, chiefly myelosuppression and infection, compared favorably with other commonly used chemoimmunotherapy combinations. While patients with del(17p13) abnormalities had inferior outcomes, 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

Alemtuzumab is a recombinant humanized IgG_1 kappa monoclonal antibody targeted against CD52, a cell surface antigen which 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.[49,50] It is also expressed on tumor cells, including T-cell prolymphocytic leukemia (T-PLL), CLL, hairy cell leukemia, NHL, and acute lymphoblastic leukemia (ALL).[51] Alemtuzumab showed significant activity in several pilot studies in previously untreated CLL,[52,53] prompting a phase III study evaluating IV alemtuzumab versus chlorambucil in untreated CLL patients.[54] Patients who received alemtuzumab 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) were both superior for alemtuzumab. Notably, patients with del(17p13) had better responses with alemtuzumab treatment compared with chlorambucil. 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. There were no differences in terms of grade 3 or 4 hematologic toxicities between the 2 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 cytomegalovirus (CMV) polymerase chain reaction test compared with 7.5% of the patients treated with chlorambucil.

Because of its activity in genomic high-risk disease, alemtuzumab has been added to several fludarabine-based combination therapies, particularly for higher-risk patients (reviewed in Alinari et al[55]). While this strategy appears feasible, it remains uncertain whether the addition of alemtuzumab significantly improves outcomes. Building on the FCR backbone, the MDACC group developed the CFAR (cyclophosphamide, fludarabine, alemtuzumab, and rituximab) regimen for patients with relapsed disease.[56] In a study of CFAR in previously untreated patients with high-risk disease, including patients with del(17p13) or β2-microglobulin higher than twice the upper limit of normal, the 92% ORR and 70% CR rate were comparable to rates reported for FCR. While 52% of patients with del(17p13) attained CR, the 18-month median time to progression was inferior to the 38 months observed among all evaluable patients.[57] A French group conducted a randomized study comparing the FCR regimen to a regimen substituting alemtuzumab for rituximab (FC-Cam).[58] The study was discontinued early after an excess of deaths in the FC-Cam arm, but the FCR arm appeared superior in terms of efficacy. ORR and CR rates in the FCR group (91% and 74%, respectively) were significantly higher than those reported for FC-Cam–treated patients (85% and 58%, respectively). 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% unconfirmed CR, and 35% PR, independent of FISH status. Twelve of 56 patients died during or within 6 months following their final chemotherapy. Five of these deaths were attributed to therapy.[59] The combination of alemtuzumab and rituximab has also been evaluated by several groups, which found improved response versus the single agents, but the clinical benefit remains unclear.[60–62] Until further phase III studies comparing these or other alemtuzumab-containing combinations to present treatment standards have demonstrated superiority and 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 1 of 2 doses of ofatumumab (500 and 1000 mg/m^2) in combination with standard-dose FC. Overall response rates (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; thus, ofatumumab should not be substituted for rituximab outside the setting of a clinical trial. Ofatumumab by itself is not approved for upfront use in CLL.[63]

MAINTENANCE AND CONSOLIDATION STRATEGIES

Because all patients with CLL will ultimately relapse following initial therapy, consolidation and/or maintenance strategies are appealing. The use of maintenance rituximab has become the standard of care in follicular lymphoma following large controlled trials demonstrating a significant PFS improvement compared with observation.[64] No randomized controlled trials have been completed to date to determine whether there is a similar benefit in CLL/SLL. In a phase II study of 75 previously untreated patients, all patients received 4 weekly doses of rituximab at 375 mg/m^2 following 6 cycles of fludarabine, and those with minimal residual disease (MRD) went on to consolidation with 4 monthly cycles of 375 mg/m^2 rituximab followed by 12 monthly cycles of 150 mg/m^2.[65] 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; however, 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 Alinari and colleagues[55]). A study of alemtuzumab administered at 10 or 30 mg intravenously 3 times weekly to CLL patients with residual disease after their most recent therapy resulted in an ORR of 46%, with 11 of 29 patients treated with 30 mg achieving an MRD-negative marrow.[66] Infections, including CMV reactivation, occurred in 37% of patients, and 3 patients developed Epstein-Barr virus–positive large B-cell lymphoma. The phase II NCRN CLL207 trial evaluated the use of alemtuzumab consolidation in patients with MRD-positive marrow after treatment.[67] 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 an at least 1 log reduction in MRD continued therapy. Thirty-six percent of patients experienced a significant adverse event, including 2 treatment-related deaths (EBV lymphoproliferative disorder and parainfluenza 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.[67] The GCLLSG performed a phase III trial where patients responding to fludarabine-based induction therapy were randomized to receive alemtuzumab 30 mg IV 3 times weekly for a maximum of 12 weeks or observation.[68] While this study was closed prematurely because of severe infections in the alemtuzumab arm, among the patients treated (n = 21), alemtuzumab consolidation appeared to improve both the quality of response as well as the duration of PFS.[69] The CALGB has performed 2 studies administering alemtuzumab after fludarabine or fludarabine and rituximab.[70] While improved response was noted with alemtuzumab in both studies, reactivation of CMV and unacceptable infectious toxicities occurred, most notably deaths from infection among patients already in CR at the end of induction chemoimmunotherapy.[70,71] This problematic infectious toxicity was also observed in a community-based clinical trial administering alemtuzumab after fludarabine and rituximab.[72] Accordingly, 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 been evaluated in the consolidation setting as well. In a phase II study, 44 patients received lenalidomide consolidation following induction with 6 cycles of PCR. Response improved in 21% of patients treated with consolidation, which was generally well-tolerated, but the results have yet to fully mature.[73] The randomized frontline study of the North American intergroup evaluating FR versus FCR (CALGB 10404) has a third arm designed to explore the benefit of lenalidomide consolidation after fludarabine-based chemoimmunotherapy.

TREATMENT FOR RELAPSED OR REFRACTORY DISEASE

Despite advances in first-line therapy for CLL, patients invariably relapse and often acquire high-risk chromosomal abnormalities, resulting in resistance to therapy. Patients who have fludarabine-refractory disease have a median survival of less than 1 year. It is important to emphasize that the IWCLL criteria for initiating therapy in previously untreated patients also apply to patients with relapsed CLL. Thus, asymptomatic relapsed patients should be observed, and treatment should be initiated only upon development of cytopenias or symptoms.

Rituximab has proven effective as an agent used for retreatment; 58 patients with NHL who were previously treated with rituximab and relapsed were retreated with 4 weekly doses of rituximab at 375 mg/m^2. The overall response was 40%, with 11% CR and 30% PR.[74] In a study of relapsed CLL patients, lymphocyte count was reduced by 50%, with a response duration of at least 4 weeks in 13 of 29 patients, but the overall median response was only 20 weeks in the 7 patients who achieved a PR.[75] Of 177 previously treated patients given FCR in a phase II study from the MDACC, CR was achieved in 25% of patients with an ORR of 73%, and of the 37 complete responders, 32% had molecular complete remissions.[76] The international phase III REACH trial compared FC to FCR in 552 patients with relapsed or refractory CLL. Treatment with FCR resulted in an ORR of 70%, versus 58% for FC alone, and the CR rates were 24% versus 13% for FCR and FC, respectively. The observed PFS in the FCR arm was 30.6 months compared with 20.6 months in the FC arm.[77] Hematologic toxicities were the most significant adverse events, similar to what was seen in the upfront FCR trials.

Alemtuzumab was initially approved following the CAM 211 study in which 93 patients with relapsed or refractory CLL following treatment with fludarabine and an alkylating agent were treated with a 1-week dose escalation followed by 30 mg 3 times weekly for an additional 11 weeks.[78] The ORR was 33% (2% CR, 31% PR) with a median response duration of 8.7 months. The most common adverse events noted were infusional toxicity, followed by cytopenias and infections resulting from profound cellular immune suppression. Reactivation of herpes viruses, including CMV, as well as other opportunistic infections was noted. Prophylaxis against opportunistic infections, together with monitoring for CMV reactivation, is highly recommended during and after treatment with alemtuzumab. Treatment with valganciclovir 450 mg orally twice daily can provide effective prophylaxis against CMV reactivation, but can exacerbate disease- or treatment-related cytopenias.[79] Because of the infusional toxicities, interest in subcutaneous administration of alemtuzumab ultimately led to a phase II study by the GCLLSG,[80] where 103 patients with fludarabine-refractory CLL received at least 1 dose of alemtuzumab, administered subcutaneously at 30 mg 3 times weekly for up to 12 weeks. The ORR was 34% (4% CR, 30% PR). The median PFS was 7.7 months and the median OS was 19.1 months. This trial confirmed earlier studies that alemtuzumab was effective for del(17p13.1) CLL.[81,82]

A phase I/II study of ofatumumab therapy in relapsed/refractory patients demonstrated that it is generally well tolerated, even at high doses, and it is efficacious in refractory patients, with an ORR of 50%. Infusion-related adverse events are similar to those reported with rituximab and decreased following the first infusion. Infections were common, with 51% of patients reporting infections, one of which was fatal (infectious interstitial lung disease).[83] Ofatumumab has been demonstrated to be efficacious in patients with fludarabine- and alemtuzumab-refractory or bulky fludarabine-refractory (BFR) CLL, regardless of whether those patients had previously been treated with rituximab. Fifty-eight percent of patients treated in a phase II study with double refractory (DR) CLL responded, as did 47% of BFR patients. Fifty-nine percent and 54% of DR and BFR patients, respectively, had been previously exposed to rituximab with no significant differences in ORR or PFS between the groups.[84,85] National Comprehensive Cancer Network (NCCN) guidelines support the use of ofatumumab in patients with relapsed or refractory disease.

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 requires treatment sooner, has an inferior response to treatment, and relapses sooner following initial therapy.[8] Response to standard treatment is poor, and these patients should ideally be treated in a clinical trial. Due to the poor prognosis associated with del(17p13), younger, fit patients should be considered for reduced-intensity allogeneic stem cell transplant in first remission, as several studies have demonstrated that transplant can mitigate the poor prognosis associated with the loss of *TP53*.[86] Additionally, patients who relapse within 2 years of intensive chemoimmunotherapy should be considered for transplant in second remission. Of note, an OS advantage has never been demonstrated with autologous transplant in CLL, but several randomized studies have demonstrated an event-free survival benefit when autologous transplant is used in first remission for younger patients with high-risk disease who have achieved at least a very good partial remission.[87–90] Autologous transplant for CLL is not included in NCCN guidelines and should only be pursued as part of a clinical trial.

COMPLICATIONS AND SUPPORTIVE CARE

Autoimmune complications seen in patients with CLL include autoimmune hemolytic anemia (AIHA),

immune thrombocytopenic purpura (ITP), and much less commonly pure red blood cell aplasia (PRCA).[91] Evaluation when AIHA is suspected should include direct antiglobulin test (DAT), measurement of serum lactate dehydrogenase and haptoglobin levels, and reticulocyte count. Bone marrow evaluation should be done for all suspected immune cytopenias.[92] Corticosteroids are effective first-line treatment for autoimmune cytopenias, and most patients with AIHA or ITP can be managed with these. Rituximab, intravenous immunoglobulin (IVIG), splenectomy, or cyclosporine can be considered in steroid-refractory cases.[93] Synthetic thrombopoietin-like agents such as romiplostim are reserved for refractory cases of ITP.[94] Purine analog–based therapy has been associated with AIHA, although it is not contraindicated in patients with a history of AIHA. However, such patients who receive purine analog–based therapy should be monitored carefully and this therapy should be discontinued if AIHA is severe.[95]

Infectious complications are increased in patients with CLL and are related to the reduction in immunoglobulin levels seen in these patients.[96] In fact, infection is the leading cause of death in patients with CLL. For prevention of infections, measures to be considered include vaccination, prophylactic medications, and intravenous immunoglobulin (IVIG). Vaccinations against influenza and pneumococcus are recommended and live vaccines should be avoided.[97] Antiviral prophylaxis with acyclovir or equivalent and *Pneumocystis carinii* pneumonia prophylaxis with sulfamethoxazole/trimethoprim or equivalent is recommended for patients receiving purine-analog therapy and/or alemtuzumab during treatment and thereafter. CMV reactivation is seen with alemtuzumab therapy, and regular monitoring for CMV infection with polymerase chain reaction testing should be done with patients on therapy. Prophylaxis with ganciclovir can be considered but at this time is controversial.[79] Lastly, IVIG has been associated with a significant decrease in occurrence of infections but no improvement in OS.[98] In patients with serum IVIG less than 500 mg/dL with recurrent infections requiring treatment or hospitalization, guidelines recommend monitoring IVIG levels and administration of monthly IVIG to maintain nadir levels of 500 mg/dL.

CONCLUSION

CLL is a heterogeneous disease, and while some patients have an indolent disease course, others progress quickly to requiring treatment. Disease course and response to therapy can often be predicted through risk stratification, including traditional staging as well as genomic risk stratification, including interphase cytogenetics and somatic hypermutation of the IGVH gene. As patients can acquire cytogenetic abnormalities, FISH should be done in patients at diagnosis and prior to any treatment. The IWCLL has provided guidelines that help practitioners determine when to start treatment, and for the first time, an OS benefit has been shown in patients who receive rituximab in combination with conventional therapy including fludarabine and cyclophosphamide. Additionally, a host of other agents, including bendamustine, alemtuzumab, and ofatumumab have been approved for use in CLL in the past few years, improving treatment options for these patients. Younger, fit patients with del(17p13) in first remission or those who relapse within 2 years of chemoimmunotherapy should be considered for reduced-intensity allogeneic stem cell transplant. In addition to treatment of disease, complications of CLL that need to be considered and potentially treated include autoimmune cytopenias and infectious complications. CLL remains incurable outside of the setting of an allogeneic stem cell transplant and ongoing studies of novel therapeutics remain a high priority in this disease. In the coming years, new insights into the pathogenesis of CLL will likely further alter our approach to treating this disease, and agents targeting various steps in the B-cell receptor signaling pathway are currently showing great promise in early phase studies.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic. Go to www.turner-white.com and select Hematology from the drop-down menu of specialties.

REFERENCES

1. O'Brien S, del Giglio A, Keating M. Advances in the biology and treatment of B-cell chronic lymphocytic leukemia. Blood 1995;85:307–18.
2. Rozman C, Montserrat E. Chronic lymphocytic leukemia. N Engl J Med 1995;333:1052–7.
3. Montserrat E, Gomis F, Vallespi T, et al. Presenting features and prognosis of chronic lymphocytic leukemia in younger adults. Blood 1991;78:1545–51.
4. Zenz T, Mertens D, Kuppers R, et al. From pathogenesis to treatment of chronic lymphocytic leukaemia. Nat Rev Cancer 2010;10:37–50.
5. Rawstron AC, Bennett FL, O'Connor SJ, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med 2008;359:575–83.

6. Rai KR, Montserrat E. Prognostic factors in chronic lymphocytic-leukemia. Semin Hematol 1987;24:252–6.
7. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198–206.
8. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910–6.
9. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2010:481–8.
10. Hamblin TJ, Davis Z, Gardiner A, et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999;94:1848–54.
11. Shanafelt TD, Witzig TE, Fink SR, et al. Prospective evaluation of clonal evolution during long-term follow-up of patients with untreated early-stage chronic lymphocytic leukemia. J Clin Oncol 2006;24:4634–41.
12. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999;94:1840–7.
13. Crespo M, Bosch F, Villamor N, et al. ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. N Engl J Med 2003;348:1764–75.
14. Wierda WG, O'Brien S, Wang X, et al. Characteristics associated with important clinical end points in patients with chronic lymphocytic leukemia at initial treatment. J Clin Oncol 2009;27:1637–43.
15. Hallek M, Langenmayer I, Nerl C, et al. Elevated serum thymidine kinase levels identify a subgroup at high risk of disease progression in early, nonsmoldering chronic lymphocytic leukemia. Blood 1999;93:1732–7.
16. Reinisch W, Willheim M, Hilgarth M, et al. Soluble CD23 reliably reflects disease activity in B-cell chronic lymphocytic leukemia. J Clin Oncol 1994;12:2146–52.
17. Sarfati M, Chevret S, Chastang C, et al. Prognostic importance of serum soluble CD23 level in chronic lymphocytic leukemia. Blood 1996;88:4259–64.
18. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446–56.
19. Dighiero G, Maloum K, Desablens B, et al. Chlorambucil in indolent chronic lymphocytic leukemia. French Cooperative Group on Chronic Lymphocytic Leukemia. N Engl J Med 1998;338:1506–14.
20. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group. J Natl Cancer Inst 1999;91:861–8.
21. Ferrajoli A, Keating MJ, O'Brien S, et al. Experience with rituximab immunotherapy as an early intervention in patients with Rai stage 0 to II chronic lymphocytic leukemia. Cancer 2011;117:3182–6.
22. Sawitsky A, Rai KR, Glidewell O, Silver RT. Comparison of daily versus intermittent chlorambucil and prednisone therapy in the treatment of patients with chronic lymphocytic leukemia. Blood 1977;50:1049–59.
23. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009;114:3382–91.
24. Keating MJ, Kantarjian H, O'Brien S, et al. Fludarabine: a new agent with marked cytoreductive activity in untreated chronic lymphocytic leukemia. J Clin Oncol 1991;9:44–49.
25. Keating MJ, O'Brien S, Lerner S, et al. Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. Blood 1998;92:1165–71.
26. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000;343:1750–7.
27. Flinn IW, Byrd JC, Morrison C, et al. Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. Blood 2000;96:71–75.
28. Eichhorst BF, Busch R, Hopfinger G, et al. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. Blood 2006;107:885–91.
29. Stilgenbauer S, Zenz T, Winkler D, et al. Genomic aberrations, VH mutation status and outcome after fludarabine and cyclophosphamide (FC) or FC plus rituximab (FCR) in the CLL8 trial (abstract). Blood 2008;112:781.
30. Oscier D, Wade R, Davis Z, et al. Prognostic factors identified three risk groups in the LRF CLL4 trial, independent of treatment allocation. Haematologica 2010;95:1705–12.
31. Jaglowski SM, Alinari L, Lapalombella R, et al. The clinical application of monoclonal antibodies in chronic lymphocytic leukemia. Blood 2000;116:3705–14.
32. Berinstein NL, Grillo-Lopez AJ, White CA, et al. Association of serum rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1998;9:995–1001.
33. Byrd JC, Murphy T, Howard RS, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol 2001;19:2153–64.
34. O'Brien SM, Kantarjian H, Thomas DA, et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 2001;19:2165–70.
35. Hainsworth JD, Litchy S, Barton JH, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2003;21:1746–51.
36. Schulz H, Klein SK, Rehwald U, et al. Phase 2 study of a combined immunochemotherapy using rituximab and fludarabine in patients with chronic lymphocytic leukemia. Blood 2002;100:3115–20.
37. Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6–14.
38. Byrd JC, Rai K, Peterson BL, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood 2005;105:49–53.
39. Woyach JA, Ruppert AS, Heerema NA, et al. Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: long-term follow-up of CALGB study 9712. J Clin Oncol 2011;29:1349–55.
40. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the

fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112:975–80.
41. Tsimberidou AM, Tam C, Abruzzo LV, et al. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. Cancer 2009;115:373–80.
42. Lin KI, Tam CS, Keating MJ, et al. Relevance of the immunoglobulin VH somatic mutation status in patients with chronic lymphocytic leukemia treated with fludarabine, cyclophosphamide, and rituximab (FCR) or related chemoimmunotherapy regimens. Blood 2009;113:3168–71.
43. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164–74.
44. Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24:1575–81.
45. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 2007;109:405–11.
46. Bergmann MA, Goebeler ME, Herold M, et al. Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. Haematologica 2005;90:1357–64.
47. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378–84.
48. Fischer K, Cramer P, Stilgenbauer S, et al. Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: a multicenter phase II trial of the German CLL Study Group (GCLLSG) (abstract). Blood 2009;114:89.
49. Rossmann ED, Lundin J, Lenkei R, Mellstedt H, Osterborg A. Variability in B-cell antigen expression: implications for the treatment of B-cell lymphomas and leukemias with monoclonal antibodies. Hematol J 2001;2:300–6.
50. Ambrose LR, Morel AS, Warrens AN. Neutrophils express CD52 and exhibit complement-mediated lysis in the presence of alemtuzumab. Blood 2009;114:3052–5.
51. Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. J Clin Pathol 1998;51:364–9.
52. Osterborg A, Fassas AS, Anagnostopoulos A, et al. Humanized CD52 monoclonal antibody Campath-1H as first-line treatment in chronic lymphocytic leukaemia. Br J Haematol 1996;93:151–3.
53. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100:768–73.
54. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616–23.
55. Alinari L, Lapalombella R, Andritsos L, et al. Alemtuzumab (Campath-1H) in the treatment of chronic lymphocytic leukemia. Oncogene 2007;26:3644–53.
56. Badoux XC, Keating M, O'Brien S, et al. Chemoimmunotherapy with cyclophosphomide, fludarabine, alemtuzumab and rituximab (CFAR) is effective in relapsed patients with chronic lymphocytic leukemia (CLL) (abstract). Blood 2009;114:3431.
57. Parikh SA, Keating M, O'Brien S, et al. Frontline combined chemoimmunotherapy with fludarabine, cyclophosphamide, alemtuzumab and rituximab (CFAR) in high-risk chronic lymphocytic leukemia (abstract). 2009;114:91.
58. Remi L, Lepretre S, Christine A, et al. CLL2007FMP, a phase III randomized multicentric trial of the French Cooperative Group On CLL and WM (FCGCLL/MW) and the "Groupe Ouest-Est D'etudes Des Leucemies Aigues Et Autres Maladies Du Sang" (GOELAMS): Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) yields a significantly better response than fludarabine (F), cyclophosphamide (C) and mabcampath (Cam) (FCCam) in previously untreated B-chronic lymphocytic leukemia patients as evaluated by a sensitive 6 color flow cytometry MRD. Blood. ASH Annual Meeting Abstracts 2010;116:698.
59. Elter T, James R, Stilgenbauer S, et al. Chemoimmuno-therapy with fludarabine, cyclophosphamide and alemtuzumab (FC-Cam) in patients with relapsed or genetic high-risk CLL: final analysis of the CLL2L Trial of the German CLL Study Group (abstract). Blood 2009;114:209.
60. Zent CS, Call TG, Shanafelt TD, et al. Early treatment of high-risk chronic lymphocytic leukemia with alemtuzumab and rituximab. Cancer 2008;113:2110–8.
61. Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 2003;101:3413–5.
62. Faderl S, Ferrajoli A, Wierda W, et al. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence. Cancer 2010;116:2360–5.
63. Wierda WG, Kipps TJ, Durig J, et al. Chemoimmunotherapy with ofatumumab, fludarabine, and cyclophosphamide (O-FC) in previously untreated patients with chronic lymphocytic leukemia. Blood 2011;117:6450–8.
64. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377:42–51.
65. Del Poeta G, Del Principe MI, Buccisano F, et al. Consolidation and maintenance immunotherapy with rituximab improve clinical outcome in patients with B-cell chronic lymphocytic leukemia. Cancer 2008;112:119–28.
66. O'Brien SM, Kantarjian HM, Thomas DA, et al. Alemtuzumab as treatment for residual disease after chemotherapy in patients with chronic lymphocytic leukemia. Cancer 2003;98:2657–63.
67. Varghese AM, Cohen D, Pocock CFE, et al. NCRN CLL207 study of alemtuzumab consolidation in CLL: final response assessment and early follow-up (on Behalf of the NCRI CLL Trials Sub-Group) (abstract). Blood 2010;116:60.
68. Wendtner CM, Ritgen M, Schweighofer CD, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission–experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia 2004;18:1093–101.
69. Schweighofer CD, Ritgen M, Eichhorst BF, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission: long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG). Br J Haematol 2009;144:95–98.
70. Lin TS, Donohue KA, Byrd JC, et al. Consolidation therapy with subcutaneous (SC) alemtuzumab after fludarabine and rituximab

(FR) induction therapy improves the complete response (CR) rate in chronic lymphocytic leukemia (CLL) and eradicates minimal residual disease (MRD) but is associated with severe infectious toxicity: final analysis of CALGB Study 10101 (abstract). Blood 2009;114:210.

71. Byrd JC, Peterson BL, Rai KR, et al. Fludarabine followed by alemtuzumab consolidation for previously untreated chronic lymphocytic leukemia: final report of Cancer and Leukemia Group B study 19901. Leuk Lymphoma 2009;50:1589–96.
72. Hainsworth JD, Vazquez ER, Spigel DR, et al. Combination therapy with fludarabine and rituximab followed by alemtuzumab in the first-line treatment of patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase 2 trial of the Minnie Pearl Cancer Research Network. Cancer 2008;112:1288–95.
73. Shanafelt T, Tun H, Hanson C, et al. Lendalidomide consolidation after first-line chemoimmunotherapy for patients with previously untreated CLL (abstract). Blood 2010;116:1379.
74. Davis TA, Grillo-Lopez AJ, White CA, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. J Clin Oncol 2000;18:3135–43.
75. Huhn D, von Schilling C, Wilhelm M, et al. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. Blood 2001;98:1326–31.
76. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. J Clin Oncol 2005;23:4070–8.
77. Robak T, Moiseev SI, Dmoszynska A, et al. Rituximab, fludarabine, and cyclophosphamide (R-FC) prolongs progression free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: final results from the international randomized phase III REACH Trial (abstract). Blood 2008;112:lba-1.
78. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002;99:3554–61.
79. O'Brien S, Ravandi-Kashani F, Wierda WG, et al. A randomized trial of valacyclovir versus valganciclovir to prevent CMV reactivation in patients with CLL receiving alemtuzumab (abstract). Blood 2005;106:2960.
80. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2009;27:3994–4001.
81. Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood. 2004;103:3278–81.
82. Stilgenbauer S, Dohner H. Campath-1H-induced complete remission of chronic lymphocytic leukemia despite p53 gene mutation and resistance to chemotherapy. N Engl J Med 2002;347:452–3.
83. Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008;111:1094–100.
84. Kipps TJ, Osterborg A, Mayer J, et al. Clinical improvement with a novel CD20 mAb, ofatumumab, in fludarabine-refractory chronic lymphocytic leukemia (CLL) also refractory to alemtuzumab or with bulky lymphadenopathy. J Clin Oncol (Meeting Abstracts). 2009;27:7043.
85. Wierda WG, Kipps T, Mayer J, et al. Activity of ofatumumab, a novel CD20 mAb, and prior rituximab exposure in patients with fludarabine- and alemtuzumab-refractory or bulky fludarabine-refractory chronic lymphocytic leukemia (CLL). J Clin Oncol (Meeting Abstracts). 2009;27:7044.
86. Dreger P, Dohner H, Ritgen M, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood 2010;116:2438–47.
87. Michallet M, Dreger P, Sutton L, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. Blood 2011;117:1516–21.
88. Sutton L, Chevret S, Tournilhac O, et al. Autologous stem cell transplantation as a first-line treatment strategy for chronic lymphocytic leukemia: a multicenter, randomized, controlled trial from the SFGM-TC and GFLLC. Blood 2011;117:6109–19.
89. Brion A, Mahe B, Kolb B, et al. Autologous transplantation in CLL patients with B and C Binet stages: final results of the prospective randomized GOELAMS LLC 98 trial. Bone Marrow Transplant 2011 Jul 4. doi: 10.1038/bmt.2011.117. [Epub ahead of print]
90. Gladstone DE, Fuchs E. Hematopoietic stem cell transplantation for chronic lymphocytic leukemia. Curr Opin Oncol 2012;24:176–81.
91. Dearden C. Disease -specific complications of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2008:2008:450–6.
92. Ding W, Zent CS. Diagnosis and management of autoimmune complications of chronic lymphocytic leukemia/small lyphocytic lymphoma. Clin Adv Hematol Oncol 2007:5:257–61.
93. Berentsen S. Rituximab for the treatment of autoimmune cyotpenias. Haematologica 2007;92:1589–96.
94. Bussel JB, Kuter DJ, Newland A et al. Long-term efficacy and safety of romiplostim for the treatment of patients with chroinic immune thrombocytopenia (ITP): 5-year update from an open-label extension study (abstract). Blood 2009;114: 681.
95. Borthakur G, O'Brien S, Wierda WG et al. Immune anaemias in patients with chronic lymphocytic leukaemia treated with fludarabine, cyclophosphamide and rituximab-incidence and predictors. Br J Haematol 2007;136:800–5.
96. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventative approaches. Best Pract Res Clin Haematol. 2010 Mar;23(1):145-53.
97. Sinisalo M, Aittoniemi J, Kayhty H, Vilpo J. Vacination against infections in chronic lymphocytic leukemia. Leuk Lymphoma 2003;44:649–52.
98. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Coooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med 1988;319:902–7.