New Alternatives in CLL Therapy: Managing Adverse Events

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Abstract

Chronic lymphocytic leukemia (CLL) is a B-cell leukemia mainly affecting older adults. Historically, CLL has been regarded as an incurable disease, and treatment has been confined to cytotoxic chemotherapy regimens. However, prognosis for patients treated with these agents remained poor, prompting the development of new, targeted agents. The introduction of rituximab, a CD20-targeted monoclonal antibody, revolutionized the treatment for this disease. Rituximab in combination with fludarabine improved response rates and length of progression-free survival. The success of rituximab in this setting has prompted the development of many more investigational agents for CLL, including other antibody agents. However, as with any medication, the potential benefit achieved with CLL therapies is mitigated by the safety risk for the patient. These agents have been associated with adverse events such as immunosuppression, reactivation of cytomegalovirus, and infusion-related reactions that can occur with antibody administration. Adverse events can greatly affect the patient’s quality of life and ability to tolerate therapy. Management of adverse events is a critical component of the overall treatment strategy for CLL, particularly in elderly patients. In this clinical roundtable monograph, 3 expert physicians discuss the latest clinical studies evaluating the treatment of CLL, focusing on the adverse events associated with each agent and the potential interventions that can be used to manage their occurrence.
Managing Adverse Events Associated With Monoclonal Antibodies and Other Alternative CLL Therapies

Thomas Kipps, MD, PhD

One of the most pivotal practice-changing events in the treatment of chronic lymphocytic leukemia (CLL) has occurred with the introduction of monoclonal antibodies to treat the disease. Although the CD52-targeted monoclonal antibody alemtuzumab was the first to be approved for CLL, other antibodies directed against a diverse array of targets are now under evaluation for this disease as well. In addition, alternative treatments are now being explored for patients with relapsed/refractory disease. However, each of these treatments is associated with an adverse event (AE) profile, and managing these AEs is an important step in maximizing the benefit-to-risk ratio for each patient.

Studies Involving Monoclonal Antibodies

Rituximab

Rituximab was only recently approved by the US Food and Drug Administration for the treatment of CLL in combination with other drugs. When given as a single agent, rituximab is not typically associated with a particularly high response rate. Therefore, high-dose rituximab monotherapy has been investigated as a potential alternative to improve response. In a study of 33 patients with either CLL or small lymphocytic leukemia, a thrice weekly dosing schedule of single-agent rituximab was found to be active and well tolerated, producing an overall response rate (ORR) of 45%.1 Similarly, a dose-escalation trial in CLL patients also showed that higher rituximab doses elicited an anti-tumor response.2 In this study, response was shown to be correlated with dose; patients receiving the lowest rituximab doses (500–825 mg/m2) had an ORR of 22%, whereas patients receiving the highest rituximab dose (2,250 mg/m2) had an ORR of 75%. Recently, a report by Adiga and Wiernik showed that high-dose (up to 3 g/m2) single-agent rituximab was effective in patients with treatment-refractory or poor-prognosis CLL.3 The ORR reported in this study of 23 patients was 90.9%, with 54.5% of patients achieving a complete response. The median progression-free survival (PFS) was 12.5 months. Thus, together these studies indicate there may be a role for single-agent rituximab, when administered at higher doses, in the treatment of CLL.

The use of rituximab clearly enhances the activity of combination therapy regimens. The updated results of the CLL8 study, which compared fludarabine/cyclophosphamide (FC) alone with FC plus rituximab (FCR), were presented by Hallek and colleagues.4 The now proven benefit in overall survival (OS) conferred by the addition of rituximab continues to reinforce FCR as a standard of care for the treatment of CLL.

In addition to the traditional FC chemotherapy regimen, novel combinations with rituximab are being explored as potential treatment regimens. One of these involves lenalidomide, an immunomodulatory agent whose single-agent activity in CLL is itself under investigation.5 For example, one study suggested that lenalidomide treatment was active in patients with high-risk CLL,6 whereas another reported complete and partial responses after lenalidomide treatment in relapsed/refractory CLL.7 However, there is a risk for life-threatening tumor flare with lenalidomide...
treatment in CLL. In an abstract by Ferrajoli and colleagues, the combination of rituximab and lenalidomide was investigated in a prospective, nonrandomized phase II study that included 44 evaluable patients with relapsed CLL. The ORR reported after 12 cycles of therapy was 64%. Although no complete responses were reported after cycle 6, the complete response rate after cycle 12 was 9%. The near partial response/partial response rates after cycles 6 and 12 were 64% and 54%, respectively. Although the median OS was not reached, the 1-year OS rate was 95%. Neutropenia (31%), fatigue (27%), and fever of unknown origin (18%) were the most common grade 3/4 AEs. Grade 3/4 tumor lysis syndrome occurred in 5% of patients, and 25% of patients had grade 1/2 tumor flare. Although the results of this study are encouraging, they are based on a small patient population that was not randomized to either agent alone, which makes it difficult to reach a conclusion regarding this combination. However, it appears that the combination of rituximab with lenalidomide can improve response compared with lenalidomide alone.

Hillmen and colleagues discussed an open-label phase II trial that evaluated rituximab combined with chlorambucil in previously untreated CLL. In this interim analysis, based on the first 50 patients enrolled, the ORR (intent-to-treat population) was 84%, which was determined to be 17.3% higher than the overall response achieved with chlorambucil alone in a historic control cohort. A total of 25 serious AEs were reported; the majority of these were infections, although febrile neutropenia also occurred. Approximately 40% of patients experienced grade 3/4 neutropenia. Together, the investigators concluded that further evaluation of this combination was warranted in CLL patients.

The use of bendamustine, either alone or combined with rituximab, was explored by Rigacci and colleagues in a multicenter, retrospective study. Here, 173 patients from 16 Italian centers were included; patients had heavily pretreated CLL or another B-cell lymphoma. The ORR was 73%, with 28% achieving a complete response. Out of 63 patients with CLL, 46 achieved a response. The OS and PFS rates in CLL patients were 72% and 27%, respectively. Grade 3/4 neutropenia (23%), thrombocytopenia (12%), and anemia (11%) were the most common hematologic toxicities. Other studies explored this combination in more detail in a prospective design as discussed by Dr. Stephan Stilgenbauer.

In a unique regimen, Del Poeta and colleagues presented data from a study that treated patients with maintenance rituximab following induction fludarabine chemotherapy. A total of 120 patients were treated with 6 monthly courses of first-line fludarabine, followed a median of 31 days later by 4 weekly doses of maintenance rituximab therapy. CLL patients who underwent consolidation and maintenance therapy showed a longer response duration than those with minimal residual disease who did not undergo maintenance therapy. Although the ORR was very good following consolidation and maintenance therapy, the lack of randomization makes the median PFS and OS rates difficult to interpret.

**Ofatumumab**

Because of the success of rituximab, other CD20-targeted strategies have been developed as potential alternatives. The fully human anti-CD20 monoclonal antibody ofatumumab is the most clinically advanced of these agents. Ofatumumab has been found to induce antibody-dependent cell-mediated cytotoxicity as well as complement-dependent cytotoxicity in CD20-positive B cells. Ofatumumab targets a unique epitope within CD20. After a phase I/II clinical study demonstrated that single-agent ofatumumab displayed marked clinical activity in relapsed/refractory CLL, its safety and efficacy was further evaluated in a larger international study in fludarabine-refractory CLL patients with a poor prognosis. In an interim analysis of this international study, single-agent ofatumumab treatment resulted in an overall response up to 47%. Because of the studies, ofatumumab was approved for the treatment of CLL refractory to fludarabine and alemtuzumab. Although it is currently indicated for use as a single-agent, current efforts have also focused on the efficacy and safety of ofatumumab in combination with other agents.

Wierda and colleagues reported the results from a multicenter, prospective, parallel-group, randomized phase II clinical trial that evaluated 2 different doses of ofatumumab in combination with fludarabine and cyclophosphamide in 61 patients with previously untreated CLL. Patients were treated with six 4-week cycles of ofatumumab plus FC; the first cycle of ofatumumab included a dose of 300 mg for all patients, while the remaining cycles administered either 500 mg or 1,000 mg ofatumumab. Both doses of ofatumumab, combined with chemotherapy, were found to be highly active as frontline therapy. The overall and complete response rates among all patients were 75% and 41%, respectively. The ORRs for patients in the 500 mg and 1,000 mg arms were 77% and 73%, respectively. Although there was a trend towards a higher rate of complete response in the 1,000 mg arm compared with the 500 mg arm (50% vs 32%), the difference between those 2 dosing cohorts did not reach statistical significance. Interestingly, subgroup analysis identified particular characteristics that described those patients who had a higher response to treatment. Patient subgroups that achieved an ORR of greater than 80% included women, patients with lower (<4 mg/L) baseline β2 microglobulin levels, patients with lower (<30,000 cells/μL) baseline lymphocyte counts, patients with an unmutated IgVH gene, patients with no cytogenetic abnormalities, and patients who completed all 6 treatment cycles. In this study, ofatumumab combined with FC was well tolerated, with a toxicity profile similar to FCR. AEs occurred more
frequently in the 1,000 mg arm compared with the 500 mg arm. The most common grade 3/4 AEs reported were cytopenias—including neutropenia (500 mg: 35%; 1,000 mg: 60%), thrombocytopenia (500 mg: 6%; 1,000 mg: 23%), and anemia (500 mg: 6%; 1,000 mg: 20%)—and infections (500 mg: 13%; 1,000 mg: 23%). The infusion-site reactions that occurred with ofatumumab were all grade 1/2 in severity and were most common after cycles 1 and 2 of treatment. Overall, it was apparent from this study that the combination of ofatumumab with FC was well tolerated and active, warranting further studies comparing the activity of this regimen with that of FCR.

**GA101**

GA101 is a third-generation humanized and glycol-engineered monoclonal antibody directed against CD20 that is being investigated for its activity against B-cell malignancies. GA101 binds to the unique epitope of CD20 with high affinity. This characteristic allows GA101 to induce antibody-dependent cell-mediated cytotoxicity at a 5- to 100-fold greater potency than observed with rituximab.

In an in vitro preclinical study, Patz and colleagues found that, compared to rituximab, GA101 could induce a higher degree of B-cell depletion in treated whole blood samples (32% vs 11%). Furthermore, GA101 was also superior to rituximab in inducing death in isolated CLL samples (21% vs 6%).

In addition to this preclinical study, an early phase I dose-escalating clinical study was reported by Morschhauser and colleagues, which evaluated GA101 in relapsed/refractory CLL. In this study, GA101 was administered as a single agent to 13 patients with CD20-positive CLL with relapsed/refractory disease for whom no other approved therapy was available. Patients received doses of GA101 that ranged from 400 mg to 2,000 mg on days 1, 8, and 22 and then subsequently every 3 weeks, for a total of 9 infusions. No dose-limiting toxicities were reported, and no dose reductions were required. The most common AEs were grade 1/2 infusion-related reactions; these occurred most often with the first infusion. Grade 3/4 hematologic toxicities that occurred included transient neutropenia (n=9), febrile neutropenia (n=1), and transient thrombocytopenia (n=1). A total of 3 patients experienced serious AEs, including febrile neutropenia, thrombocytopenia, bronchitis, gingivitis, neutropenia, and tumor lysis syndrome. Infections occurred in 10 patients. In all 13 patients, B-cells were almost completely depleted from the first infusion; this effect remained sustained over the course of treatment. The ORR was 62%, including 1 patient with a complete response but persistent cytopenias, 7 patients with a partial response, and 5 patients with stable disease. The duration of response was reported to be over 8 months in some cases. Response to GA101 was not associated with any particular FcγRIIIA genotype, suggesting it may not be influenced by polymorphisms that may contribute to rituximab resistance. The activity of GA101 is notable, particularly in this population of patients with relapsed/refractory CLL, and suggests that further studies of this antibody are needed.

**Alemtuzumab**

The CD52-directed monoclonal antibody alemtuzumab is currently approved for use as a single-agent treatment of CLL. Single-agent alemtuzumab was established as a frontline therapy for CLL in a large, randomized study in which it was compared to chlorambucil as first-line therapy for 297 patients. Compared with chlorambucil, alemtuzumab therapy resulted in a significantly improved PFS (42% reduction in risk of death or progression, hazard ratio [HR], 0.58; P=.0001) and median time to alternative treatment (23.3 vs 14.7 months; HR, 0.54; P=.0001). A significant improvement in overall response was also observed with alemtuzumab compared with chlorambucil (83% vs 55%; P<.0001). The AE profiles were largely similar between alemtuzumab and chlorambucil, except for a higher frequency of infusion-related events and cytomegalovirus (CMV) infections with alemtuzumab.

An important phase II clinical trial also showed that single-agent alemtuzumab therapy can be used for the treatment of relapsed/refractory CLL. In this study, 24 patients who had relapsed from prior therapy with fludarabine were treated with alemtuzumab. A partial response was documented in 33% of patients; no complete responses were reported. The median time to response was 3.9 months (range, 1.6–5.3 months). Responses were durable, lasting for a median of 15.4 months (range, 4.6 to ≥38.0 months). The median TTP was 19.6 months (range, 7.7 to ≥42.0 months), and the median patient survival time was 35.8 months (range, 8.8 to ≥47.1 months). A major opportunistic infection occurred in 10 patients on-study. Thus, this study showed that alemtuzumab had significant activity in CLL patients with fludarabine-relapsed/refractory disease.

Because of its demonstrated benefit as a single agent, much excitement has surrounded the possibility of combining alemtuzumab with other treatments to increase their efficacy. Two of these, the combination of fludarabine with alemtuzumab (FluCam) and the combination of fludarabine plus cyclophosphamide with alemtuzumab (FC-Cam), are discussed in detail by Dr. Stilgenbauer. Additionally, Engert and colleagues reported preliminary results from a phase III trial that compared fludarabine plus alemtuzumab to fludarabine alone as second-line treatment in 335 patients with relapsed/refractory CLL. Significantly, the median PFS was prolonged for patients who received the combination therapy compared with single-agent fludarabine (29.6 vs 20.7 months; HR, 1.63; P=.005). However, the significant PFS improvement with fludarabine plus alemtuzumab
was restricted to patients with Rai stage III or IV disease. The rates of overall response (84.8% vs 68.0%; \( P = .001 \)) and complete response (30.4% vs 16.4%; \( P = .002 \)) were also significantly improved among patients who received the alemtuzumab/fludarabine combination. Importantly, the combination treatment was well tolerated, with a similar incidence of grade 3/4 toxicities (including infectious complications) in both treatment arms.

Although FCR has established activity for the frontline therapy of patients with CLL, there is a subset of patients who do not respond well to treatment with this regimen. These patients exhibit high-risk features, such as elevated serum \( \beta \)-2-microglobulin levels and/or those with leukemia cells that have deletions in the short arm of chromosome 17 (17p).4,32 In fact, this cytogenetic abnormality can result in loss of a functional p53 tumor protein, a protein that governs the response of a cell to chemotherapy-induced genotoxic stress, and the loss of which may explain the reduced response to treatment among these patients.33 Unlike with rituximab, the 17p chromosomal deletion does not seem to have the same effect on alemtuzumab, as patients with this abnormality generally remain quite responsive to this antibody provided they do not have bulky adenopathy.34-36

Thus, Parikh and colleagues evaluated the CFAR regimen, which is comprised of alemtuzumab added to the chemotherapy regimen of FCR.37 Frontline CFAR was investigated for its ability to improve response and survival in these high-risk patients. This study included 60 patients with high-risk CLL; all patients had a \( \beta \)2 microglobulin level of 4 mg/L or higher. A median of 4 treatment courses (range, 2–6) of CFAR were administered. The median OS had not been reached, and the median time to disease progression (TTP) was 38 months. A very high (92%) rate of overall response was achieved; it included a 70% rate of complete response. The investigators found no significant correlation between the response to CFAR and several disease characteristics, including Rai stage of disease, \( IgVH \) mutation status, cytogenetic status, or high-level expression of the ZAP70 or CD38 proteins. However, patients with either the 17p chromosomal deletion or an unmutated \( IgVH \) gene experienced a significantly shortened median TTP compared with the overall population (18 months; \( P = .001 \) and 33 months; \( P = .01 \), respectively). The incidence of grade 3/4 neutropenia and thrombocytopenia was 31% in patients with either the 17p chromosomal deletion or an unmutated \( IgVH \) gene compared with 13% in the overall population; in a historic cohort of high-risk patients treated with FCR, these rates were 31% and 10%. Although 17% of patients experienced a major infection (including pneumonia and sepsis), minor infections (including Herpes zoster and urinary tract infections) occurred in 25%. Again, these rates were compared to 15% and 23% in a historic cohort treated with FCR, showing that CFAR therapy resulted in a similar incidence of hematologic toxicity and infection in this patient population. CMV reactivation occurred in 12% of patients despite prophylactic therapy; 1 patient died due to CMV pneumonia. Despite the excellent response to alemtuzumab displayed by these high-risk patients overall, the shortened TTP reached by patients with the 17p chromosomal deletion was discouraging. The reason for this outcome is unclear, and it remains to be seen if the CFAR regimen provides benefit over FCR in these high-risk CLL patients.

Consolidation therapy with alemtuzumab was explored as a possible treatment option in a phase III, randomized controlled trial of the German CLL Study Group (GCLLSG).38 In this study, patients who achieved a response to chemotherapy (either fludarabine alone or fludarabine combined with cyclophosphamide) were randomized to either treatment with alemtuzumab or observation alone. Of the 21 evaluable patients included in this study, 11 had been randomized to the alemtuzumab arm before the trial was halted prematurely, due to severe infections occurring in 7 of these 11 patients. At 6-month follow-up after randomization, 2 patients in the alemtuzumab arm had achieved a complete response, while 3 patients in the observation arm experienced disease progression. Recently, long-term follow-up (median follow-up of 48 months) of this study was reported.39 This follow-up showed that despite the increased toxicity associated with alemtuzumab, patients who were randomized to this treatment experienced a significantly prolonged PFS compared to those patients who received observation alone (\( P = .004 \)). Despite the small patient population in this study, this difference was highly significant.

The Cancer and Lymphoma Group B (CALGB) study 10101 was another trial that evaluated consolidation alemtuzumab therapy, with results first reported in 2007.40 Lin and colleagues recently presented final toxicity and response data from this study.41 In this phase II trial, 102 previously untreated symptomatic CLL patients received fludarabine plus rituximab induction therapy followed by consolidation therapy with alemtuzumab. Although the initial study design called for all patients to receive alemtuzumab consolidation therapy, a high infection incidence among patients who achieved a complete response to induction therapy caused the protocol to be amended so that only patients who achieved a partial response or stable disease would receive alemtuzumab. After induction therapy, the rates of overall, complete, and partial response were 90%, 29%, and 61%, respectively. Alemtuzumab was administered to 58 patients; of these, 72% completed the planned 6 weeks of treatment. After consolidation therapy, the rates of overall, complete, and partial response were 91%, 66%, and 26%, respectively. Over half (62%) of patients who were in partial response after induction therapy achieved a complete response with alemtuzumab. In an intent-to-treat analysis, 42% of patients achieved minimal residual disease negativity. At a median follow-
up of 34 months, the median PFS was 37 months; the 2-year PFS and OS rates were 73% and 86%, respectively. There was no significant difference in either PFS or OS between patients who did or did not receive alemtuzumab. During alemtuzumab therapy, grade 3/4 neutropenia and thrombocytopenia occurred in 43% and 19% of patients, respectively. Prior to study amendment, 5 deaths due to infection occurred among patients who achieved a complete response to induction therapy and were subsequently treated with alemtuzumab. One patient who achieved a partial response after induction therapy died due to infection after going on to receive alemtuzumab consolidation therapy. Overall, these results suggest that while patients seem to derive a benefit from alemtuzumab consolidation therapy, the potential for serious infection is great.

TRU-016
TRU-016 is an IgG fusion protein directed against the CD37 antigen, a member of the tetrasmus family that has a predominant expression on normal and malignant B cells. This agent was developed by humanizing the mouse-human chimeric protein SMIP-016, which in preclinical studies had previously demonstrated antitumor activity in lymphoid malignancies.42

A phase I clinical trial of TRU-016 was reported by Andritsos and colleagues, which demonstrated promising clinical activity in 32 patients with relapsed/refractory CLL.43 This dose-escalation study employed TRU-016 from 0.03 mg/kg up to a dose of 10 mg/kg; the maximum tolerated dose had not been reached. A total of 12 serious AEs were reported; of these, 3 may have been related to TRU-016 therapy (grade 4 neutropenia, presumed herpes zoster, and immune and idiopathic thrombocytopenic purpura). Clinical activity was evident in patients who received as little as 0.3 mg/kg TRU-016. Responses included 1 partial response in a patient with a 17p chromosomal deletion, 2 patients with complete or partial clearing of leukemia cutis, and an 83% median reduction in peripheral lymphocytosis. Based on these positive results, evaluation of this study population will continue, and future studies investigating TRU-016 are warranted.

Studies Involving Alternative Therapies

BH3 Mimetics
ABT-263 is a novel orally available BH3 mimetic that has been found to have antitumor activity in preclinical studies.44 The rationale for the use of a BH3 mimetic in hematologic malignancies is based on its ability to antagonize the effect of the anti-apoptotic Bcl-2 family member proteins, whose expression is often increased in these cancers.45 Specifically, ABT-263 has been shown to potently induce apoptosis in lymphoma cell lines and primary cells (including CLL) that overexpress the Bcl-2 protein.46

Roberts and colleagues reported results from M06-873, an ongoing phase I/II dose-escalation trial of ABT-263 in relapsed/refractory CLL.47 The ORR was 33%; of the 21 evaluable patients included, 2 patients achieved a partial response and 3 patients had an unconfirmed nodal regression. At the time of the report, the median PFS had not yet been reached. The most common AEs reported included diarrhea (52%), nausea (44%), vomiting (24%), fatigue (24%), thrombocytopenia (20%), and neutropenia (12%). Dose-limiting toxicities were observed in some patients, prompting the investigators to determine the recommended phase II dosing to be a lead-in dosage of 100 mg for 7 days, followed by 250 mg/day continuous dosing.

Based on these promising results, as well as preclinical data suggesting that ABT-263 may act additively or synergistically with other agents used to treat CLL,48 it is actively being explored in possible combination regimens.

Gene Therapy
Castro and colleagues presented an abstract suggesting that gene therapy could chemosensitize some patients to FCR therapy. This study relied on evidence that had previously shown that CLL cells containing the 17p chromosomal deletion, when co-cultured in vitro with cells transduced to express the CD40 ligand CD154, could induce expression of the p73 protein.49 Like p53, the p73 protein is a tumor suppressor that can mediate genotoxic stress–related cell death in response to chemotherapy. Additionally, direct transduction of del(17p) CLL cells with an adenovirus encoding CD154 can induce p73 expression in both the transduced as well as bystander CLL cells.

Based on this, Castro and colleagues conducted a phase Ib trial in which patients with high-risk CLL who were either fludarabine-refractory or had the 17p chromosomal deletion underwent gene therapy.50 All patients received 3 doses of autologous CLL cells that had been transduced with an adenovirus expressing CD154. Two weeks later, patients were treated with a truncated FCR regimen. Although the CLL cells initially collected from patients were shown to be resistant to fludarabine-induced apoptosis, the CLL cells collected 24 hours or more after the first infusion of autologous CLL cells became sensitive to fludarabine. At the time of the report, 2 patients had completed treatment; both achieved a complete response and 1 patient had no detectable minimal residual disease. Additionally, both patients had complete resolution of lymphadenopathy and organomegaly. Both patients had tolerated therapy well with no serious AEs. The most frequent toxicities reported included transient fever, malaise, and fatigue, all associated with cell transfusion, and cytopenias following FCR treatment. Thus, the investigators concluded that CD154 gene therapy via autologous cell delivery could induce in vivo sensitivity to FCR in high-risk patients.
Managing Adverse Events With Therapy

Administration of rituximab is associated with toxicity, particularly during the initial infusions. Rituximab infusion-related reactions can include rigors, chills, hypotension, and dyspnea. However, patients generally become acclimated to rituximab with subsequent administrations, reducing the frequency and severity of infusion reactions over time. The occurrence of these infusion reactions may be mitigated by lowering the speed of the infusion. In our practice, we typically administer rituximab at a low rate of 100 mg as an initial dose on the first day. Similarly, the infusion-related reactions that occur with administration of ofatumumab may in many cases be attenuated simply by lowering the rate of infusion.

Other toxicities observed with rituximab and ofatumumab are generally hematologic AEs. Chief among these is neutropenia. The true relation of neutropenia to rituximab or ofatumumab administration can sometimes be difficult to interpret, as many of these patients may already have impaired marrow function even before receiving treatment. Additionally, these antibodies are often used in conjunction with other agents that may be the actual cause of the neutropenia.

Intravenous administration of alemtuzumab can also be associated with infusion-related reactions, including hypotension and chills. The appearance of some of these reactions is more dramatic than those associated with rituximab or ofatumumab. It may be necessary to initiate alemtuzumab at a very low dosage of 1 mg, and to gradually increase it to 3 mg and 10 mg; subsequently, the antibody may then be administered at the final dose of 30 mg 3 times weekly. In our experience, patients often become acclimated to alemtuzumab over time, as they do to rituximab or ofatumumab.

Because of the significant infusion-related reactions associated with alemtuzumab, there has been a great interest in administering the antibody subcutaneously. When given via the subcutaneous route, it is usually injected in the stomach area. The incidence of acute infusion-related reactions is decreased when the drug is administered in this fashion. However, this route of administration should be used with caution, as pharmacokinetic studies indicate that the plasma concentration of the drug is lower when given subcutaneously compared with intravenously.

The other major toxicity associated with alemtuzumab use is immunosuppression. The likely explanation for this reaction is the binding of the antibody to CD52 on T cells, which may result in T-cell depletion and profound lymphopenia. Because of this, patients treated with alemtuzumab must be followed very closely to detect the presence of opportunistic infections. To prevent the occurrence of opportunistic infections, prophylactic antibiotic therapy should be used. There is also a high incidence (in nearly 50% of patients) of CMV reactivation. This AE requires recognition either by polymerase chain reaction or clinical suspicion and may require treatment with valganciclovir.

References


Adverse Events in Chemoimmunotherapy Regimens

Stephan Stilgenbauer, MD, PhD

Historically, CLL has been regarded as an incurable disease. Although treatment with conventional chemotherapy agents, including alkylating agents and purine analogs, could produce a response, patient prognosis often remained poor. However, prolonged disease remission and improved rates of survival are now possible with the introduction of new agents and regimens, including chemoimmunotherapy. Chemoimmunotherapeutic regimens for CLL incorporate monoclonal antibodies with traditional chemotherapeutic agents. Rituximab, a chimeric monoclonal antibody directed against the B-cell receptor CD20, is currently approved for the treatment of CLL in combination with chemotherapy such as FC. This chemoimmunotherapy regimen has become the most effective treatment for CLL, as the addition of rituximab causes improved response rates and longer PFS compared with fludarabine and cyclophosphamide alone. Based on the success of FCR, other novel chemoimmunotherapy regimens, such as rituximab plus bendamustine and alemtuzumab-containing combinations, have also been explored.

Bendamustine Plus Rituximab

Currently approved for the treatment of CLL, bendamustine combines the structure of an alkylating agent with a purine-like benzimidazole ring. Although the exact mechanism of action of bendamustine in malignant cells is unclear, preclinical studies suggest it may induce cell death through both apoptotic and non-apoptotic pathways. Several cellular effects have been attributed to bendamustine, including DNA damage, increased expression of proapoptotic genes, inhibition of mitotic checkpoint control, and induction of mitotic catastrophe. The approval of bendamustine for the treatment of CLL was largely based on the results of a pivotal open-label, multicenter, randomized phase III clinical trial of 319 patients (≤75 years of age) with previously untreated advanced CLL. These patients were randomly assigned to receive a maximum of 6 cycles of treatment with either bendamustine or chlorambucil, and response to treatment was assessed according to the National Cancer Institute Working Group criteria. Over twice as many patients in the bendamustine group achieved a complete or partial response to treatment compared with the chlorambucil group (68% vs 31%; P<.0001), and the number of complete responses alone was also dramatically higher with bendamustine (31% vs 2%). Median PFS was significantly improved with bendamustine compared with chlorambucil (21.6 vs 8.3 months; P<.0001). Although the toxicity profile of bendamustine was considered to be manageable, its use was associated with a higher frequency of grade 3/4 AEs (40% vs 19%), including severe infections (8% vs 3%).

Based on the beneficial activity of single-agent bendamustine for the frontline treatment of CLL, and because of the success achieved with the addition of rituximab to FC chemotherapy over chemotherapy alone, the addition of rituximab to bendamustine has also been investigated as a potential chemoimmunotherapy regimen in hematologic malignancies. This combination was shown to be effective in patients with mantle cell and low-grade non-Hodgkin lymphoma. In a pilot study, the combination of rituximab with bendamustine plus mitoxantrone was effective and well tolerated in patients with relapsed/refractory CD20-positive hematologic malignancies, including CLL. Subsequently, a phase II clinical study of the GCLLSG reported that the combination of bendamustine with rituximab was highly active in 62 evaluable patients with relapsed/refractory CLL, with approximately three-quarters of patients achieving an overall response (77.4%). In that study, the most common grade 3/4 AEs reported included myelosuppression (12.2% neutropenia, 9.1% thrombocytopenia, and 6.1% anemia) and infections (5.2%, including 3 patients with a grade 5 infection).

More recently, Fischer and colleagues presented findings from a similar GCLLSG trial evaluating the same chemoimmunotherapy combination in the frontline treatment of CLL. This was a prospective, multicenter, open-label, nonrandomized phase II trial in 110 evaluable patients with previously untreated CLL requiring therapy who were enrolled between March 2007 and September 2008. All patients received up to 6 cycles of bendamustine plus rituximab (median of 5.0 treatment cycles; 71.8% of patients received all 6 cycles), and the median follow-up time reported was 15.4 months. The majority of patients in this study achieved an overall response (90.9%); of these, 32.7% were a complete response and 55.5% were a partial response. Differences in response to treatment were apparent among genetic subgroups. For example, the ORR was high in patients with chromosome 12 trisomy (89.5%), 11q deletion (90.5%), and unmutated IGHV gene (88.9%), but was comparatively lower in patients with 17p deletion (42.9%). Similarly to the prior GCLLSG trial, the most common grade 3 or higher AEs reported in this study were myelosuppression (14.6% leukopenia, 6.5% neutropenia, 6.1% thrombocytopenia, and 4.9% anemia) and infections.
(5.1%, including 3 patients who experienced fatal infections). The total treatment-related mortality was 3.4%.

From these reports, it is apparent that the combination chemoimmunotherapy regimen of bendamustine plus rituximab in the first-line treatment of advanced CLL patients was very efficacious, with an AE profile that confirmed prior experience. Based on these results, the GCLLSG has initiated a randomized phase III trial comparing this regimen (bendamustine plus rituximab) with FCR for fit patients with CLL (excluding patients with 17p deletion), the current standard first-line treatment of CLL.12

Alemtuzumab-Based Chemoimmunotherapy

The CD52-directed monoclonal antibody alemtuzumab, currently indicated as a single-agent treatment of CLL, has also been investigated for a potential benefit in chemoimmunotherapy regimens.13 The approval of single-agent alemtuzumab for CLL was largely based on a randomized study in which it was compared to chlorambucil as first-line therapy in 297 patients.14 Compared with chlorambucil, alemtuzumab therapy resulted in a significantly improved PFS (42% reduction in risk of death or progression, HR, 0.58; P<.0001) and median time to alternative treatment (23.3 vs 14.7 months, HR, 0.54; P<.0001). A significant improvement in overall response was also observed with alemtuzumab compared with chlorambucil (83% vs 55%; P<.0001). The AE profiles were largely similar between alemtuzumab and chlorambucil, except for a higher frequency of infusion-related events and CMV infections with alemtuzumab.

The chemoimmunotherapeutic combination regimen of FluCam was first evaluated in relapsed/refractory CLL in a phase II clinical study.15 In this study of 36 patients, an 83% ORR was reported. Fungal pneumonia infections developed in 2 patients, 2 patients experienced a CMV reactivation, and 1 patient died due to sepsis resulting from Escherichia coli infection.

In an attempt to improve upon the FluCam regimen, Elter and colleagues reported the final results of the CLL2L (Multicenter Phase II Trial of Fludarabine and Cyclophosphamide in Combination With Alemtuzumab for Patients With Relapsed or High Risk Chronic Lymphocytic Leukemia) trial of the GCLLSG, which evaluated the chemoimmunotherapy combination regimen of FC-Cam in a multicenter phase II clinical study.16 A total of 56 evaluable patients with relapsed or genetic high-risk CLL were included in this analysis. Up to 6 cycles of chemoimmunotherapy were permitted by the protocol; 38 patients completed at least 4 cycles, and the median number of treatment cycles was 5.0. An ORR of 68% was reported, with 22% achieving a complete response, 11% an unconfirmed complete response, and 35% a partial response. Importantly, the efficacy of the combination was dependent upon the patient’s prior therapy exposure; 81% of patients who had previously received fludarabine achieved an overall response, but this rate was reduced to 63% in patients who had previously received both fludarabine and cyclophosphamide. The most common grade 3/4 AEs were thrombocytopenia and neutropenia. A total of 5 patients died due to treatment-related causes. Among the serious AEs reported were fever of unknown origin (12 patients), CMV reactivation (5 patients), pneumonia (5 patients, 2 cases due to aspergillosis), autoimmune hemolytic anemia (1 patient), and herpes zoster reactivation (1 patient). These results prompted the study investigators to conclude that the addition of cyclophosphamide resulted in some increased toxicity compared with the FluCam regimen originally developed.

Rituximab Combined with Fludarabine/Cyclophosphamide

The addition of FCR has now become the standard of care for the treatment of CLL. This was largely based on the benefit shown with this chemoimmunotherapy regimen compared with chemotherapy (FC) alone in the REACH (Rituximab Plus Chemotherapy in Relapsed/Refractory Chronic Lymphocytic Leukemia) study, an international, multicenter, clinical trial of 552 patients with previously treated CLL who were randomized to receive either FCR or FC alone.3 After a median follow-up time of 25 months, it was evident that the addition of rituximab significantly improved median PFS (30.6 vs 20.6 months, HR, 0.65; P<.001). Several other outcomes were also significantly improved with this chemoimmunotherapy regimen compared with chemotherapy alone, including overall response (69.9% vs 58.0%; P=.0034) and complete response (24.3% vs 13.0%; P<.001) rates, median duration of response (39.6 vs 27.7 months; P=.0252), and median time to new CLL treatment (not reached vs 34.3 months; P=.0024). At the time of this follow-up, there was no statistically significant difference in OS between the 2 treatment groups.

CLL8 was another pivotal clinical trial that helped to establish FCR as the standard of care for CLL patients. Unlike the REACH trial, which focused on previously treated CLL patients, the CLL8 study included only previously untreated patients; a total of 817 patients were randomized to receive treatment with either FCR or FC. In the initial analysis, 2-year PFS was significantly improved with FCR compared with FC (76.6% vs 62.3%; P=.003), and overall response (95% vs 88%) and complete response (52% vs 27%) rates were also greatly increased with the addition of rituximab.17 Although there was no statistically significant difference in OS between the 2 treatment groups in this initial analysis, there was a trend towards a benefit in 2-year OS with FCR (91% vs 88%; P=.18).

Updated results of the CLL8 trial were recently presented by Hallek and colleagues, which included a median
follow-up time of 37.7 months.18 Significantly more treatment cycles were delivered in the FCR arm compared with the FC arm (median number of treatment cycles: 5.2 vs 4.8; \( P=.006 \)), and more patients in the FCR arm required dose reductions of greater than 10% during at least one treatment course (47% vs 27%; \( P=.001 \)). At this extended follow-up, overall response (95.1% vs 88.4%) and complete response (44.1% vs 21.8%; \( P=.001 \)) rates remained improved in the FCR group compared with the FC group. Furthermore, PFS also continued to be significantly increased in the FCR group (51.8 vs 32.8 months; \( P<.001 \)). Importantly, this extended analysis showed that OS was significantly improved with the addition of rituximab (OS rate at 37.7 months: 84.1% vs 79.0%; \( P=.01 \)); the median OS remained unreached in both treatment arms. As expected from the initial analysis, the incidence of hematologic toxicity, particularly neutropenia, was higher in the FCR arm compared with FC; however, this did not correspond to an increase in the rate of infection (25.5% vs 21.5%; \( P=.4 \)). The rate of treatment-related mortality was equal in both arms (2.0%). Thus, the investigators concluded overall that FCR as compared to FC offers significant improvement in efficacy, notably with an improved OS, without significantly causing a higher frequency of infection. Based on these results, this study group considers FCR to be the new standard of care in physically fit CLL patients requiring treatment. Of note, efficacy of FCR remains unsatisfactory for CLL patients with 17p deletion.

**Comparing Rituximab-based and Alemtuzumab-based Chemoimmunotherapy Regimens**

The positive efficacy results associated with both FCR and FC-Cam chemoimmunotherapy regimens, discussed above, prompted the initiation of a multicenter French and Belgian phase III clinical trial, CLL2007FMP. These chemoimmunotherapy combinations were evaluated in 165 medically fit, previously untreated patients with advanced CLL. After stratification according to IGHV mutational status and 11q deletion, patients were randomized to receive 6 cycles of either FCR or FC-Cam. Although 178 patients were enrolled, study recruitment was halted prematurely at 165 patients due to an increase in patient mortality within the FC-Cam arm.

Lepretre and colleagues recently reported the preliminary analysis of this study, which included an efficacy analysis in the first 100 patients enrolled and a safety analysis of the entire patient cohort.19 A similar proportion of patients within each treatment arm received all 6 treatment cycles (76.5% and 71.4% in the FCR and FC-Cam arms, respectively). Most cases of treatment discontinuation were due to persistent grade 3/4 neutropenia. Although the ORR was higher in the FCR arm compared with the FC-Cam arm (96% vs 85%), this difference was not statistically significant. There was also a trend for an improved rate of complete response in the FCR arm over the FC-Cam arm (78% vs 58%; \( P=.072 \)). PFS and OS were not yet evaluable in this preliminary analysis.

A similar proportion of patients in the FCR and FC-Cam arms experienced grade 3/4 AEs (90.2% vs 87.8%; \( P=.76 \)). The most frequent of these was neutropenia (74.6% and 79.6%, respectively). Intriguingly, although the frequency of neutropenia remained stable across the FCR treatment cycles (17.6% for cycle 1 and 17.9% for cycle 6), it steadily increased with the FC-Cam treatment cycles (28.4% for cycle 1 and 45.5% for cycle 6). A total of 63 cases of serious AEs were reported, the majority of which were febrile neutropenia. The distribution of serious AEs was very different between the treatment arms, with 19 events among 18 patients in the FCR arm compared to 44 events among 35 patients in the FC-Cam arm. In this analysis, a total of 7 patients (all in the FC-Cam arm) died; the causes of death included 3 cases of diffuse large B-cell lymphoma, 1 case of mucormycosis, 1 case of septic shock resulting from *Pseudomonas aeruginosa* infection, and 2 cases of heart failure secondary to neutropenia.

In this preliminary analysis, the investigators concluded that the FC-Cam regimen for the treatment of advanced CLL appeared to be associated with an unfavorable safety profile that presented severe limitations with its use. Thus, these researchers suggested that other alemtuzumab-containing chemoimmunotherapeutic regimens be studied instead.

**Rituximab Combined With Fludarabine in CLL**

In the CALGB study 9712, the chemotherapy agent fludarabine was investigated as a treatment either concurrently with or sequentially following rituximab therapy in symptomatic untreated patients. In this phase II clinical trial, a total of 104 patients were randomized to receive either 6 monthly courses of fludarabine concurrently with rituximab followed 2 months later by rituximab consolidation therapy, or sequential fludarabine alone followed 2 months later by rituximab consolidation therapy.

A median follow-up of 23 months was previously reported.20 The incidence of AEs was similar between both arms during the consolidation phase of therapy, but a higher incidence of grade 3/4 neutropenia (74% vs 41%) and infusion-related toxicity (20% vs 0%) was evident with the concurrent compared with the sequential arm. However, the ORR achieved was also higher in the concurrent arm compared with the sequential arm (90% vs 77%).

Recently, Woyach and colleagues presented the long-term follow-up (median follow-up of 92 months) results of CALGB study 9712.21 Among the entire study population, the ORR was 84%; it was higher in the concurrent treatment groups compared with the sequential treatment groups (90% vs 77%). At this follow-up, the median OS
was 85 months, with a 5-year OS rate of 71%. The median PFS was 37 months, and the 5-year PFS rate was 27%. Overall, the estimated median OS and median PFS within the concurrent group (84 months and 32 months) were somewhat lower than that estimated within the sequential group (91 months and 40 months).

In regard to the AEs reported within CALGB study 9712, the primary focus dwelled on the incidence of secondary myeloid neoplasms (especially therapy-related myelodysplastic syndrome or acute myelogenous leukaemia). Only 1 patient was determined to have developed therapy-related myelodysplastic syndrome following relapse. Overall, the investigators concluded that with the regimen used, based on the long-term efficacy and safety data acquired, in particular related to treatment-related myeloid neoplasms, this regimen looks very favorable and does not appear to increase the number of treatment-related myeloid neoplasms.

**Summary**

Overall, from these studies it appears that treatment with chemoimmunotherapeutic regimens lead to an increase in hematologic toxicity, most notably neutropenia. Chemoimmunotherapy treatment also can result in an increase in opportunistic infections. However, the occurrence of either of these AEs seems to be dependent primarily on whether the treatment is being given as a first-line or subsequent therapy; of these, a higher risk of AEs and infectious complications occur when given to relapsed/refractory patients. Secondly, the type of antibody used also seems to be an important determinant of the ensuing AEs; antibodies that result in a depletion of T cells can be associated with viral reactivation, most notably CMV. Conversely, an increase in infectious complications can occur when given to relapsed/refractory patients. The concurrent group (9712, the primary focus dwelled on the incidence of secondary myeloid neoplasms) and the sequential group on CLL and WM (FCGCLL/MW) and the “Groupe Ouest-Est d’Etudes Des Leucémies Aigües Et Autres Maladies Du sang” (GOELAMS) : CLL2007FMP (for fit patients) with advanced B-chronic lymphocytic leukemia: experience on safety and efficacy within a randomised multicenter phase III trial of the French cooperative group on CLL and WM (FCGCLL/MW) and the “Groupe Ouest-Est d’Etudes Des Leucémies Agües Et Autres Maladies Du sang” (GOELAMS) : CLL2007FMP (for fit medically patients).

**References**

19. Lepretre S, Aurran T, Mahe B, et al. Immunochemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine (F), cyclophosphamide (C) and MabCampath (Cam) (FC-Cam) in previously untreated patients (pts) with advanced B-chronic lymphocytic leukemia (B-CLL): experience on safety and efficacy within a randomised multicenter phase II trial of the French cooperative group on CLL and WM (FCGCLL/MW) and the “Groupe Ouest-Est d’Etudes Des Leucémites Agües Et Autres Maladies Du sang” (GOELAMS) : CLL2007FMP (for fit medically patients).
CLL Treatment for the Elderly Patient

Asher Chanan-Khan, MD

From 2003–2007, the median age of diagnosis for CLL in the United States was 72 years, and the majority (69.7%) of patients were 65 years or older.1 The age distribution of the disease in the elderly is striking: 26.7% of patients are between 65–74 years, 29.3% are between 75–84 years, and 13.2% are 85 years or older. However, many of the landmark studies, which did so much to advance our understanding of the biology of CLL and to introduce therapies that have finally begun to dramatically change the course of disease, were conducted in considerably younger patient populations.2 For example, in the studies that evaluated single-agent fludarabine, the median patient age was 64 years; in studies of FCR for frontline treatment, median age was 58 years; and in studies examining FCR in the relapse setting, median age was 59 years (Table 1).3,4

Because of the high prevalence of this disease in the older population, it is important to take into account particular characteristics of this population when determining a course of treatment. For example, although molecular and cytogenetic prognostic factors may be important determinants of prognosis in younger patients, they may have less of an impact on OS in older patients. Response to therapy in the older patient may be mitigated by poor performance status, comorbidities, or even an inability to receive the full dosage needed to achieve the desired effect. In fact, survival is significantly decreased among elderly patients with 2 or more comorbidities and among those who have a particularly severe comorbidity.5 The 5-year survival rate of patients with a low comorbidity burden (<2 and/or not severe) is significantly greater than for patients with a high comorbidity burden (≥2 and/or severe; 75% vs 53%; P<.001).

Bendamustine

Knauf and colleagues reported on the use of bendamustine specifically in an elderly CLL patient population.6 In this open-label, multicenter, phase III clinical trial, 319 patients with previously untreated advanced CLL were randomized to receive up to 6 cycles of either bendamustine or chlorambucil. The median patient age was 64 years (range, 35–78 years). Regardless of patient age (≥65 years vs <65 years), the median number of treatment cycles was 6 in each study arm. In the overall patient population, the ORR was significantly higher in patients treated with bendamustine compared with chlorambucil (68% vs 31%; P<.0001), as was the median PFS (21.6 vs 8.3 months; P<.0001). When the population was assessed by age, there was no significant difference in the response rate between patients 65 years or older and those younger than 65 years (63.5% vs 71.6% with bendamustine and 32.5% vs 28.4% with chlorambucil). Median PFS also did not significantly differ between these 2 age groups. The investigators concluded that bendamustine was superior to chlorambucil for the frontline treatment of advanced CLL, regardless of patient age. Thus, this study showed that bendamustine was an active agent for elderly patients.

Chlorambucil

Hillmen and colleagues described an open-label phase II trial that evaluated the addition of rituximab to chlorambucil for the frontline treatment of CLL.7 Data for the first 50 (47 evaluable) of the planned 100 enrolled patients were described. The median age of these patients (70.5 years; range, 48–86 years) reflected the typical CLL patient. This combination was effective, resulting in an ORR of 84%. The investigators further compared this study to a historic cohort of matched patients who received chlorambucil alone, finding that the addition of rituximab improved the ORR by 17.3% compared with the historic cohort. However, it is also notable that the median age in this current study is older than the median age of the historic cohort. The most common AEs reported in the study were gastrointestinal disorders. Additionally, 17 patients experienced a total of 25 serious AEs, the most common of which were infections and febrile neutropenia. Grade 3/4 neutropenia was reported in 40% of the patients.

Fludarabine

Rai and colleagues presented the long-term survival analysis of the North American Intergroup Study C9011, which compared single-agent fludarabine with single-agent chlorambucil and the combination of fludarabine and chlorambucil in previously untreated patients with CLL.8 Study C9011 included 509 patients. In this long-term analysis, it was found that single-agent fludarabine resulted in significantly longer PFS compared with single-agent chlorambucil at 2 years (45% vs 26%), 3 years (31% vs 10%), and 4 years
(21% vs 6%). This lengthy follow-up also showed that OS was improved in the fludarabine group compared with the chlorambucil group at 6 years (43% vs 38%) and 8 years (31% vs 19%). This improvement in OS emerged only after the previous 5-year analysis, which found no difference between the 2 groups.9 The OS of patients in the fludarabine plus chlorambucil group at 4 years, 6 years, and 8 years was 54%, 37%, and 26%, respectively.

In contrast, Eichhorst and colleagues recently reported the finding that first-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly CLL patients with advanced disease.10 In this multicenter phase III trial of the GCLLSG, a total of 193 patients (median age, 70 years) were randomized to receive single-agent fludarabine or chlorambucil. Higher overall (72% vs 51%; P=.003) and complete (7% vs 0%, P=.011) response rates were achieved with fludarabine compared with chlorambucil. Although time to treatment failure was significantly shorter in the chlorambucil arm compared with the fludarabine arm (11 vs 18 months; P=.004), PFS was not significantly different (18 vs 19 months). Additionally, there was no improvement in OS between the 2 treatment arms (46 vs 64 months). Thus, this led the study authors to conclude that elderly patients did not derive a significant benefit from fludarabine versus chlorambucil.

### Table 1. Age of Patients in Chronic Lymphocytic Leukemia Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Median Age, Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rai et al9</td>
<td>Frontline</td>
<td>Fludarabine compared with chlorambucil</td>
<td>509</td>
<td>64</td>
</tr>
<tr>
<td>Keating et al3</td>
<td>Frontline</td>
<td>Fludarabine, cyclophosphamide, and rituximab</td>
<td>224</td>
<td>58</td>
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<tr>
<td>Wierda et al4</td>
<td>Relapse</td>
<td>Fludarabine, cyclophosphamide, and rituximab</td>
<td>177</td>
<td>59</td>
</tr>
</tbody>
</table>

#### References

Monoclonal Antibodies for CLL
- Rituximab
- Ofatumumab
- GA101
- Alemtuzumab
- TRU-916

Combination Therapy in CLL
- Bendamustine plus rituximab
- Alemtuzumab plus fludarabine
- Rituximab plus fludarabine
- Fludarabine plus cyclophosphamide with alemtuzumab
- Fludarabine plus cyclophosphamide with rituximab

Managing Adverse Events of CLL Treatment
- Infusion-related reactions
  - The occurrence of infusion reactions may be mitigated by lowering the rate of speed of the infusion
- Immunosuppression
  - Patients should be followed very closely to detect the presence of opportunistic infections
  - To prevent the occurrence of opportunistic infections, prophylactic antibiotic therapy should be used
- Cytomegalo virus reactivation
  - Recognition either by polymerase chain reaction or clinical suspicion
  - May require treatment with valganciclovir

Factors to Consider in Management of Elderly CLL Patients
- Although molecular and cytogenetic prognostic factors may be important determinants of prognosis in younger patients, they may have less of an impact on overall survival in older patients
- Survival is significantly decreased among elderly patients with 22 comorbidities and among those who have a particularly severe comorbidity

Treatment of Elderly Patients With CLL
- Response to therapy in the older CLL patient may be mitigated by:
  - Poor performance status
  - Comorbidities
  - Inability to receive the full dosage needed to achieve the desired effect

CLL8 and REACH Trials in Patients Older Than 70 Years
Across BOTH studies,
- 100 patients received rituximab and fludarabine plus cyclophosphamide
- 99 patients received fludarabine plus cyclophosphamide

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