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Recent Advances in Chronic Lymphocytic Leukemia: A Post-iwCLL 2009 Discussion

Moderator

Kanti R. Rai, MD
Chief, Division of Hematology-Oncology
Long Island Jewish Medical Center
New Hyde Park, New York

Discussants

Wolfgang U. Knauf, MD, PhD
Professor
Onkologische Gemeinschaftspraxis
Frankfurt, Germany

John G. Gribben, MD, DSc
Professor
Barts and The London School of Medicine
London, United Kingdom

Abstract

Chronic lymphocytic leukemia (CLL) is a relatively common form of adult leukemia that results in the overproduction of lymphocytes. Because it is generally an indolent malignancy, it is often treated with a watchful waiting approach. Several molecular and cytogenetic prognostic factors have been identified, which, when combined with existing staging systems specific for CLL, can help physicians determine patient prognosis and whether there is a need for additional treatment over observation alone. For more advanced stages of CLL, treatment options generally include chemotherapy, monoclonal antibody therapy, and low-dose external radiation therapy. Standard medications currently used for the treatment of CLL include fludarabine, chlorambucil, cyclophosphamide, bendamustine, and rituximab; alemtuzumab is also approved as salvage therapy in the setting of resistant and/or refractory disease. For younger patients considered to be medically fit, stem cell transplantation is an alternative and potentially curative strategy. The Thirteenth International Workshop on CLL (iwCLL) was held October 16–18, 2009, in Barcelona, Spain, where many recent advances in the management of CLL were presented. Several important studies from the 2009 iwCLL are discussed in detail in this roundtable. Topics in this roundtable include current and emerging prognostic factors for CLL, the role of bendamustine in the treatment of CLL, and the impact of recent clinical trials on the controversial use of stem cell transplantation in CLL patients.

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Overview of the Prognostic Stratification in CLL

Kanti R. Rai, MD

Although generally considered an indolent malignancy, chronic lymphocytic leukemia (CLL) has a clinical course that is highly variable among individuals. While many patients present with low grade CLL and are preferentially treated with a "watchful waiting" approach, nearly half develop a more aggressive life-threatening disease that progresses rapidly.[1] Instead of watchful waiting, this particular subset of patients may benefit from treatment prior to the occurrence of disease progression. Therefore, identifying those early-stage patients who will go on to develop aggressive CLL is a critical necessity to improve patient outcomes and survival. Reliable disease staging and the recognition of prognostic markers for classification are important strategies to identify those patients who may potentially benefit from early treatment.

Classical Staging of CLL

Developed over 3 decades ago, the Rai staging system and the Binet staging system continue to be the 2 traditional classification systems for CLL.[2,3] Both staging systems, which can estimate patient prognosis at the time of diagnosis, correlate the degree of tumor burden with median patient survival (Table 1). In the Rai system, patients are classified into 5 categories (0, I, II, III, IV), each of which are assigned a risk group (low: Rai stage 0; intermediate: Rai stages I and II; high: Rai stages III and IV).[3] Patients in all stages have evidence of lymphocytosis, and additional criteria such as the presence of lymphadenopathy or thrombocytopenia dictate patient stage. Median patient survival ranges from 19 months for patients with high risk CLL to more than 150 months for patients with the lowest risk disease. In contrast, the Binet staging system classifies patients into 3 groups (A, B, C) based on the number of nodal sites involved and indication of myelosuppression (anemia and/or thrombocytopenia).[2] Patients with Binet stage A disease are low risk with a median survival that was not reached in clinical studies; patients with Binet stage B disease are intermediate risk with a median survival of 84 months; and patients with Binet stage C disease are considered high risk with a median survival of 24 months.

Although these classical CLL staging systems have been validated and are widely used, the vast majority (>80%) of newly diagnosed CLL patients are grouped as low risk.[1] Further, these staging systems are unable to select those patients whose disease progresses more rapidly and aggressively than expected. Therefore, a great deal of attention has turned to the search of other factors that can be used to calculate patient prognosis. Certain prognostic factors that have been identified are patient-related, such as gender and age, whereas others are disease-related, including performance status, cell morphology, and bone marrow histology.[1] However, an improved understanding of the pathogenesis of CLL has allowed molecular and

Table 1. Rai and Binet Staging Systems

	Risk Group	Criteria	Median Survival (months)
Rai stage			
0	Low	Lymphocytosis*	>150
I	Intermediate	Lymphocytosis + lymphadenopathy	101
II	Intermediate	Lymphocytosis + splenomegaly or hepatomegaly	71
III	High	Lymphocytosis + anemia†	19
IV	High	Lymphocytosis + thrombocytopenia‡	19
Binet Stage			
A	Low	<3 nodal sites§ involved	Not reached
B	Intermediate	≥3 nodal sites involved	84
C	High	Anemia and/or thrombocytopenia¶	24

*Absolute lymphocyte count in whole blood >5,000/mm^3.

†Hemoglobin <110 g/L, with or without enlargement of lymph nodes, spleen, or liver.

‡Platelets <100 x 10^9/L, with or without anemia or enlargement of lymph nodes, spleen, or liver.

§Five possible nodal sites: axillary, cervical, inguinal, spleen, and liver.

¶Hemoglobin <100 g/L, with or without enlargement of lymph nodes, spleen, or liver.

cytogenetic biomarkers to emerge as important and established prognostic factors.

Currently Used Molecular and Cytogenetic Prognostic Factors for CLL

Genomic aberrations, detected by fluorescence in situ hybridization (FISH), were shown to be important independent prognostic factors for CLL by Döhner and colleagues.[4] In their study, FISH was used to analyze mononuclear cells from blood samples taken from 325 patients (median age, 62 years) with CLL from a single institution. The median time from diagnosis to FISH assessment was 15 months (interquartile range [IQR], 1–43 months). Patient samples were assessed for a number of genomic aberrations, including deletions (of chromosome bands 6q21, 11q22-23, 13q14, or 17p13), trisomy (of bands 3q26, 8q24, or 12q13), and translocations (involving band 14q32). Of the 325 patients evaluated, 82% had genomic aberrations detected by FISH. The most frequently occurring genomic aberration was 13q deletion (55%); this was followed by 11q deletion (18%), and 12q trisomy (16%), as well as numerous other aberrations that occurred at a lower frequency. Patients had either 1 (53.8%), 2 (20.6%), or more than 2 (8.0%) genomic aberrations. The investigators then used a hierarchical model of genetic subgroups in which each patient case was assigned to one category only—a total of 5 major categories were established to which 300 of the total 325 patients could be assigned. These 5 categories were 17p deletion (7%), 11q deletion (17%), 12q trisomy (14%), normal karyotype (18%), and 13q deletion as the sole abnormality (36%); the remaining patients were grouped as having various abnormalities (8%). Patients in the 17p deletion and 11q deletion groups had the most advanced disease of these groups (P<.001); in contrast, the 13q deletion group had the highest proportion of patients with Binet stage A (72%). The treatment-free interval, an indicator of disease progression, differed significantly according to each patient genetic subcategory. Patients in the 17p deletion and 11q deletion groups experienced the most rapid disease progression, whereas patients in the 12q trisomy and normal karyotype groups exhibited improved rates; patients in the 13q deletion group exhibited the best and slowest rate of disease progression (median treatment-free interval: 9, 13, 33, 49, and 92 months for the 17p deletion, 11q deletion, 12q trisomy, normal karyotype, and 13q deletion groups, respectively). Importantly, the median survival times for patients within these groups differed accordingly (17p deletion: 32 months; 11q deletion: 79 months; 12q trisomy: 114 months; normal karyotype: 111 months; and 13q deletion: 133 months; the median survival of patients grouped in the various abnormalities group was not reached). Therefore, this study concluded that patients with 17p deletion had the worst prognosis, followed by patients with 11q deletions and patients with 12q trisomy. Patient prognosis was improved in the subgroup with normal karyotype, and was the best among patients with a 13q deletion as the sole abnormality. The investigators concluded from this study that the genomic aberrations identified and detectable by FISH are important and independent prognostic factors for CLL disease progression and patient survival. Therefore, patients with 13q deletion as the sole abnormality or with a normal karyotype are considered low risk, patients with 12q trisomy are considered intermediate risk, and patients with 11q deletion or 17p deletion are considered high risk. Since this first demonstration of the use of FISH-detected genomic aberrations as prognostic factors in CLL, several other publications have subsequently confirmed their independent prognostic validity.[5-10] Because of the overall availability of the FISH technique in most clinical settings, determination of the cytogenetic subtype is a useful tool for the initial prognostication of a CLL patient.[1]

The mutation status of the variable segments of the immunoglobulin heavy chain gene (IgV_H) has also emerged as an important prognostic factor for CLL.[11] An association between somatic mutations (>2%) in the IgV_H gene and specific cytogenetic abnormalities were first described in 1997.[12] This prognostic value of the IgV_H gene was independently confirmed 2 years later by Hamblin and colleagues and Damle and colleagues.[13,14] By sequencing the tumor cells of 84 patients with CLL, Hamblin and colleagues found that a lack of IgV_H gene mutations were associated with advanced and progressive disease, as well as a worsened survival, regardless of the Binet stage of the patient.[14] For example, the median survival for Binet stage A patients was significantly longer among those with an IgV_H gene mutation compared with those that did not have an IgV_H gene mutation (293 vs 95 months, P=.0008). Damle and colleagues further showed that patients who lacked IgV_H gene mutations responded poorly to chemotherapy and experienced shorter survival rates, whereas patients with IgV_H gene mutations generally required minimal to no chemotherapy and had improved survival.[13] Since these first reports, numerous studies have validated the prognostic significance of IgV_H gene mutations in CLL, several of which have confirmed that patients with a mutation in the IgV_H gene achieve longer rates of overall survival (OS) compared with patients having no IgV_H gene mutation.[9,15-17] Currently, the mutational status of the IgV_H gene is considered a gold standard for determining CLL patient prognosis at diagnosis.[1] However, determining the mutational status of the IgV_H gene is time-consuming, expensive, laborious, and requires certain laboratory equipment. Therefore, several alternative biomarkers have been explored as potential surrogate markers for patient prognosis.

New and Emerging Molecular and Cytogenetic Prognostic Factors for CLL

Expression of the transmembrane glycoprotein CD38 on the surface of CLL cells was initially shown to strongly correlate with IgV_H gene mutational status by Damle and colleagues.[13] In this study, the concordance rate between CD38 expression and IgV_H gene mutation status was 92%. Further, CD38-positive expression was associated with a higher need for chemotherapy and a shorter patient OS rate. However, subsequent studies have disputed this correlation, concluding instead that CD38 expression should be considered an independent prognostic factor.[15,18-20] Although a cutoff of 30% expression is often used to differentiate between CD38-positive and -negative status, this value was set empirically and has been disputed.[1] Despite this controversy, CD38 remains an important prognostic marker for CLL, and has the added value of being able to be conveniently analyzed in most clinical laboratories.

The expression of zeta-association protein of 70 kDa (ZAP-70) was identified in a gene microarray analysis as being highly differentiated between CLL patients with a mutated versus unmutated IgV_H gene. Remarkably, ZAP-70 expression could be used to classify patients with IgV_H gene mutations versus those without mutations with 100% accuracy.[21] Crespo and colleagues later confirmed that flow cytometric analysis of ZAP-70 was correlated with IgV_H gene mutation status, showing that all evaluated patients with 20% or more ZAP-70-positive CLL cells also had no IgV_H gene mutation, while 21 of the 24 patients with less than 20% ZAP-70-positive cells carried an IgV_H gene mutation ($P<.001$). Further, this same study showed that ZAP-70 status was correlated with prognosis, including rate of disease progression and patient survival.[22] Patients with 20% or more ZAP-70–positive cells had a worse prognosis compared with those having less than 20% ZAP-70–positive cells. These conclusions have been subsequently confirmed by several other reports. Notably among these was a study of 307 CLL patients by Rassenti and colleagues, which demonstrated that in multivariate analysis, ZAP-70 was the strongest prognostic factor when compared with both CD38 and IgV_H gene mutation status.[23] Further, determination of the IgV_H gene mutation status or CD38 expression level did not add any additional prognostic value in cases of ZAP-70–positive expression. For patients with ZAP-70–negative expression, who had improved prognosis, IgV_H gene mutation status and CD38 expression helped to further classify patients into low or intermediate risk groups. Despite its obvious value for determining CLL patient prognosis, the main drawback to the use of the ZAP-70 biomarker is the lack of a standardized method to determine ZAP-70 expression. While flow cytometry is considered the best method to accurately determine ZAP-70 expression specifically on CLL cells, a number of issues remain regarding its widespread implementation.[1]

Several presentations at the 2009 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) focused on research involving prognostic markers in CLL. One of these provided evidence that the fluorescence intensity of ZAP-70 expression was a more important parameter of ZAP-70 expression than merely the proportion of CLL cells staining positive or negative.[24] In this study, the difference in fluorescence intensity between ZAP-70–positive CLL cells, compared with ZAP-70-positive T cells (which normally express the protein) was a more powerful predictor of the prognostic capability of ZAP-70 than ruling ZAP-70 expression as positive or negative based on the proportion of CLL cells staining.

Another important study presented at the 2009 iwCLL compared the usefulness of the various factors to determine prognosis in a large CLL patient population.[25] This study evaluated 329 patients with Binet stage A CLL. At a median follow-up of 4 years, 37% of the patients had required treatment for their disease. Several prognostic factors were determined in these patients, showing a wide range of patients considered to have an unfavorable status according to each parameter. A total of 9% of patients had unfavorable FISH cytogenetics, 35% had unmutated IgV_H gene status, 13–38% were considered CD38-positive, and 21% were ZAP-70–positive. However, in a multivariate analysis, only IgV_H gene mutation status was a significant independent predictor of prognosis, measured by the treatment-free interval. After a median follow-up of 18 years, 44% had completely concordant prognostic test results across all 4 measured prognostic factors showing a favorable prognosis; these patients had the best median treatment-free interval (approximately 96 months). A total of 11% of patients had completely concordant prognostic test results showing an unfavorable prognosis; these patients had the worst median treatment-free interval (29 months). The remaining 44% of patients had discordant prognostic test results; the median treatment-free interval of these patients was between the other 2 concordant groups (54 months). These results highlight that nearly half of all Binet stage A CLL patients have discordance between their prognostic factors, representing a subpopulation of patients whose prognosis is difficult to determine. For these patients, it is especially important that physicians use their best clinical judgment to determine if treatment is needed on an individual case-by-case basis. For patients who appear clinically well, with excellent performance status and no disease symptoms, a watchful waiting approach is likely warranted despite the presence of an unfavorable prognostic factor. Conversely, a patient with early-stage disease who is showing signs of CLL-related symptoms may benefit from early treatment despite the presence of one or more favorable prognostic factors. Thus, while prognostic

factors represent a useful and important tool in the management of patients with CLL, their use should not replace a physician's sound clinical judgment.

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The Role of Bendamustine in CLL

Wolfgang U. Knauf, MD, PhD

Because of its efficacy in a number of hematologic malignancies including non-Hodgkin lymphoma and multiple myeloma, bendamustine has also been explored for its activity in CLL. Based on a phase III randomized trial that showed it to be superior to chlorambucil in previously untreated CLL patients, bendamustine was recently approved in the United States for this indication.[1]

Bendamustine—a New-Old Drug for CLL

Bendamustine is a cytoxic chemotherapeutic agent with both alkylating and antimetabolite properties.[2] Importantly, despite the dual structural similarities, bendamustine does not display cross-resistance with alkylating agents either in vitro or in the clinical setting.[3] Bendamustine is referred to as a "new-old" drug because it was first synthesized nearly 4 decades ago in the former German Democratic Republic. It was originally designed with the intention of particularly replacing cytoxic alkylating agents such as cyclophosphamide, chlorambucil, and melphalan. The chemical structure of bendamustine shares similarities with other alkylating agents, including a nitrogen mustard residue. However, bendamustine contains a benzimidazole ring, which may confer nucleoside-like properties to the drug and increase its stability. Additionally, the added presence of an alkancarbonacid makes bendamustine more water-soluble.

Bendamustine was approved in the United States for the treatment of CLL based on a phase III clinical study which demonstrated it was superior to chlorambucil with a manageable safety profile. In this open-label, multicenter study, 319 patients with previously untreated CLL were randomized to receive bendamustine or chlorambucil regimens.[4] All patients had either Binet stage B or C disease and were 75 years old or younger. One primary study endpoint, overall response, was significantly higher among patients in the bendamustine arm compared with those in the chlorambucil arm (68% vs 31%, $P<.0001$). Additionally, the rate of complete response was higher among patients who received bendamustine (31% vs 2%). Interestingly, the rate of complete response in patients with Binet stage B disease was 35.3% in those who received bendamustine versus 2.7% in those who received chlorambucil; the rate of complete response in patients with Binet stage C disease was 19.6% in those who received bendamustine versus 0% in those who received chlorambucil. Responses to bendamustine were durable, and the median duration of response was significantly increased in the bendamustine arm compared with the chlorambucil arm (21.8 vs 8.0 months, $P<.0001$; Figure 1).

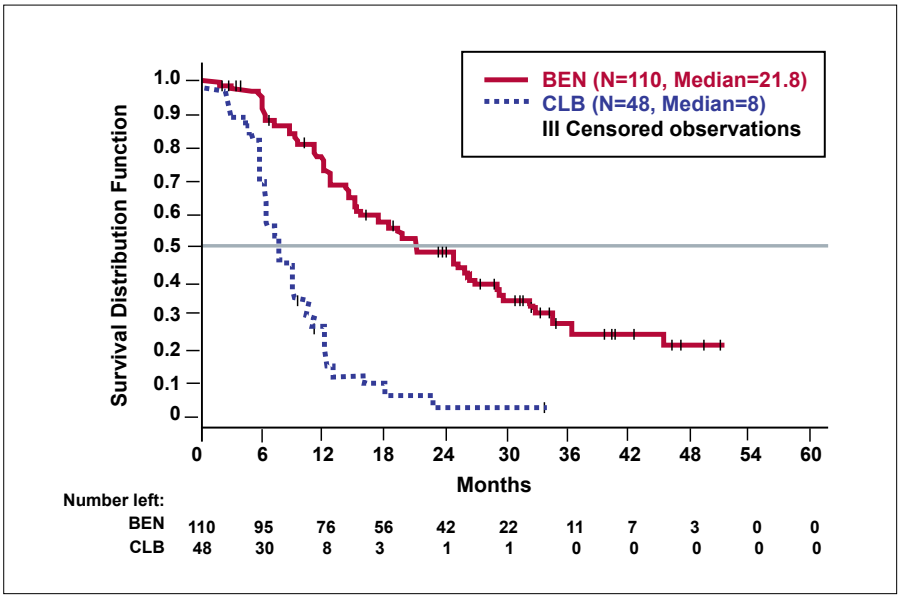

Figure 1. Duration of overall responses.

The median duration of response was 21.8 months (95% CI, 17.4–27.0) with bendamustine (BEN)and 8.0 months (95% CI, 6.3–9.3) with chlorambucil (CLB; $P<.0001$)

Data from Knauf et al. *J Clin Oncol.* 2009;27:4378-4384.

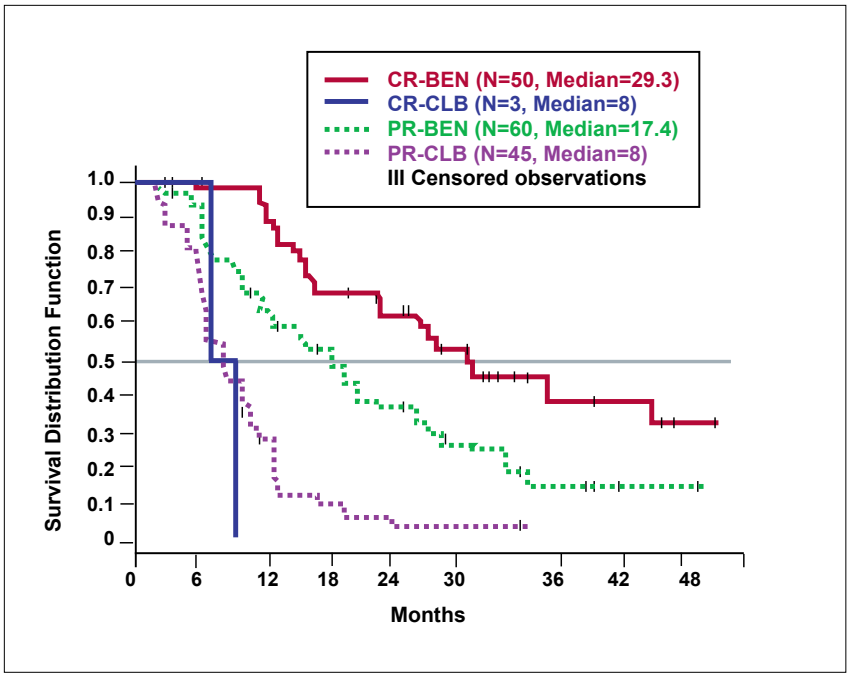

Figure 2. Duration of complete/partial responses (CR/PR).

Data from Knauf et al. *J Clin Oncol.* 2009;27:4378-4384.

BEN=bendamustine; CLB=chlorambucil

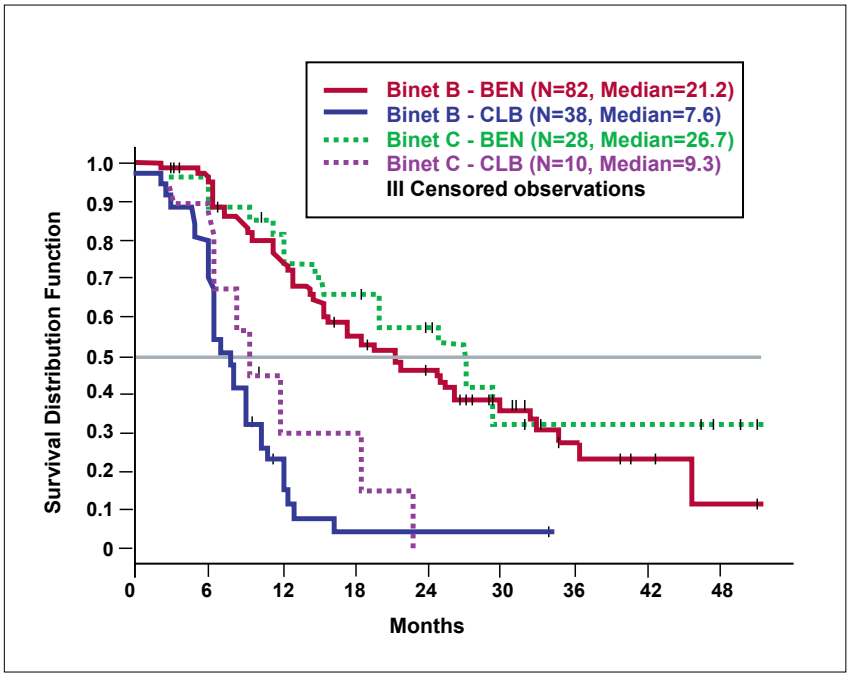

Figure 3. Duration of overall responses by Binet stage (Binet stage B: $P<.0001$; Binet stage C: $P=.0006$.)

Data from Knauf et al. *J Clin Oncol.* 2009;27:4378-4384.

BEN=bendamustine; CLB=chlorambucil

Increased duration of response for the bendamustine arm occurred regardless of whether it was a complete or partial response and irrespective of the patient's Binet stage (Figures 2 and 3). The second primary study endpoint, median progression-free survival (PFS), was also significantly increased among patients treated with bendamustine compared with chlorambucil (21.6 vs 8.3 months, $P<.0001$; Figure 4).

Although grade 3 or 4 hematologic adverse events were more common in the bendamustine arm than the chlorambucil arm (40% vs 19%), this toxicity was considered manageable and of short duration. Further analysis of this study is focused on determining the effect of treatment on overall survival in patients with CLL.

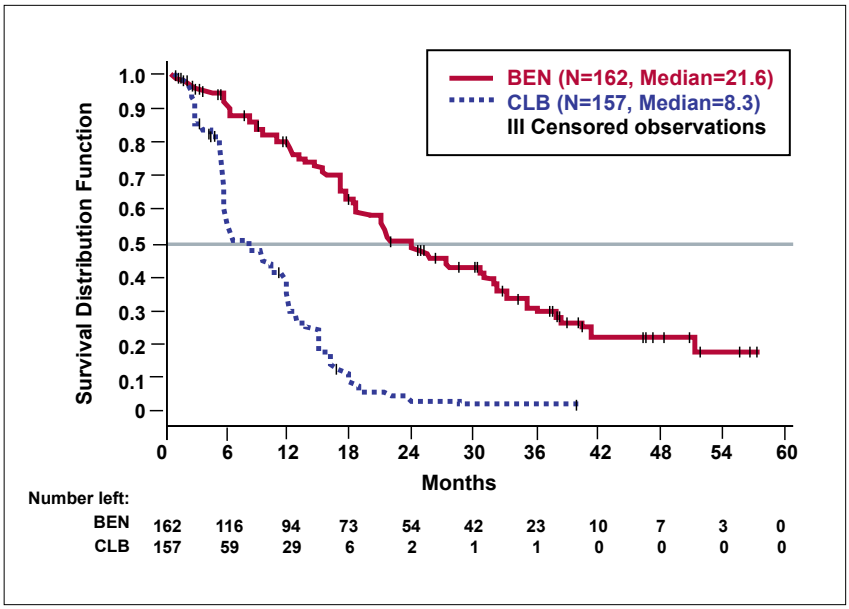

Figure 4. Progression-free survival based on ICRA by treatment group—intention-to-treat population.

The median time to progression was 21.6 months (95% CI, 18.6–31.0) with bendamustine (BEN) and 8.3 months (95% CI, 5.9–11.3) with chlorambucil (CLB; *P*=.0001).

Data from Knauf et al. *J Clin Oncol.* 2009;27:4378-4384.

Bendamustine for Second-Line CLL Treatment

Because of its activity as first-line therapy in CLL and other hematologic malignancies, bendamustine has also been investigated for its use as a second-line therapy in CLL. Early clinical trial results have suggested that bendamustine may indeed be beneficial in this setting.

A study by Bremer in 2002 showed that bendamustine treatment resulted in a high rate of durable remission and a median survival time of 32 months among 15 patients with previously treated CLL.[5] Similarly, a phase I/II study by the German CLL Study Group reported that bendamustine had excellent efficacy in 16 patients with generally heavily pre-treated and treatment-refractory CLL disease.[6] In this study, 56% of patients achieved a response to bendamustine therapy; some of these patients received only a reduced dose of bendamustine. Other trials have evaluated bendamustine in combination with either rituximab or mitoxantrone in the setting of relapsed or refractory CLL, producing response rates ranging from 67–95%.[7-9]

Recently, Niederle and colleagues presented findings from a clinical trial evaluating bendamustine as second-line treatment for CLL.[10] This study directly compared bendamustine with fludarabine in CLL patients who had relapsed after 1 prior therapy. The majority of patients (95%) had received a chlorambucil-based regimen as a prior chemotherapy; none of the patients had previously been exposed to either fludarabine or bendamustine. A total of 96 patients were randomized to receive either bendamustine or fludarabine; both agents were administered until best response or to a maximum of 8 cycles. In the interim analysis presented, 86 patients were eligible for review. After a median follow-up of 2 years, the median PFS was increased among patients receiving bendamustine (83 vs 63 weeks; hazard ratio, 0.93; 95% confidence interval [CI], 0.59–1.47). However, the difference in PFS between the 2 treatment groups did not reach statistical significance. Furthermore, the rate of overall response was also increased in the bendamustine arm compared with the fludarabine arm (78% vs 65%), as was the rate of complete response (29% vs 10%). Although bendamustine treatment was associated with a slightly higher incidence of hematologic adverse events, the rate of grade 3/4 infection was similar between the 2 groups. Therefore, the investigators concluded that bendamustine may be considered a reasonable alternative to fludarabine in the treatment of relapsed/refractory CLL.

New Results with Bendamustine

Interim results of a multicenter phase II trial, which evaluated the combination of bendamustine with rituximab in patients with relapsed or refractory CLL, were presented by the German CLL Study Group at the 2008 American Society of Hematology (ASH) Annual Meeting and Exposition.[11] Patients had received a median of 2 treatments prior to the study. Patients received bendamustine combined with rituximab for up to 6 treatment cycles (mean, 4.5 treatment cycles). Of the total of 81 patients that were included, 62 patients were available for response assessment. Among these patients, the rate of overall response was 77.4% (62.9% partial response and 14.5%

complete response). Response differed according to the patient's cytogenetic subgroup: The overall response rate among patients with favorable cytogenetics was 92.3%, whereas only 44.4% of patients with high-risk cytogenetics achieved an overall response. Furthermore, the rate of overall response among patients with unmutated IgV_H status (therefore poor prognosis) was 74.4%. Although 2 of 30 evaluable patients achieved negative minimal residual disease (MRD) status in the peripheral blood, no patients achieved MRD negativity in the bone marrow. Although several cases of adverse events that were grade 3 or higher (most frequently myelosuppression and infections) were reported, most were considered to be successfully managed. These interim results are expected to be updated at the 2009 ASH meeting.

In the meantime, bendamustine has become subject to prospectively randomized phase III trials. For instance, the German CLL study group together with a number of centers from across Europe has initiated a trial comparing bendamustine plus rituximab with the combination of fludarabine, cyclophosphamide, and rituximab. Also, bendamustine is going to be evaluated in protocols incorporating new investigational drugs like forodesine and lenalidomide.

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Stem Cell Transplantation in CLL

John G. Gribben, MD, DSc

Because many patients with CLL have indolent disease, they are not generally proper candidates for aggressive therapies such as stem cell transplantation (SCT). However, there are now sufficient clinical and laboratory parameters to make it possible to identify those patients with a poor prognosis, and the role of more aggressive treatments for CLL is being explored. One of the therapies currently under investigation is hematopoietic SCT.

Current Role of Stem Cell Transplantation in CLL

In general, hematopoietic SCT is not an acceptable treatment option for most CLL patients, as the majority of cases follow an indolent course, and many patients are too old to attempt this aggressive therapeutic approach. A consensus report from the European Group for Blood & Marrow Transplantation (EBMT) identified those CLL patients who would most benefit from allogeneic SCT.[1] This consensus suggested that younger CLL patients with one of the following characteristics may be good candidates: no response or relapse within 1 year following treatment with purine analogs, evidence of relapse within 2 years after having achieved a response with either a purine analog-based regimen or autologous SCT, and patients carrying p53 abnormalities.

Although SCT has become a mainstay of treatment for several hematologic malignancies, its use thus far in CLL has been restricted by a lack of studies directly comparing it to standard treatment options.[2] Several phase II clinical trials have been performed, demonstrating that autologous SCT may be a feasible approach for CLL therapy.[3-5] However, these studies failed to demonstrate a plateau in PFS with autologous SCT, suggesting that it may not be a superior treatment compared with standard therapy. Further, the rate of transplant-related mortality in these studies was 1–10%, and a somewhat alarming rate of 8% post-transplant acute myeloid leukemia/myelodysplastic syndrome was reported. Similarly, allogeneic SCT has also been tested but not confirmed to be a favorable treatment for CLL. Myeloablative allogeneic SCT has an advantage over autologous SCT by producing a potential graft-versus-leukemia (GVL) effect. However, this technique is associated with significant rates of morbidity and mortality.[2] One study in CLL patients reported a 46% rate of transplant-related mortality associated with allogeneic SCT.[6] Additionally, myeloablative allogeneic SCT has strict age-related restrictions limiting its use in CLL. Therefore, most interest in allogeneic SCT is focused on reduced intensity conditioning allogeneic SCT approaches, which rely on exploitation of the GVL effect.

Much of the current research focused on SCT in CLL that was presented at the 2009 iwCLL meeting evaluated this therapy in the setting of prospective, randomized clinical trials.

French Cooperative Study Group on CLL Trial

The French Cooperative Study Group on CLL conducted a prospective randomized trial evaluating autologous SCT. Eligible patients were over 66 years of age and had previously untreated Binet stage B or C CLL.[7] At baseline, several prognostic factors were assessed in centralized labs, including ZAP-70 expression, CD38 expression, karyotype and FISH analysis, and IgV_H mutational status. Patients first received induction therapy with 3 cycles of mini-CHOP (low-dose doxorubicin plus cyclophosphamide, vincristine, and prednisone) followed by 3 cycles of fludarabine. Following the completion of this initial treatment, patients were assessed for response. Those with a complete response were then randomized to receive either autologous SCT with a consolidation treatment of cyclophosphamide plus total body irradiation, or a watch and wait approach. Patients who did not achieve a complete response went on to receive salvage therapy with a DHAP regimen (dexamethasone, cytarabine, and cisplatin) and were then randomized to receive either autologous SCT with consolidation treatment of cyclophosphamide plus total body irradiation, or 3 cycles of fludarabine combined with cyclophosphamide. (Figure 1)

A total of 241 patients were enrolled and 236 underwent treatment. At baseline, the median patient age was 56.4 years (range, 33.3–66 years). The majority of patients had Binet stage B disease compared with stage C disease (185 vs 56 patients). A total of 206 patients completed the initial 6 induction treatment cycles. Following induction, the overall response rate was 89.8%, and 43.6% of patients achieved a complete response.

Of the patients who achieved a complete response, 42 went off study treatment due to several reasons including death or another serious adverse event (n=13), physician decision (n=12), uncontrolled disease progression (n=8), major protocol violation (n=4), consent withdrawal (n=3), and other cancers (n=2). Therefore, 105 patients were randomized to either consolidation therapy with autologous SCT (n=53) or

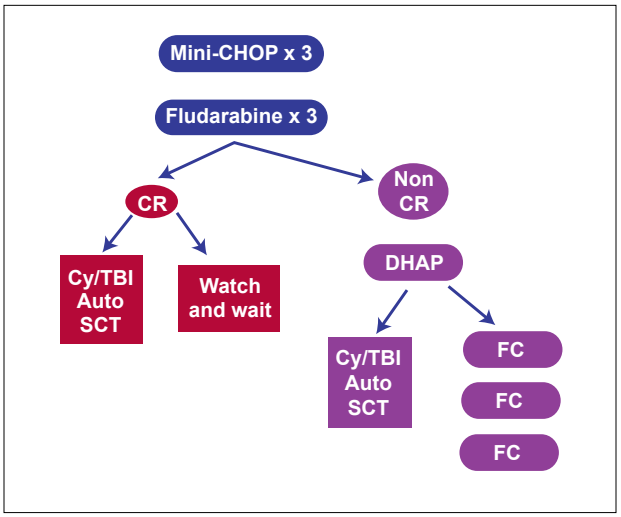

Figure 1. Autologous stem cell transplantation in CLL. Results from a prospective randomized trial.

CHOP=doxorubicin plus cyclophosphamide, vincristine, prednisone; CR=complete response; Cy/TBI=cyclophosphamide plus total body irradiation; DHAP=dexamethasone, cytarabine, cisplatin; FC=fludarabine plus cyclophosphamide; SCT=stem cell transplantation.

a watch and wait strategy (n=52). At a median follow-up of 3 years, patients who had been randomized to the autologous SCT experienced a significantly improved event-free survival (EFS) rate compared with patients randomized to the watch and wait approach (84.2% vs 30.1%; *P*<.0001). However, there was no statistically significant difference in the 3-year OS between the 2 groups (97.9% vs 97%).

Among the patients who did not achieve a complete response following induction therapy, 94 continued on to receive DHAP salvage therapy and then randomized to either fludarabine combined with cyclophosphamide (n=48) or consolidation therapy and autologous SCT (n=46); however, 28 patients randomized to autologous SCT came off study, largely due to a failure to mobilize stem cells. At 3 years, the EFS rate did not differ significantly between the autologous SCT and fludarabine/cyclophosphamide groups (45.7% vs 43.7%). Similarly, there was no significant difference in 3-year OS (82.3% vs 86.2%). The lack of benefit in either EFS or OS is not surprising, given that nearly half of the patients randomized to receive autologous SCT did not complete therapy. Notably, 4 patients within the study have developed myelodysplastic syndrome to date.

Overall, these results prompted the investigators to conclude that autologous SCT is a safe procedure in CLL patients and associated with a low rate of treatment-related mortality. However, while this aggressive treatment significantly improves the duration of response, evidenced by an increased EFS rate, the results do not translate into an improved OS. In this study, autologous SCT was only demonstrated to be beneficial in patients who achieve a complete response to induction therapy.

European Group for Blood & Marrow Transplantation Intergroup Study

A randomized phase III trial was also performed by the EBMT to compare autologous SCT with a watch and wait approach.[8] This study enrolled CLL patients with Binet stage A progressive disease (13%), stage B disease (67%), or stage C disease (20%). The study was originally designed to randomize 270 patients to therapy. However, the study was terminated early due to poor patient accrual; therefore, only 223 patients were enrolled. The majority of patients were male (74%).

Induction therapy was chosen at the discretion of the investigators. Following these various induction regimens, 59% of patients were in complete response, and 41% achieved either a very good partial or nodular partial response. All patients had achieved either a complete response, a very good partial response, or a nodular partial response following first- or second-line therapy. Most patients (82%) were enrolled with their first remission, while 18% were enrolled with their second remission. Following induction therapy, patients were randomized to receive either autologous SCT (n=112) or observation (n=111).

The objective of this study was to determine whether an autologous SCT would increase the 5-year PFS from 30% to 50%. At the time of the interim analysis, presented at the 2009 iwCLL meeting, a total of 186 patients were still alive, of whom 147 had complete response and 39 had relapsed disease. Of the 19 patients who had died, most of the cases (14 patients) had been from disease relapse. The 5-year PFS was significantly increased in the autologous SCT arm compared with the observation arm (65% vs 48%; *P*=.005). The median PFS was 43 months in the observation only group and had not been reached in the autologous SCT group. A multivariate analysis confirmed that PFS was significantly improved among patients who had been treated with autologous SCT (HR, 0.41; 95% CI, 0.23–0.75; *P*=.0004). Notably, the use of autologous SCT halved the 5-year risk of disease relapse (51% vs 25%; HR, 0.4; 95% CI, 0.23–0.71; *P*=.002). However, there was no difference in the 5-year OS rate between the 2 groups (92% vs 91%).

Therefore, the investigators concluded that for CLL patients in either a first or second remission, consolidation therapy with autologous SCT reduced the risk of disease progression by over 50%, but had no impact on OS.

German CLL Study Group CLL3 Trial

One of the primary concerns associated with the use of autologous SCT is the increased risk of the development of secondary malignancies. Therefore, the German CLL Study Group conducted a trial to evaluate the occurrence of secondary malignancies following early autologous SCT.[9] This study included patients who were 61 years of age with either poor risk Binet stage A or Binet stage B or C CLL. Patients were only included if they had either no or 1 prior line of treatment. The ratio between males and females was 5:1, and the median age at diagnosis was 51 years (range, 27–60 years); 70% of patients had an unmutated IgV_H rearrangement.

A total of 216 patients were registered in this trial, and 169 patients were eligible for the current analysis. Patients underwent cytoreduction with either CHOP, fludarabine, or fludarabine/cyclophosphamide, and peripheral blood stem cell mobilization with the Dexa-BEAM regimen. Patients subsequently received myeloablative therapy with total body irradiation and cyclophosphamide, followed by reinfusion of the purged stem cells. A total of 78% of patients received the planned autologous SCT. Reasons for not undergoing SCT among the 38 patients included mobilization failure (n=14), unknown reasons (n=11), patient preference (n=6), disease progression (n=4), and early death (n=3).

After a median follow-up of 99 months (range, 4–137 months), the median OS was 10.5 years among patients treated with autologous SCT and 6.1 years among patients who did not receive this therapy. This represented a significant improvement in OS among patients who underwent autologous SCT (HR, 0.26; 95% CI, 0.13–0.54; $P<.0001$). The median PFS was also improved in patients treated with autologous SCT (6.8 vs 4.8 years; HR, 0.39; 95% CI, 0.23–0.67; $P=.0007$).

In this interim analysis, 20 secondary malignancies had been observed among the study participants. These malignancies included myelodysplastic syndrome or acute myeloid leukemia (n=6), genitourinary tumors (n=3), or gastrointestinal cancer (n=3). The 10-year actuarial incidence of the development of secondary malignancies was 20% (95% CI, 11–30%). However, there was no significant difference in the 10-year incidence of any secondary malignancy among individuals treated with and without autologous SCT. After the onset of a secondary malignancy, median OS was 22 months (range, 2–50 months), with no difference among the type of cancer.

From these results, the investigators concluded that secondary neoplasms are a serious issue after early autologous SCT for patients with poor prognosis CLL. However, these secondary neoplasms do not appear to occur more frequently after autologous SCT compared with other diseases. Despite this, the OS provided by the use of early autologous SCT is promising for this high-risk CLL patient population.

Summary Conclusion from Studies

Based on these 3 studies that were presented at the 2009 iwCLL meeting, there still remains a controversy surrounding the use of autologous SCT to treat patients with CLL. Although the results provided by these studies are intriguing and show promising effects on PFS, there is presently no evidence that a more aggressive therapy such as autologous SCT confers an advantage in OS. In light of the increased safety concerns associated with autologous SCT, physicians should refrain from offering it to their CLL patients outside the setting of a clinical trial until an OS advantage is conclusively shown.

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Slide Library

FISH Cytogenetics Enable Us to Divide CLL Patients into 3 Risk Categories:

Risk Categories	By FISH
Low	Del 13q, none detectable
Intermediate	Trisomy 12
High	Del 11q, Del 17p

IgV_H Gene Mutation Testing Yields 2 Broad Categories of Risk

Risk Categories	By IgV_H Mutation
Low	Mutated (>2%)
High	Unmutated

CD38 Co-Expression on CLL Lymphocytes Yields 2 Broad Categories of Risk:

Risk Categories	By CD38 Expression
Low	CD38 Negative
High	CD38 Positive

ZAP-70 Expression Testing on CLL Lymphocytes Yields 2 Broad Categories of Risk:

Risk Categories	By ZAP-70 Expression
Low	ZAP-70 Negative
High	ZAP-70 Positive

Rassenti Conclusions

Three prognostic markers analyzed

Multivariate analysis:

- ZAP-70 was the strongest marker including in early stage and asymptomatic disease.
- Mutation status and CD38 did not improve the predictive power of ZAP-70 negative patients for time-to-first treatment.

Bendamustine vs Chlorambucil: Response

Quality of response by ICRA – ITT population

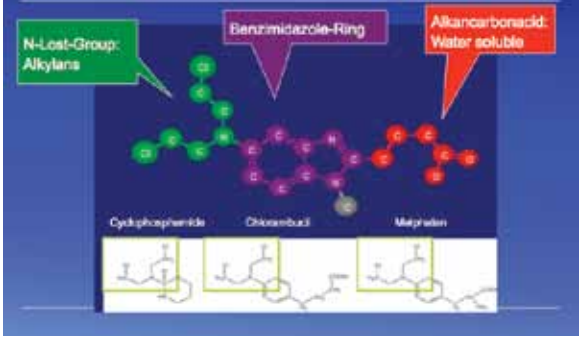
	Bendamustine (n=162)	Chlorambucil (n=157)
Overall response	110 (68%)	48 (31%)
Complete response	50 (31%)	3 (2%)
Nodular partial response	17 (10%)	4 (3%)
Partial response	43 (27%)	41 (26%)

Bendamustine vs Fludarabine as Second Line Treatment in CLL

	Bendamustine (n=46)	Fludarabine (n=43)
ORR	78%	65%
CR	29%	10%
Med. PFS	83 weeks	64 weeks

Adapted from Niederle et al, ICML Lugano 2008

Chemical Structure of Bendamustine



Stem Cell Transplant for CLL

- Most patients with CLL have indolent course and are not candidates for aggressive therapy approaches
- It is possible to identify poor risk patients with short survival
- No randomized clinical trial had previously been reported demonstrating advantage of SCT in CLL
- Phase II studies of autologous SCT
  - Feasible
  - No demonstration of plateau on PFS
- Myeloablative SCT
  - Not applicable to many patients with CLL
  - Very high transplant-related mortality
- Most interest recently in reduced intensity conditioning transplant
  - Exploitation of the graft versus leukemia effect

Conclusions from the French Society of Bone Marrow Transplantation and Cell Therapy & The French Cooperative Study Group Trial

- ASCT is a safe procedure which significantly improves response duration in patients attaining CR after this first-line treatment.
- There is no improvement in OS to date.
- For patients not in CR, ASCT or consolidation with 3 FC courses provide similar results in response duration and OS.

Conclusions from the EBMT Trial

- In CLL patients in first or second remission, consolidating auto-HSCT reduces the risk of progression (PFS) by more than 50%
- No effect on overall survival

Conclusions from the GCLLSG CLL3 Trial

- Secondary neoplasms are a serious problem after early SCT for poor-risk CLL, but do not appear to occur more frequently after SCT than that reported for other diseases.
- The overall survival provided by the early SCT approach is, nevertheless, promising for this high-risk patient selection.

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