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Finding the Right Dose: Improving Patient Outcomes in CLL and NHL

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Abstract

The treatment for patients with hematologic malignancies was revolutionized with the introduction of the monoclonal antibody therapy rituximab. However, many questions remain regarding the incorporation of rituximab in the treatment plan for these patients, including the optimal dosage and scheduling of the drug. Additionally, available clinical data regarding the use of rituximab as maintenance therapy are controversial. In addition to these questions, many patients eventually experience disease relapse, despite experiencing an initial benefit with rituximab therapy, and therefore require effective therapeutic alternatives. The recent approval of bendamustine has allowed one such alternative to emerge. Bendamustine has been evaluated in clinical trials as both a single agent and as a part of a combination regimen with rituximab. However, the standard bendamustine treatment regimen is still being modified. This roundtable will discuss each of these agents in more detail, including clinical studies which have contributed to the establishment of current treatment protocols. By understanding the optimal use of these agents, clinicians can more effectively incorporate them into patient treatment, allowing patients to experience the best response possible.

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Bendamustine and Rituximab—Optimizing Dose and Schedule

Bruce D. Cheson, MD

Rituximab

Randomized clinical trials have established that rituximab prolongs progression-free survival (PFS) in patients with chronic lymphocytic leukemia (CLL). Therefore, rituximab is now an integral component of treatment for CLL in both the frontline and relapsed/refractory disease settings.

The CLL8 study, conducted by the German CLL Study Group (GCLLSG), evaluated the addition of rituximab to fludarabine/cyclophosphamide (FCR) with fludarabine/cyclophosphamide (FC) alone as frontline therapy for patients with CLL.[1] A total of 817 patients were randomized to receive 6 courses of either FC or FCR. At the time of analysis, the median follow-up time was 25.5 months. The 2-year PFS was significantly improved among patients who received FCR compared with FC (76.6% vs 62.3%; *P*<.0001). In addition, patients in the FCR arm experienced significantly superior rates of response compared with the FC arm (OR, 95% vs 88%; *P*=.001; CR, 52% vs 27%; *P*<.0001). An update of the CLL8 study is expected to be presented at the 2009 American Society of Hematology Annual Meeting and Exposition, which will report on an evaluation of the impact of rituximab therapy on patient survival.

The REACH (Rituximab in thE study of relApsed Chronic lympHocytic leukemia) study was a phase III international randomized trial which compared FCR with FC in patients with relapsed/refractory CLL.[2] The study included 552 patients who received either FCR or FC every 4 weeks. After 3 cycles, patients were restaged; those who exhibited a response (either complete response [CR], partial response [PR], or stable disease [SD]) continued to receive their designated treatment for another 3 cycles. The primary endpoint of the study, median PFS, was significantly improved among patients randomized to receive FCR compared with FC (30.6 vs 20.6 months; HR, 0.65; 95% CI, 0.51–0.82; *P*=.0002). PFS remained superior among patients treated with FCR across all Binet stage subgroups.

Higher doses of rituximab or alternative administration schedules have not been established to be superior to the standard dose (375 mg/m^2) in clinical studies. In a dose-escalation trial conducted at M.D. Anderson Cancer Center, 50 patients with CLL or other mature B-cell lymphoid malignancies were treated with 4 weekly infusions of rituximab.[3] Patients were initiated at 375 mg/m^2 and dose-escalated from 500 mg/m^2 to 2,250 mg/m^2. Although this study demonstrated a higher rate of PR correlating with higher doses of rituximab, these doses will likely not be pursued in future studies due to the expense of rituximab. A schedule of rituximab thrice weekly over 4 weeks has also been investigated in CLL and small lymphocytic lymphoma (SLL) patients.[4] Although this schedule was associated with clinical efficacy and acceptable toxicity, it has not been shown to be superior to that achieved with the conventional administration of rituximab.

In the United States, the 3 most commonly used rituximab-containing regimens are FCR, fludarabine plus rituximab (FR), and bendamustine plus rituximab (BR). When using the FCR regimen, the dose of rituximab is frequently increased to 500 mg/m^2, beginning with the second treatment cycle, based on favorable results from a study conducted at the M.D. Anderson Cancer Center.[5] This single-arm study treated 224 CLL patients with FCR as initial therapy; rituximab was administered at 375 mg/m^2 for the first cycle and increased to 500 mg/m^2 for the subsequent cycles 2–6. Treatment with this FCR combination resulted in an overall response (OR) rate of 95% (95% CI, 92–98%), with a high CR rate of 70% (95% CI, 63–76%). However, it remains unproven if this increase in dosage is indeed associated with an improved patient outcome. Notably, the results of this study suggest that this FCR regimen produces a modestly higher response rate compared with the FR regimen, which was evaluated in the Cancer and Leukemia Group B (CALGB) 9712 study.[6] The CALGB 9712 study evaluated the addition of rituximab (375 mg/m^2) to fludarabine compared with fludarabine alone. Following 6 courses of FR or fludarabine alone, stable or responding patients received 4 weekly consolidation doses of rituximab. After consolidation, FR treatment was associated with an OR rate of 90% and a CR rate of 47%. Although comparison of the M.D. Anderson study with the CALGB 9712 study suggests that the FCR regimen produced improved response rates compared with FR (OR, 95% vs 90%; CR, 70% vs 47%), it is important to note that the M.D. Anderson study included patients with a median age that was 6 years younger than those in the CALGB study, as well as

a lower proportion of patients with advanced stage disease (33% vs 41%). The 2 regimens are currently being compared in a CALGB-led intergroup study.

The benefit of rituximab maintenance therapy in CLL also remains unknown. Although this has been evaluated in small studies, none to date have clearly demonstrated a benefit in comparison with other maintenance therapy.[7-9] Therefore, rituximab is not currently used in the maintenance setting.

Bendamustine

The U.S. Food and Drug Administration (FDA) approval of bendamustine was based on the results of a phase III randomized, open-label, multicenter study in 319 patients with previously untreated advanced-stage CLL.[10] Patients were randomized to receive either bendamustine (100 mg/m^2 on days 1 and 2) or chlorambucil (0.8 mg/kg on days 1 and 15) every 4 weeks for a maximum of 6 cycles. Significantly more patients in the bendamustine arm experienced a CR or PR compared with the chlorambucil arm (68% vs 31%; *P*<.0001), and more patients receiving bendamustine achieved a CR (31% vs 2%). Bendamustine treatment also resulted in a significantly superior median PFS (21.6 vs 8.3 months; *P*<.0001). Both grade 3 and 4 hematologic toxicities (40% vs 19%) and severe infections (8% vs 3%) occurred more frequently with bendamustine compared with chlorambucil; however, bendamustine was still considered to have a manageable safety profile.

Based on this study, the recommended dosage of single-agent bendamustine in patients with CLL is 100 mg/m^2 on days 1 and 2, every 4 weeks (Table 1). However, in clinical practice, bendamustine is more frequently given in combination with rituximab for initial treatment. In this case, the dosage of bendamustine is reduced to 90 mg/m^2 on days 1 and 2, every 4 weeks. In the setting of relapsed/refractory CLL, bendamustine is more commonly dosed at 70 mg/m^2 on days 1 and 2 every 4 weeks in combination with rituximab. Although the optimal dosage of rituximab in this setting is also not clear, the standard dose of 375 mg/m^2 is generally used when combined with bendamustine. Patients are premedicated against nausea and vomiting, but prophylactic antimicrobials are generally not used because the risk of opportunistic infection is relatively low, and their use is not considered to be cost-effective.

Table 1. Dose Recommendations for Bendamustine Therapy

Indication	Dose (mg/m^2), days 1 and 2*
CLL	
Initial therapy, single agent	100
Initial therapy, with rituximab	90
Relapsed/refractory, single agent (fludarabine naïve)	70 (100)
Relapsed/refractory, with rituximab	70†
Follicular/low-grade NHL	
Initial therapy, with rituximab	90
Relapsed/refractory, single agent	120
Relapsed/refractory, with rituximab	90
Aggressive B-NHL	
Relapsed/refractory, single agent	120
Relapsed/refractory, with rituximab	90
T-cell, NK, Hodgkin Lymphoma	
Relapsed/refractory	Unknown
Multiple myeloma	
Relapsed/refractory	100

*All are every 4 weeks except aggressive B-cell which is every 3 weeks.
†Escalate to 90 mg/m^2 if tolerated.

Summary

Although the optimal doses and schedules of rituximab and bendamustine to treat CLL or non-Hodgkin's lymphoma (NHL) have not been determined, the standard doses described here are likely to continue to be used in the future. As new combination strategies and new agents are introduced, it is unlikely that rigorous clinical studies will be conducted to evaluate these basic dosing questions. While these drugs themselves have not been demonstrated to cure patients, they serve as important building blocks upon which newer and better regimens may be created. One direction includes the use of lower doses to minimize toxicity. For example, a consensus meeting was recently convened to determine the optimal dose and schedule of bendamustine.[11] During this meeting, it was determined that the administration of bendamustine (120 mg/m^2 on days 1 and 2) every 3 weeks, as approved for NHL, should be extended to every 4 weeks to improve patient tolerability and acceptance. When combined with bendamustine, rituximab is generally administered once per cycle, as it is when combined with fludarabine. In patients with severe autoimmune complications, it is possible to consider first using it in combination with bendamustine instead of fludarabine, in order to achieve higher dose levels more quickly and to circumvent further autoimmune complications.

Several new agents have also been investigated in the treatment of CLL and NHL. For example, the anti-CD52 monoclonal antibody alemtuzumab was recently approved as

a single agent for the treatment of CLL. The recommended dosage schedule of alemtuzumab is intravenous infusion 3 times per week for up to 12 weeks.[12] During the first week, the dosage of alemtuzumab is dose escalated from 3 mg to 10 mg to 30 mg. Many patients experience infusion-related adverse events, including flu-like symptoms, during the initial week(s) of administration.[13] Although these symptoms are generally mild to moderate in severity, they are associated with patient discomfort and can lead to the discontinuation of therapy.[14] A phase II trial investigated the tolerability of the subcutaneous administration of alemtuzumab.[15] Grade 1 or 2 injection-site reactions were frequently reported with the first dose, but their incidence gradually tapered off and subsided by the sixth dose. Although this study suggests that this alternative administration of alemtuzumab is well-tolerated, its efficacy as compared with standard intravenous administration remains to be determined. Aside from infusion-related reactions, another major issue associated with alemtuzumab therapy for CLL patients is the possibility of infectious complications. A number of both randomized and nonrandomized studies suggest that the occurrence of infectious complications, including opportunistic and fatal infections, may be prohibitive against the use of alemtuzumab following chemotherapy.[16,17] However, despite this risk, the use of alemtuzumab after chemotherapy may be beneficial in some cases, in order to fully eradicate minimal residual disease, which is associated with prolonged survival.[18]

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Optimizing Rituximab Therapy

Jonathan W. Friedberg, MD

Over the past several years, the management of patients with hematologic malignancies has been greatly advanced with the introduction of monoclonal antibody therapies.[1] Chief among these is rituximab, a chimeric monoclonal antibody directed against the CD20 antigen. CD20 is primarily expressed on the surface of both normal and malignant B cells. Rituximab is thought to induce B-cell death through several proposed mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis.[2,3]

Optimal Dosing of Rituximab

Rituximab is currently indicated for the treatment of both previously untreated and relapsed/refractory NHL. Although rituximab is now almost ubiquitously used in the treatment of CD20-positive B-cell NHL, the optimal dosage and schedule of administration of the antibody therapy has not been established. The approved dosage is 375 mg/m^2, which is administered once weekly for 4–8 weeks.[4] This dosage and schedule was determined empirically, and relatively few clinical studies have addressed the optimal dosage of rituximab in lymphoma.

When rituximab is administered as a monotherapy, the standard regimen (once weekly over 4 weeks) results in the accumulation of satisfactory blood levels of the antibody that are maintained for a period of weeks to months.[5,6] Conversely, when rituximab is administered in combination with chemotherapy, its use is generally restricted to once per chemotherapy cycle. This generally equates to once every 3–4 weeks, depending on the treatment regimen. A phase II study in which the frequency of rituximab therapy was increased in combination with cyclophosphamide, doxorubicin, prednisone, vincristine (CHOP) chemotherapy (DENSE-R-CHOP) suggested a modest benefit in efficacy, although an increase in toxicity was also observed.[7] The DENSE-R-CHOP regimen includes an increased number of rituximab doses at the beginning of treatment, thereby increasing the total number of rituximab doses compared with standard R-CHOP. These results have prompted the development of a randomized trial in diffuse large B-cell lymphoma (DLBCL) to further evaluate the benefit of an increased number of rituximab doses when administered in combination with chemotherapy. This trial will randomize elderly patients with diffuse large B-cell lymphoma (DLBCL) to receive standard R-CHOP or DENSE-R-CHOP. Because 3 treatment-related deaths occurred in the phase II trial, mandatory prophylaxis against opportunistic infections will be administered to patients in the DENSE-R-CHOP arm.

Maintenance Therapy with Rituximab Monotherapy

Maintenance therapy with rituximab is not beneficial in the treatment of DLBCL, as was demonstrated in a 2-stage randomized trial.[8] In this study, 632 older patients (≥60 years) with untreated DLBCL were randomly assigned to receive either CHOP or R-CHOP. Following therapy, responding patients (in both arms) were re-randomized to receive either maintenance rituximab or observation. At a median follow-up of 3.5 years, the 3-year failure-free survival (FFS) rate was significantly higher among patients in the R-CHOP group compared with the CHOP group (53% vs 46%, *P*=.04). However, no significant differences in survival were observed according to induction or maintenance therapy, and the FFS rate was not prolonged for patients who received maintenance rituximab following R-CHOP. Because of the apparent lack of benefit associated with maintenance rituximab in patients with DLBCL, especially among patients who received induction R-CHOP treatment, its use in this setting has not been further explored.

The benefit of maintenance rituximab is more controversial in patients with follicular lymphoma (FL). The optimal schedule of single-agent rituximab in FL was demonstrated in the SAKK 35/98 study, which included 202 patients with either chemotherapy-naive or pre-treated FL.[9] All patients received 4 standard weekly doses of rituximab (375 mg/m^2); those patients who responded or had SD were randomized to receive either 4 additional doses of rituximab consolidation therapy (administered at 2 month intervals) or observation. At a median follow-up of 35 months, the median event-free survival (EFS) was significantly prolonged among patients who received prolonged rituximab therapy compared with observation alone (23 vs 12 months; *P*=.02; Figure 1). This study was recently

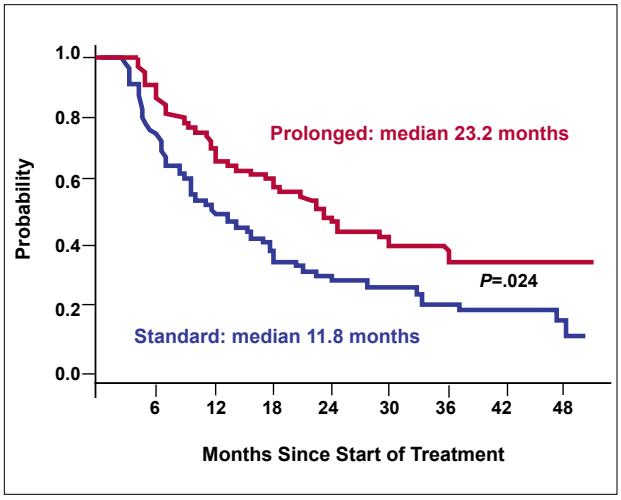


Figure 1. Prolonged versus standard rituximab event-free survival.

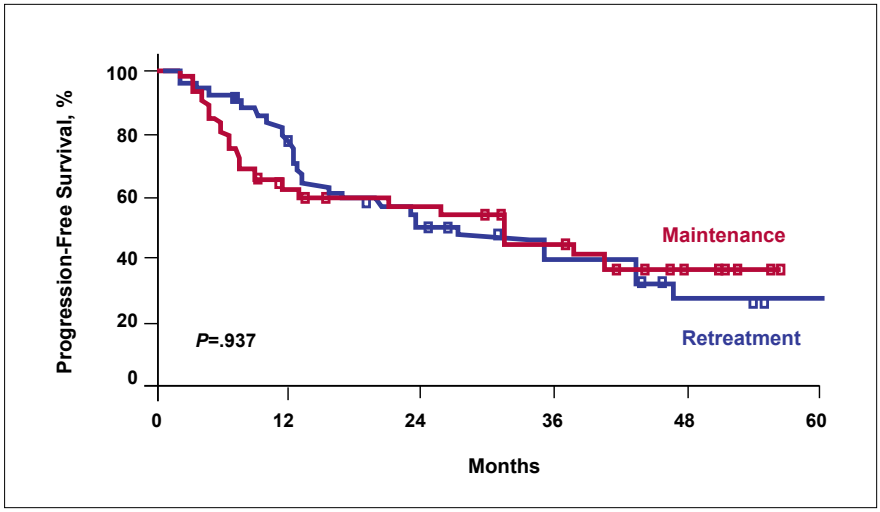
Adapted from *Blood.* 2004;103:4416.

updated at the 2009 American Society of Clinical Oncology (ASCO) Annual meeting, which presented the results of a long-term follow-up.[10] After a median follow-up of 8.9 years, the median EFS was significantly prolonged among patients who received rituximab consolidation compared with observation (24 vs 13 months, *P*=.0012). Importantly, no long-term toxicity resulting from treatment was observed. The authors concluded that patients treated with extended rituximab therapy (8 doses of rituximab over 1 year) have approximately a 25% chance of remaining in remission at 5 years, and a 20% chance of remaining in remission at 8 years. Because of the relatively low toxicity that was associated with extended therapy, the 8 dose extended schedule of rituximab should be seriously considered when using it as a single-agent treatment for FL. However, one important caveat to this conclusion is that the benefit associated with extended rituximab treatment was relatively limited to those patients who had exhibited a major response to induction rituximab therapy; and the majority of these patients were those with newly diagnosed (treatment-naive) disease.

There are several clinical studies addressing the question of whether rituximab should be given on a predetermined maintenance schedule or if its subsequent administration should be held until the time of relapse. A randomized phase II trial of the Minnie Pearl Cancer Research Network, which included 114 patients treated with a standard 4-week course of rituximab, randomized responding patients to receive maintenance rituximab or rituximab re-treatment at the time of progression.[11] Both OR and CR rates were higher among patients in the maintenance arm, and the median PFS was also prolonged among patients receiving scheduled maintenance rituximab compared with rituximab re-treatment at progression (31.3 vs 7.4 months; *P*=.007). However, the duration of rituximab benefit was similar between the 2 groups, suggesting that either approach may be a reasonable strategy (Figure 2). It is also important to note from this study that the duration of rituximab benefit was limited in both groups.

The question of rituximab scheduled maintenance versus re-treatment has been subsequently explored in the Eastern Cooperative Oncology Group (ECOG) 4402 Rituximab Extended Schedule Or Retreatment Trial (RESORT) study, which recently met its accrual goal.[12] This phase III trial is designed in a similar fashion to the previously described phase II Minnie Pearl Cancer

Figure 2. Duration of rituximab benefit is limited. Within 3 years, a majority of patients become refractory to rituximab. New treatments are still needed for follicular NHL.



Research Network trial. The study is currently ongoing, and results have not yet been reported.[13]

One major concern associated with extended rituximab therapy is the possibility of developing an increased resistance to rituximab. Although the evidence to date does not suggest this, it is possible that issues with resistance could emerge with longer maintenance regimens. Until future studies investigate this, the regimen established in the SAKK 35/98 trial—standard rituximab therapy (375 mg/m^2 weekly over 4 weeks) followed by 4 subsequent doses given at 2 month intervals—is considered the optimal schedule for rituximab monotherapy. An ongoing SAKK follow-up trial is exploring prolonged maintenance (5 years) in this setting.

Rituximab Maintenance Therapy Following Rituximab Combined with Chemotherapy

Although there are several studies that have evaluated the role of maintenance rituximab following chemotherapy, there is limited data on the role of maintenance rituximab following rituximab-containing chemotherapy regimens.

A prospective, randomized phase III trial conducted in the Netherlands evaluated the benefit of maintenance rituximab following induction chemotherapy with or without rituximab.[14] A total of 465 patients with relapsed/refractory FL were first randomized to receive induction therapy with CHOP or R-CHOP. Following therapy, patients with either a CR or PR were re-randomized to receive maintenance rituximab (375 mg/m^2 every 3 months for a maximum of 2 years) or observation. As expected, compared with CHOP, induction therapy with R-CHOP was associated with a significantly improved OR rate (72.3% vs 85.1%; *P*<.001) and CR rate (15.6% vs 29.5%; *P*<.001). R-CHOP was also associated with a significantly improved median PFS from first randomization compared with CHOP (33.1 vs 20.2 months; HR, 0.65; *P*<.001). Compared with observation alone, maintenance therapy with rituximab resulted in a significantly improved median PFS from second randomization (14.9 vs 51.5 months; HR, 0.40; *P*<.001). The benefit of maintenance rituximab on median PFS remained significant in patients after both CHOP (HR, 0.30; *P*<.001) and R-CHOP (HR, 0.54; *P*=.004). The 3-year overall survival (OS) was also improved with rituximab maintenance therapy compared with observation (85% vs 77%; HR, 0.52; *P*=.011), although the significance of this benefit is not completely clear.

Several observations regarding this study are important to consider when evaluating the data. First, in the United States, most FL patients are treated upfront with R-CHOP and would therefore not be candidates to receive CHOP again at relapse.[15] Second, the patients included in this study were rituximab-naive; however, in the United States, most patients in the relapse setting are not rituximab-naive. Third, the observed response to induction therapy with either CHOP or R-CHOP was relatively low in this study, suggesting the included group of patients may be unique in some way. Therefore, the implications of this study for treatment of patients with relapsed/refractory FL in the United States may be limited, and not practice-changing. However, it does suggest that a maintenance regimen with rituximab may be beneficial following initial R-CHOP therapy. Although this is not yet known, the Primary RItuximab and MAintenance (PRIMA) trial will ultimately inform us in this regard.[16] The PRIMA trial randomized patients who had received an initial chemo-immunotherapy regimen (the majority of which were R-CHOP) to either rituximab maintenance therapy or observation. This study is completed, and the results are eagerly awaited.

Conclusions

Despite the profound success of rituximab, and its favorable impact on patients with both indolent and aggressive NHL, there are few studies that have explored the optimal dose and schedule of this antibody. When used as a single agent in indolent lymphoma, the SAKK schedule (375 mg/m^2 weekly x 4; then single dose q2 months x 4) is safe, and has demonstrated a favorable impact on PFS with long-term follow-up. Although most studies that combine rituximab with chemotherapy simply add rituximab to an existing chemotherapy schedule, studies are currently underway in Germany exploring whether additional doses of rituximab may improve outcome in this setting.

There is no role for rituximab maintenance following R-CHOP in DLBCL. A single study has suggested modest benefit when rituximab maintenance is used following R-CHOP in relapsed follicular lymphoma; however, the study population is quite different from patients currently treated in the United States. The phase III PRIMA trial should definitively define whether there is benefit to rituximab maintenance following initial rituximab-containing chemotherapy in de novo follicular lymphoma. Until those results are mature, rituximab maintenance in this setting is best reserved for clinical trials, or specific situations.

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Optimal Dosing and Scheduling of Bendamustine

Mathias J. Rummel, MD, PhD

Overview of Bendamustine

Although monoclonal antibodies such as rituximab have dramatically revolutionized the treatment approach for patients with indolent lymphoid malignancies, many patients eventually experience a disease relapse and require new therapeutic agents. Bendamustine has emerged as one such therapeutic alternative. Bendamustine is an intravenously administered agent that was approved in March of 2008 for the treatment of patients with CLL.[1] It also received approval in October of 2008 for the treatment of patients with indolent B-cell NHL that had progressed during or within 6 months of treatment with a rituximab-containing regimen.

Although bendamustine displays structural similarities to both alkylating agents and antimetabolites, it does not exhibit cross-resistance with other cytotoxic drugs.[2,3] Bendamustine has been shown to possess unique mechanisms of action, which may explain its activity in patients with lymphoma that has relapsed or is resistant to alkylating agent-based treatment.[2]

Bendamustine was first constructed in the former East German Democratic Republic during the early 1960s. Despite a lack of clinical data to validate its use, bendamustine was initially used as monotherapy for patients with NHL, CLL, multiple myeloma, Hodgkin lymphoma, and breast cancer. After the re-unification of Germany, several clinical studies were initiated to more systemically study and determine the role of bendamustine in these malignancies.

Clinical Trials of Single-Agent Bendamustine

Despite a large body of empirical evidence supporting the use of bendamustine, there was a need to perform phase I dose-finding studies in order to determine the optimal dosage of the drug. However, these studies were limited to patients with solid tumors, and therefore it was unknown if the findings were translatable to patients with lymphoid malignancies.[4-8] From these dose-finding studies, it was apparent that a total single-agent bendamustine dose of approximately 300 mg/m^2 every 4 weeks was the maximally tolerated dose.

The GCLLSG recommended a much lower dose of bendamustine (70 mg/m^2 on days 1 and 2 every 4 weeks) for patients with relapsed or refractory CLL.[9] Recently, findings from a phase I study of pre-treated (fludarabine-naive) CLL patients led the authors to recommend the dose of 100 mg/m^2 on days 1 and 2 every 4 weeks for future clinical investigation.[10] This same recommended dose of bendamustine was also shown to be safe and effective as frontline therapy in previously untreated CLL patients.[11]

A pivotal open-label, multicenter phase III trial demonstrated that single-agent bendamustine was superior to single-agent chlorambucil in patients with previously untreated CLL.[11] In this study, 319 patients were randomized to receive either bendamustine (100 mg/m^2 on days 1 and 2) or chlorambucil (0.8 mg/kg on days 1 and 15) every 4 weeks for a maximum of 6 cycles. Single-agent bendamustine therapy resulted in a significantly higher rate of PR compared with chlorambucil (68% vs 31%; P<.0001); of these, bendamustine also produced a higher rate of CR (31% vs 2%). Bendamustine significantly lengthened the median PFS compared with chlorambucil (21.6 vs 8.3 months; P<.0001). Although more patients in the bendamustine arm experienced grade 3 or 4 hematologic toxicity or infection, its toxicity profile was considered to be manageable.

Two phase II clinical trials in the United States have evaluated single-agent bendamustine in patients with NHL that was relapsed or refractory to rituximab. Both evaluated bendamustine administered at a dose of 120 mg/m^2 on days 1 and 2 every 3 weeks.[12,13] In the first of these studies, 44% of 76 patients were able to complete the planned 6 cycles of treatment, while the median number of cycles completed was 5 (range, 1–9).[12] Adverse events (23%) and disease progression (14%) were the most common reasons for treatment termination. Interestingly, this study also showed that previous treatment with radio-immunotherapy may be associated with an increased risk of bendamustine dose delays or termination. An OR rate of 77% was reported in this trial, with a 34% rate of CR or unconfirmed CR. The median PFS of patients in this study was 7.1 months, and the median duration of response was 6.7 months. The second phase II trial showed similar activity.[13] In this study, which included 100 NHL patients with rituximab-refractory disease, the OR rate was 84%, which included a 32% rate of CR or unconfirmed CR. The median PFS was 9.7 months, and the median duration of response was 9.3 months. Together, these 2 studies demonstrate that single-agent bendamustine

is active in NHL patients with rituximab-refractory disease, producing response rates that are comparable with the 2 other agents (I^{131}-tositumomab and Y^{90}-ibritumomab) currently approved in this setting.[14, 15]

The general schedule of administration of bendamustine over days 1 and 2 of each cycle was determined empirically. Initial studies of intravenous bendamustine administered over a less convenient 5 consecutive day schedule, which was then reduced to the 2-day schedule now used. Reducing this to a 1-day schedule has not been well investigated, primarily due to the thought that this schedule would be too toxic for the patient. Therefore, dosages of single-agent bendamustine generally should be administered with the 2-day schedule.

Clinical Trials of Bendamustine in Combination with Rituximab

The GCLLSG CLL2M phase II study was conducted to evaluate the combination of bendamustine with rituximab in patients with relapsed CLL. Patients received bendamustine (70 mg/m^2 on days 1 and 2) plus rituximab (375 mg/m^2 on day 1 for the first course; increased to 500 mg/m^2 for subsequent courses). An initial report of 31 evaluable patients showed an OR rate of 65%, of which 13% were CRs.[16] The most frequent grade 3 or 4 adverse events reported were related to myelosuppression, including thrombocytopenia (11.9%), lymphopenia/neutropenia (10.8%), and anemia (6.3%).

In NHL, there is far more clinical trial experience evaluating bendamustine in combination with rituximab compared with bendamustine monotherapy. Clinical data have demonstrated that the addition of rituximab to bendamustine results in a slight increase in toxicity, and therefore the dose of bendamustine is generally lowered when given in combination with rituximab. However, the question of whether it is truly necessary to reduce the dose of bendamustine when combined with rituximab has not been evaluated in a clinical study.

Bendamustine was evaluated in combination with rituximab for the treatment of NHL in a multicenter study by the Study Group indolent Lymphomas (StiL).[17] In this study, bendamustine (90 mg/m^2 on days 1 and 2 every 4 weeks) was administered with rituximab (375 mg/m^2 on day 1) to patients with relapsed or refractory NHL. An OR rate of 90% (95% CI, 80–96%) was achieved, with a 60% rate of CR (95% CI, 47–72%). The median PFS among these patients was 24 months (5 to >44 months), and the median OS was not yet reached (Figure 1). The major toxicity experienced was grade 3 or 4 myelosuppression, including leukopenia (16%) and thrombocytopenia (3%). Data from the StiL study were later confirmed in a U.S. trial of patients with relapsing (nonrituximab refractory)

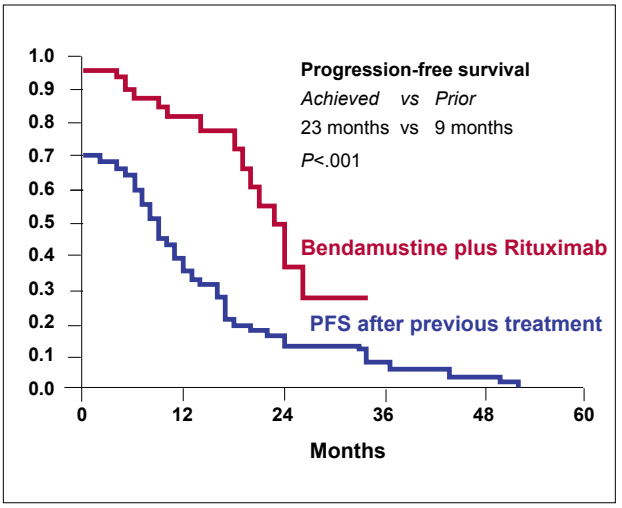

Figure 1. Bendamustine plus rituximab.

NHL.[18] A similar regimen of bendamustine (90 mg/m^2 on days 2 and 3 every 4 weeks) combined with rituximab (375 mg/m^2 on day 1) was used. Similar to the data reported in the StiL, an OR of 92% was achieved, with a 55% rate of CR. The median PFS was 22.9 months (95% CI, 20.3–26.3 months).

Based on these favorable results, the StiL has developed 2 prospective, randomized phase III trials comparing the combination of bendamustine plus rituximab with 2 standard combination regimens. The first compares the addition of rituximab to bendamustine with R-CHOP as first-line therapy in patients with NHL (Figure 2).[19] A preliminary analysis showed comparable response rates between the 2 regimens, with a much lower toxicity associated with rituximab plus bendamustine. An OR rate of 93% was reported for both arms. More patients in the R-CHOP arm experienced grade 3 or 4 leukopenia compared with the rituximab plus bendamustine arm (41% vs 16%). A similar proportion of patients in each arm completed 6 cycles of therapy (82% in the rituximab plus bendamustine arm compared with 86% in the R-CHOP arm). Updated results of this study are expected to be reported soon. In addition, these updated results will also evaluate the activity and superiority of rituximab plus bendamustine compared with R-CHOP across patient subgroups, including younger versus older patients and those who will undergo stem cell transplantation at the time of relapse. The second trial initiated by the StiL is investigating the combination of bendamustine with rituximab compared with fludarabine plus rituximab in patients with relapsed/refractory NHL.

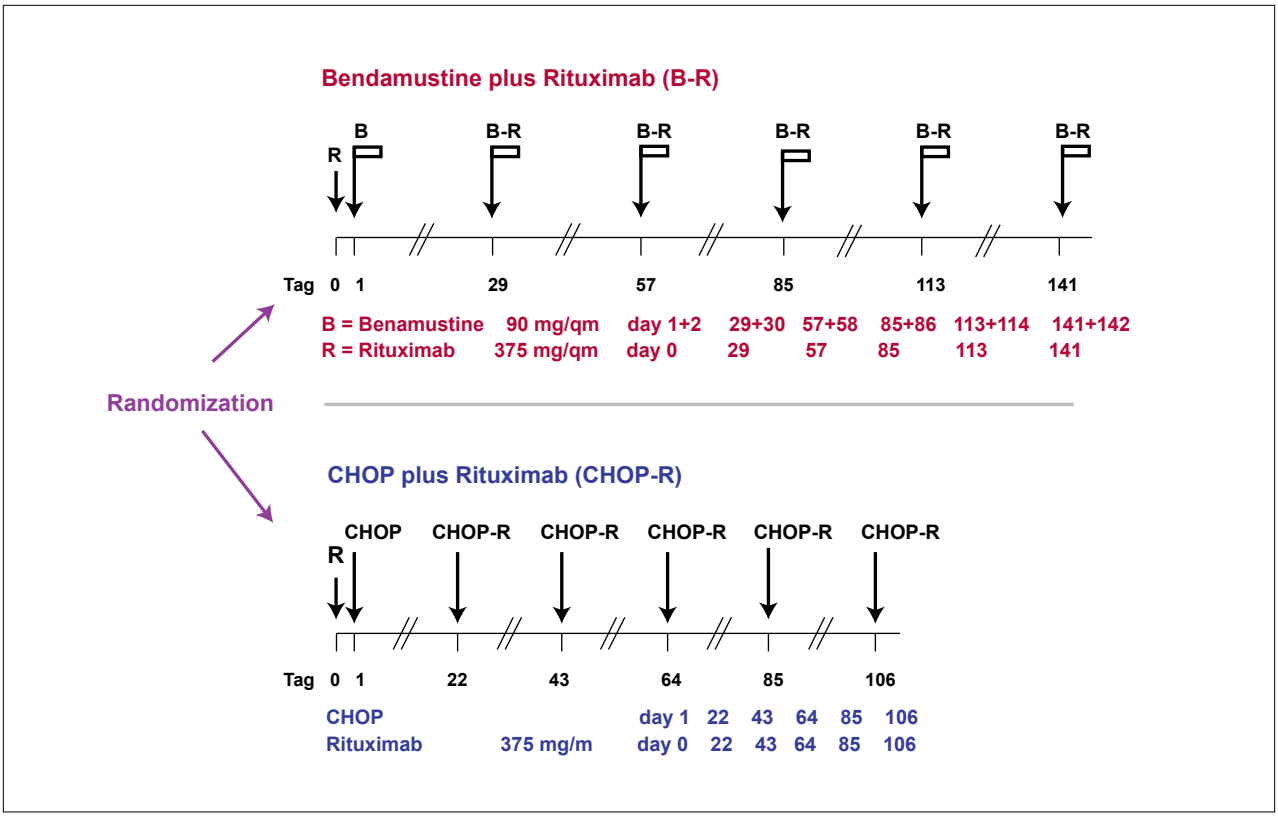

Figure 2. Bendamustine plus rituximab versus R-CHOP.

Standard Treatment with Bendamustine

Several doses and schedules of bendamustine are currently used. In the United States, the approved dose of single-agent bendamustine is 100 mg/m^2 on days 1 and 2 of a 28-day cycle for CLL, and 120 mg/m^2 on days 1 and 2 of a 21-day cycle for NHL.[20] However, this dose is typically dropped to 90 mg/m^2 on each day when administered in combination with rituximab, due to concerns of myelosuppression. The administration of bendamustine every 3 weeks versus every 4 weeks has not been extensively investigated in clinical studies.

In general, 6 cycles of chemotherapy are given to patients. However, because bendamustine results in myelosuppression, especially in the relapse setting, it is possible that patients would benefit from a more conservative approach resulting in fewer bendamustine cycles. In several of the clinical trials evaluating bendamustine in patients with relapsed/refractory disease, many patients did not receive all 6 planned cycles of bendamustine. Although the median number of cycles was lower (4.8 cycles), treatment still resulted in an impressive response rate. Bendamustine generally induces a fast response, with responses observed after 2 cycles at most. In cases where there is no response to 2 cycles of bendamustine treatment, the compound will likely not be active in that patient and an alternative therapy should be given.

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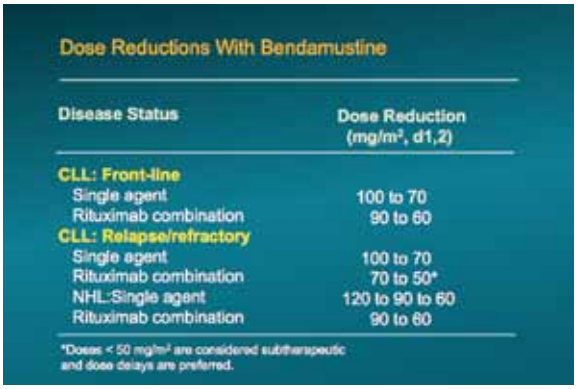

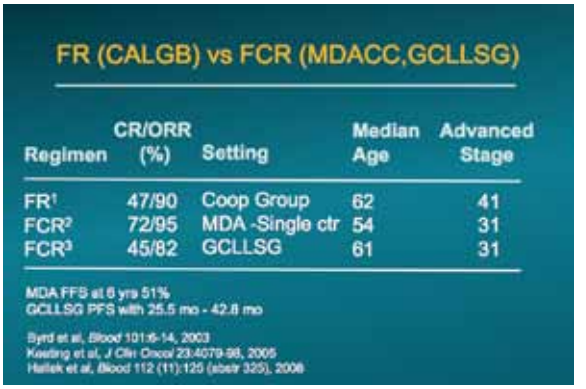

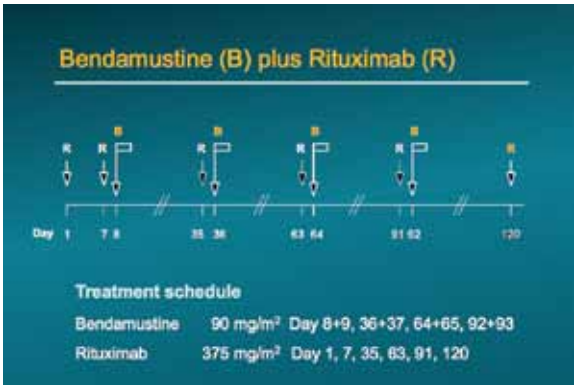

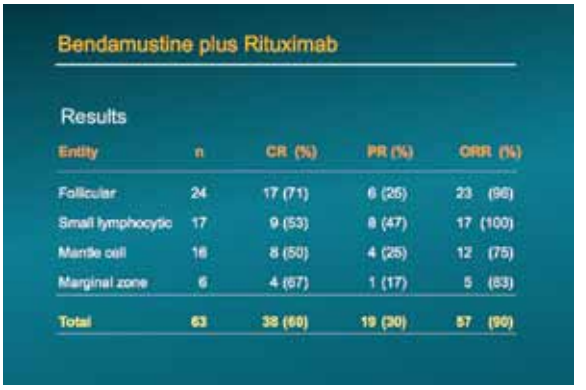

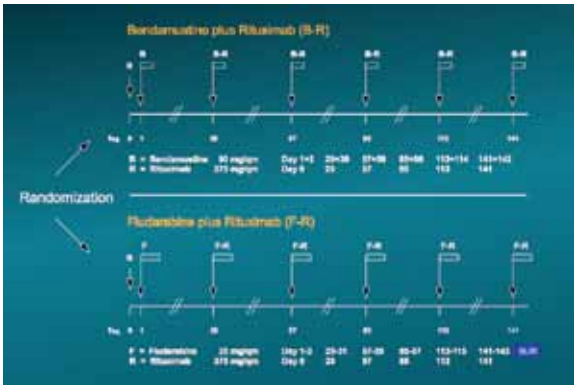

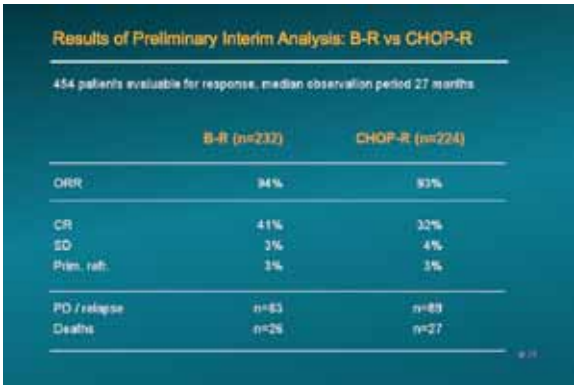

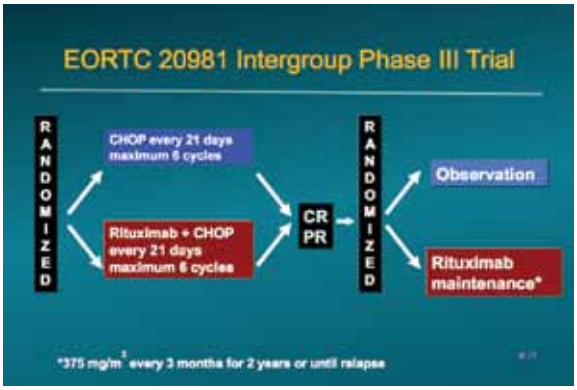

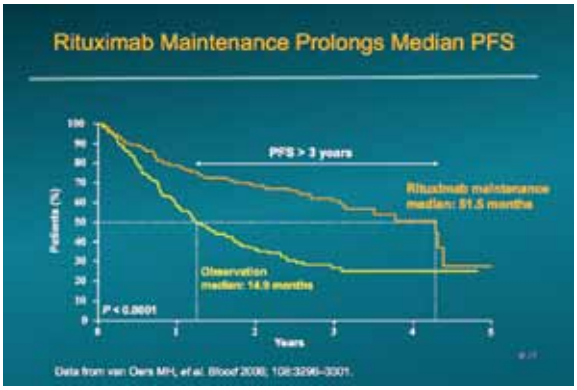

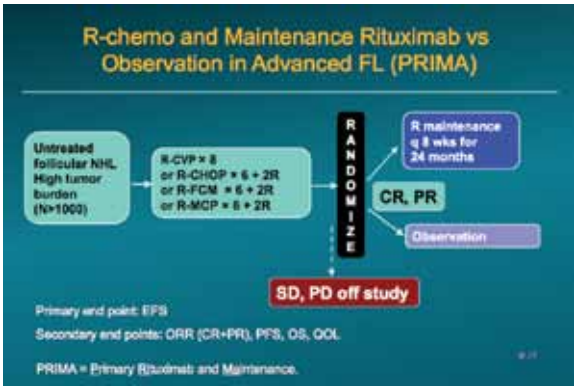

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