Clinical Roundtable Monograph

Current Treatment Options for NHL Patients Refractory to Standard Therapy: Recent Data in Single-Agent and Combination Therapy

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Abstract

Rituximab plays an important role in the treatment of non-Hodgkin lymphoma (NHL). In spite of high response rates achieved with this monoclonal antibody, however, many patients with NHL tend to relapse and become refractory to rituximab over time. At the 2009 meeting of the American Society of Hematology (ASH), researchers presented results from several new approaches that may provide a boost to the NHL treatment armamentarium. Important long-term safety data were presented for bendamustine, a bifunctional alkylating agent that was approved by the US Food and Drug Administration in 2008 for chronic lymphocytic leukemia and indolent B-cell NHL that is resistant to rituximab. In addition, emerging evidence concerning the combination of bendamustine, rituximab, and bortezomib was presented. Other trials discussed the use of novel monoclonal antibodies such as ofatumumab, GA101, PRO131921, and inotuzumab ozogamicin, which are directed at new biological targets for the treatment of NHL. Researchers also discussed recent trials of lenalidomide, an oral immunomodulator, alone and in combination with rituximab. Other novel agents discussed at the ASH meeting included clofarabine and CAL-101.

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New Drug Combinations for Non-Hodgkin Lymphoma

Bruce D. Cheson, MD

At the 2009 American Society of Hematology (ASH) meeting, we heard a number of exciting presentations of novel agents and combinations of drugs for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma (NHL). Bendamustine is a bifunctional alkylating agent that was approved by the US Food and Drug Administration (FDA) in 2008 for chronic lymphocytic leukemia (CLL), and indolent B-cell NHL that is resistant to rituximab. Bendamustine has been studied alone and in combination with rituximab in refractory patients. The results are promising and suggest that bendamustine may become an important addition to the NHL treatment armamentarium. Clofarabine has also shown some activity, particularly in patients with low-grade histologies, although its value has yet to be proven definitively.

Bendamustine as a Single-Agent Therapy

The US approval of bendamustine was based largely on a pivotal study by Kahl and colleagues[1] and supported by another study by Friedberg and associates.[2] These single-agent studies were of particular interest because they were conducted in patients with rituximab-refractory disease. In studies, bendamustine induced response rates that were higher than those reported for other drugs used in this patient population.

There has been considerable interest in seeing how the data for bendamustine held up after prolonged follow-up. At the 2009 ASH meeting, I presented the pooled data[3] from these 2 studies with a more detailed analysis and longer follow-up than the original publications. In the primary analysis, 68% of patients had follicular lymphoma, 20% had small lymphocytic lymphoma, 11% had marginal zone lymphoma, and 1% had lymphoplasmacytic lymphoma. One-third of the patients were refractory to their last chemotherapy, and 28% were refractory to their last alkylator-based therapy. More than half of the patients had received at least 6 cycles of bendamustine.

The pooled analysis provided insight into the long-term effects of bendamustine therapy. The most common non-hematologic toxicities were what we usually expect with bendamustine; they included primarily grade 1/2 nausea, fatigue, vomiting, and diarrhea. There were 50 infections in 48 patients, including herpes zoster in 18, herpes simplex in 7, candidiasis in 16, cytomegaloviral infection in 5, pneumocystis pneumonia in 2, and atypical mycobacterial infection and tuberculosis in 1 patient each. In the pooled analysis, secondary malignancies occurred in 6 patients: 3 developed myelodysplastic syndromes, 1 developed chronic myelomonocytic leukemia, 1 developed squamous cell carcinoma, and 1 developed acute myeloid leukemia (AML).

Of the 176 participants in the 2 studies, 161 were evaluable for the current efficacy analysis because their lymphoma was classified as indolent. The remaining 15 patients had transformed disease and were not included in the analysis. The overall response rate (ORR) was 76%, with 23% of patients achieving a complete response (CR) or CR unconfirmed (CRu). At a median follow-up time of 17 months, the median duration of response was 9 months. Responses tended to occur relatively soon after the initiation of therapy during cycles 1–3: in 75% of responders, the best response occurred during these cycles. Of particular note is that 34% and 24% of initial responders were still in response at 1 and 2 years, respectively. These figures are impressive for any single-agent in rituximab-refractory patients. In addition, response rates did not seem to correlate with Follicular Lymphoma International Prognostic Index (FLIPI) risk groups, patient age, the extent of prior therapy, or other risk factors. Even patients who were refractory to prior alkylators had a good response rate to bendamustine therapy: among the 127 patients previously treated with alkylators, the ORR was 88% in those sensitive to alkylators, compared with 59% in refractory patients. Median progression-free survival (PFS) was 9 months in the pooled analysis, with a slightly longer PFS among alkylator-sensitive patients than among alkylator-refractory patients.

The long-term data from these trials showed that bendamustine provides a high, durable response rate with good tolerability. Although several secondary malignancies occurred, the rate did not appear to be higher than what we would expect in a comparable population treated with other drugs or combination therapies typically used in this setting.

Ogura and colleagues[4] presented data from another study of single-agent bendamustine at the 2009 ASH con-

ference. This phase II study in 69 patients with relapsed or refractory indolent B-cell NHL or mantle cell lymphoma took place in Japan. Most patients had stage III–IV indolent B-cell NHL (86%) or mantle cell lymphoma (64%). Patients had received a median of 2 prior regimens, and 96% had received prior rituximab. About 40% of patients completed the planned 6 cycles of therapy. The CR rates in the follicular and mantle cell lymphoma patients were 66% and 73%, respectively, with an ORR of 91%. The overall CR was 67%. The response rates in this study appeared to be higher than those found in the US studies. Whether this increase represents differences in patient selection or prior therapy is unclear, but the results help confirm bendamustine as a useful agent in this population.

Bendamustine in Combination Therapy

Many drugs are available for the treatment of lymphoma, but their use in combination may be the key to realizing their full potential. Although bendamustine, bortezomib, and rituximab each have activity in patients with indolent lymphoma, combination therapy may provide a more effective approach. Phase I results for the VERTICAL (A Phase II Study of VELCADE [Bortezomib] in Combination With Bendamustine and Rituximab in Subjects With Relapsed or Refractory Follicular Lymphoma) trial, which identified the optimal dose of this combination, were originally presented at the 2009 American Society of Clinical Oncology (ASCO) meeting by Matous and colleagues.[5] This study tested 3 dose levels of bendamustine (50, 70, and 90 mg/m^2) in combination with bortezomib at 1.6 mg/m^2 and rituximab at 375 mg/m^2 every 5 weeks for 5 cycles. The investigators identified the phase II bendamustine dose level of 90 mg/m^2 and found that hematologic adverse events were manageable with the combination of drugs tested.

Fowler and colleagues[6] presented phase II results from the VERTICAL trial at the ASH meeting. VERTICAL was a single-arm, multicenter, phase II trial, with bortezomib and rituximab given on days 1, 8, 15, and 22 and bendamustine given on days 1 and 2 to a total of 63 patients. Five cycles were administered 5 weeks apart. The median age was relatively standard for this group of patients, at 58 years. Thirty-five percent of the patients enrolled had high-risk FLIPI scores. Patients had received a median of 2 prior therapies, and 39% were rituximab-refractory.

In the 49 patients with at least 1 post-baseline assessment at the time of analysis, the ORR was 84%, with 47% of patients achieving a CR and 37% achieving a partial response (PR). The regimen was well-tolerated, with few neurologic toxicities, and low rates of febrile neutropenia (5%) and infections. Although the results are promising, the value of adding bortezomib to the rituximab/bendamustine combination remains to be proven in a randomized trial.

A similar combination regimen was developed by Friedberg and colleagues.[7] In their trial, six 28-day cycles were planned, in which bendamustine was given on days 1 and 4, rituximab was given on day 1, and bortezomib was given on days 1, 4, 8, and 11. At baseline, patients had received a median of 4 prior therapies, and 32% were rituximab-refractory. Of the 31 patients enrolled thus far, 25 were evaluable for response at the time of the analysis. In these patients, the ORR was 84% and the CR/CRu rate was 52%. The PR rate was 32%, and 4% of patients had stable disease.

The use of bendamustine and rituximab alone has yielded an ORR of over 90%, with a CR/CRu between 50% and 60%.[8] The median time to progression is almost 2 years. Thus, while the results of recent combination trials are encouraging, it is difficult to know if the addition of bortezomib yields a better response than the 2-drug combination alone. These types of comparisons are being planned by the US Cooperative Groups focusing on indolent lymphoma and mantle cell lymphoma in the frontline setting.

Clofarabine for Non-Hodgkin Lymphoma

Although data with bendamustine alone and in combinations are encouraging, lymphoma patients often still require other treatment options. One promising agent is clofarabine, a second-generation nucleoside analog that has been used primarily in AML, acute lymphocytic leukemia, and myelodysplastic syndromes. Nabhan and associates[9] studied clofarabine in patients with relapsed and refractory NHL, including those who were rituximab-refractory. Histologies were varied and included 12 patients with diffuse, large-cell lymphoma, 5 with follicular lymphoma, 5 with small lymphocytic lymphomas, and 4 with anaplastic large T-cell lymphoma. Intravenous clofarabine was given on an outpatient basis over 1 hour on cycle days 1–5 for six 28-day cycles. The initial phase I portion of the study used a standard 3-by-3 design. When the maximum tolerated dose was determined, the phase II portion of the study was initiated. Of the 33 patients enrolled, 29 were evaluable for response and toxicity. The median number of prior therapies was 3, and 74% of the participants were considered to be rituximab-refractory.

In this trial, the median number of clofarabine cycles delivered was 4, and the maximum tolerated dose for phase II was 4 mg/m^2. The ORR was 51%, which included a 24% CR rate. The median duration of response was 7 months, but the median time to disease progression was 3.5 months, with a median overall survival of only 8 months. Most of the responses—particularly the CRs—tended to occur in patients with low-grade histologies rather than in those with large-cell lymphomas.

Thus, clofarabine did demonstrate activity, although it was of relatively brief duration. Whether combinations of clofarabine and other drugs will be pursued remains to be seen. Clofarabine represents another option for patients with relapsed and refractory disease. The hope is that the rational combination of new and novel drugs currently in clinical trials will further prolong the survival of patients with follicular and low-grade NHL.

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Novel Monoclonal Antibodies in the Treatment of Lymphoma

Jonathan W. Friedberg, MD

Rituximab is a drug that confers clear survival benefit in both indolent and aggressive lymphomas when combined with chemotherapy. It also has significant activity when used as a single agent in indolent histologies. Giving the drug on an extended schedule or in a maintenance program has significant impact on failure-free survival in indolent lymphoma. The main issue of concern with rituximab is that the majority of lymphoma patients will eventually become refractory to it. Indolent lymphomas frequently recur in the setting of recent rituximab treatment, either alone or in combination with chemotherapy.

Because of the tendency for lymphoma to become rituximab-refractory, there is a great deal of interest in developing new monoclonal antibodies. One of the problems in developing these new approaches is that we do not fully understand rituximab's mechanism in vivo. There are a variety of possible mechanisms for its efficacy, including antigen-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, and direct apoptosis.[1,2] In addition, some studies suggest that rituximab may contribute to subsequent T-cell response and the so-called *vaccinal effect*,[3] in which the death of follicular lymphoma cells causes a specific T-cell response to follicular lymphoma cells.

Several groups of researchers are pursuing alternative antibody approaches to the treatment of NHL. Data for several novel monoclonal antibodies were presented at the 2009 ASH meeting. The most interesting of these agents include ofatumumab, GA101, and PRO131921.

Ofatumumab

Ofatumumab is a novel anti-CD20 monoclonal antibody for lymphoma that was approved in 2009 for the treatment of relapsed CLL. It differs from rituximab in that it binds to the CD20 antigen at a unique epitope and increases complement-mediated cytotoxicity. Hagenbeek and colleagues[4] studied ofatumumab in a group of high-risk patients with follicular lymphoma. Among the 116 rituximab-refractory patients who were enrolled, over half were also refractory to their last course of chemotherapy. Patients were treated with 8 weekly infusions of ofatumumab at doses of up to 1,000 mg.

The primary endpoint for this trial was response to the 1,000 mg dose over 6 months from the start of treatment. Unfortunately, the results were disappointing, with an ORR of only 10% in the 1,000 mg group and 11% in the overall study population. The low ORR suggests that the resistance to rituximab cannot be overcome in most patients with this particular antibody. However, ofatumumab may still prove to have increased activity in patients who are sensitive to rituximab. Although ofatumumab appears to have better activity than rituximab in single-arm CLL studies, there are no head-to-head comparisons available to evaluate the 2 agents in that setting.

GA101

Another antibody in development for the treatment of NHL is GA101, the only type II antibody currently under study. Type II antibodies (such as tositumomab) differ from type I antibodies in their binding and lipid raft formation properties. In addition, type II antibodies are believed to have an increased potential for direct cytotoxicity compared with type I antibodies.[5]

Sehn and associates presented data from a phase I trial on GA101 at the ASH meeting.[6] The study enrolled 22 patients, including 10 with follicular lymphoma, 5 with CLL, 3 with diffuse large B-cell lymphoma (DLBCL), and 4 with other histologies. GA101 was given weekly for 4 weeks at a dose of 100–2,000 mg, followed by an extended maintenance program, similar to a single-agent rituximab regimen. Patients had received a median of 4 prior treatments, and half of the patients enrolled in this study were rituximab-refractory. Patients experienced very few severe adverse events, including 5 cases of grade 3/4 neutropenia, 1 case of tumor lysis syndrome, 1 episode of hypoxia, and 1 case of febrile neutropenia. Sixteen infusion-related reactions occurred with the first infusion, and 8 similar events occurred with all subsequent infusions. Several minor infections also occurred.

In this trial, the ORR was 25% and consisted entirely of PRs. Thirteen patients achieved stable disease, and

responses were noted in both rituximab-sensitive and rituximab-refractory patients. This trial suggests that GA101 is a safe and effective therapy, and that extended maintenance dosing does not appear to incur significant additional toxicities. The results provide an indication that patients who are refractory to rituximab are responding to GA101, so it appears that this new antibody may have some future promise in refractory patients.

A second study of GA101 was an update of a phase I trial originally presented by Salles and colleagues[7] at the 2008 ASH meeting. The original presentation included data for 12 NHL patients receiving GA101. In that analysis, the researchers found that GA101 was generally well-tolerated, with the most common adverse events including grade 1/2 infusion-related reactions and minor infections. The ORR was 58%, including a 25% CR rate and a 33% PR rate.

In the current report, also from Salles and associates,[8] the investigators shared final phase I results for 21 patients, along with some correlative studies. The median patient age was 64, and participants included those with follicular lymphoma (n=13), mantle cell lymphoma (n=4), DLBCL (n=1), Waldenström macroglobulinemia (n=1), small lymphocytic lymphoma (n=1), and lymphoplasmacytoid lymphoma (n=1). Patients had received a median of 4 prior therapies; 95% had previous exposure to rituximab and 48% had received stem cell transplantation. GA101 was given on days 1, 8, and 22, and every 3 weeks thereafter, for a total of 9 infusions. The study evaluated doses ranging from 50 mg to 2,000 mg per infusion in a 3-by-3 design.

Overall, GA101 was well-tolerated, with 1 case of grade 3 tumor lysis syndrome, 2 instances of grade 3 neutropenia, and 1 episode each of grade 3 anemia and grade 3 thrombocytopenia. The researchers found a significant increase in several plasma cytokines following the first infusion of GA101, which recovered by day 8. The rise in cytokines is indicative of the toxicities that can occur at the time of the first infusion of GA101 and corresponds to the grade 1/2 infusion reactions that tended to occur at that time. The researchers also found rapid B-cell depletion, which was sustained in the majority of patients. However, they observed no changes in immunoglobulin levels. The ORR was 43%, which included 5 CRs and 4 PRs. Interestingly, responses occurred at all FcγIIIRA genotypes, including the polymorphism that is typically unfavorable towards rituximab.

Taken together, these presentations show the promise of GA101 and the potential presented by this new target for treatment of refractory and relapsed NHL patients. Currently, a phase III trial is evaluating this antibody head-to-head against rituximab in relapsed follicular lymphoma.

Novel Antibodies in Early Development for NHL

Several new antibodies are in early-stage development for lymphoma. At the ASH meeting, I presented data on PRO131921, a third-generation humanized anti-CD20 antibody.[9] It is an engineered antibody that is believed to produce increased antibody-dependent cytotoxicity and complement-dependent cytotoxicity compared with rituximab. In animal models, it appears to mediate cell kill better than rituximab. In this trial, we enrolled 24 patients with relapsed and refractory indolent NHL at dose levels ranging from 25 mg/m² to 800 mg/m². The majority of patients—83%—had follicular lymphoma. All had been previously treated with rituximab, and some had not responded to recent rituximab therapy. The median number of prior therapies was 2.

PRO131921 had a similar safety profile to other agents, with slightly increased infusion reactions and a severe infusion reaction in 1 patient. The response rate was reasonable, particularly at the higher dose levels, where it approached 50%. Of the 22 patients evaluable at day 78 or later, 6 achieved a PR, 13 had stable disease, and 3 had progressive disease. Although this particular agent is unlikely to be further developed due to a corporate decision, it is important to note that pharmacokinetic studies showed a significant correlation between higher drug exposures and responses as measured by tumor shrinkage. The formal pharmacokinetic analysis in this study suggests that there is variability among patients in their metabolism of antibodies, and that pharmacokinetics should be evaluated in future studies when antibodies are given. Until now, the doses of antibodies provided to NHL patients have been determined in a somewhat arbitrary fashion. This study suggests that pharmacokinetic studies should become a part of the drug development process for antibodies in the future.

Antibodies Targeting Antigens Other Than CD20

There are several monoclonal antibodies in development that focus on targets other than CD20. The first is an anti-CD22 antibody. Dang and colleagues[10] presented findings on inotuzumab ozogamicin (CMC-544). Inotuzumab is a humanized antibody conjugated to calicheamicin, a potent cytotoxin that is used in gemtuzumab ozogamicin in the treatment of AML. In this study, inotuzumab was combined with rituximab in a group of patients with relapsed follicular lymphoma and DLBCL. The treatment program included 375 mg of rituximab given intravenously on day 1, followed by inotuzumab on day 2. The regimen was repeated for up to eight 28-day cycles. After the investigators established the maximum tolerated dose of 1.8 mg/m², 119 patients moved forward in the study. Not surprisingly, patients with recurrent DLBCL were generally older, with a median age of 72 years.

In the group of patients with follicular lymphoma, the ORR was very high, at 87%, and the median PFS was 23.6 months. In the DLBCL group, the ORR was 80%,

with a median PFS of 15 months. In a subgroup analysis, rituximab-refractory DLBCL patients fared worse than those who were more sensitive to rituximab. The rituximab-refractory patients in this study had an ORR of 20%, with a PFS of only 2 months.

Although this study was not randomized, the results do suggest that inotuzumab may be a promising agent in the treatment of NHL. Because it was given in combination with rituximab in this trial, it is difficult to tease out the effects of the new antibody compared with the effects of rituximab. However, the response rate that we expect of single-agent rituximab in the DLBCL population is only in the 30% range, so the data on the combination appear to be better, with acceptable levels of toxicities.

Almost all cases of B-cell lymphoma are CD19 positive, so CD19 is another new target for future monoclonal antibodies for NHL. Younes and associates[11] presented preliminary phase I data on SAR3419, an antibody conjugated to the toxin DM4, a tubulin inhibitor that binds to the vinca site. The researchers enrolled patients with relapsed/refractory CD19-positive B-cell lymphoma. To date, 29 patients had been enrolled on 7 dose levels, ranging from 10 to 270 mg/m^2. The patient population was highly refractory: patients had received a median of 4 prior therapies, and 7 patients had a history of prior autologous or allogeneic stem cell transplant (SCT).

During the dose-ranging portion of the study, the dose-limiting toxicity was reversible severe blurred vision, which was associated with microcystic epithelial corneal changes at doses of 208 mg/m^2.

At the time of the analysis, 25 patients had completed at least 2 cycles and were evaluable for tumor response. Reductions in tumor measurements were seen in 68% of patients, with 2 patients achieving PR and 3 achieving CR. It is remarkable that responses were noted even in this preliminary report of phase I data. SAR3419 shows significant promise, although the potential for increased toxicity when it is added to rituximab will need to be factored into any evaluation of the drug's possible benefits.

Randomized trials are required to definitively prove whether new antibody developments—be they changes in the antibody structure or pathways not targeted by rituximab—will truly result in improved clinical benefit for patients. Researchers will have many choices in designing future trials.

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Novel Agents for Non-Hodgkin Lymphoma

Brad S. Kahl, MD

Lenalidomide is an oral immunomodulator approved for use in patients with multiple myeloma and myelo-dysplastic syndromes with 5q deletion. Lenalidomide, which is a derivative of thalidomide, is believed to induce tumor cell death through its anti-angiogenic and immunomodulating properties.

At the 2009 ASH meeting, Witzig and colleagues[1] presented phase II data on lenalidomide in 217 patients with relapsed aggressive lymphoma. Approximately half of the patients enrolled had DLBCL, 26% had mantle cell lymphoma, 9% had grade 3 follicular lymphoma, and 15% had transformed lymphoma. Patients were given 25 mg lenalidomide daily for 21 days, followed by a 7-day break each cycle. The median patient age was 66 years, and patients had received a median of 3 prior regimens. The ORR was 35%, with a 13% CR/CRu rate and a 22% PR rate. Disease was stable in 21% of patients.

The response to lenalidomide was lowest in the DLBCL group: the ORR was 28% for this group, compared with 42% in both the mantle cell lymphoma group and the grade 3 follicular lymphoma group, and 45% in the transformed lymphoma group. For the entire study population, the median PFS was 3.5 months, and the median duration of response was 11.6 months. This duration is respectable for a single-agent oral drug in this group of patients. As is the case for ORR, the duration of response appeared to be best in the non-DLBCL groups. Although the median duration was 4.5 months in the DLBCL group, it was greater than 1 year in the transformed lymphoma group, and it was not reached in the other patient groups.

The toxicity of lenalidomide warrants noting. In this trial, grade 3/4 adverse events included neutropenia in 41% of patients, thrombocytopenia in 19%, anemia in 9%, and leucopenia in 7%. These toxicities resulted in dose reductions or therapy interruptions in 44% of the study population and drug discontinuation in 22% of patients.

This study shows that lenalidomide can produce durable remissions in aggressive, relapsed lymphoma, but more so in certain histologies, such as mantle cell lymphoma, grade 3 follicular lymphoma, and transformed lymphoma. Myelosuppression at the dose tested remains a significant concern, and it appears that additional studies on dosing and scheduling are warranted to optimize treatment.

RENEW (A Study to Evaluate the Efficacy of Lenalidomide as Maintenance Therapy After Completion of First-line Combination Chemotherapy in Patients With Mantle Cell Lymphoma) is an international, randomized phase III trial evaluating lenalidomide as a maintenance therapy after chemotherapy for older patients with mantle cell lymphoma. Lenalidomide will be compared against placebo, which should provide a better sense of the utility of this drug in the maintenance setting.

In another recent study of lenalidomide in the NHL population, Vose and associates[2] evaluated the drug in patients with relapsed/refractory disease who had received prior autologous SCT (autoSCT). The researchers pooled the results of 2 phase II studies: the previously discussed trial by Witzig and colleagues[1] and a study by Wiernik and associates,[3] which produced an ORR of 39% and a CR rate of 13%. As seen in other trials, responses to lenalidomide were less impressive for patients with DLCBL compared with other histologies: the ORR was 29% for DLCBL compared with approximately 60% for other histologies.

In this pooled analysis, there were 87 patients who met the criteria of relapsed aggressive lymphoma after autoSCT. In this group, the ORR was 39%, compared with 34% for the non-autoSCT study population. The CR/CRu rate was 13% for autoSCT patients, compared with 15% for non-autoSCT patients. The rate of PR was 26% for autoSCT patients and 19% for non-autoSCT patients. In autoSCT patients, the median PFS for all 87 patients was 3.8 months, and the duration of response for the 34 responders was 9.7 months. The rates of grade 3/4 adverse events were 44% for neutropenia, 33% for thrombocytopenia, and 9% for anemia. In particular, patients with a history of autoSCT were more likely to develop thrombocytopenia than were those without a history of autoSCT. The rates of all-grade thrombocytopenia were 51% in the autoSCT group and 30% in the non-autoSCT group (P=.001). For grade 3/4 thrombocytopenia, the rates were 33% and 16%, respectively (P=.002). These higher rates among autoSCT patients are not surprising, as patients who have undergone trans-

plantation typically have some impairment to their stem cell health and bone reserve, causing them to tolerate subsequent therapies somewhat less well. This difficulty often manifests as thrombocytopenia, which is demonstrated in this analysis.

In spite of the high rates of adverse events noted with lenalidomide, the good news from this research is that prior autoSCT does not appear to decrease the rate or quality of patient responses to lenalidomide. Of course, individuals will need to pay close attention to issues of thrombocytopenia, and more work must be done to establish the optimum dose and schedule of lenalidomide in future studies.

Lenalidomide in Combination With Rituximab

One of the postulated mechanisms of action for rituximab is antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC requires immune system effector cells, and preclinical data[4,5] indicate that lenalidomide enhances T-cell and K-cell mediated immune synapse formation, which potentiates ADCC, and creates a synergistic effect with rituximab. Thus, recent research has explored the combination of lenalidomide and rituximab in the treatment of NHL.

Dutia and associates[6] provided a preliminary report on an ongoing phase II trial of lenalidomide in combination with rituximab in 15 patients with relapsed indolent lymphoma (including follicular, small lymphocytic, and marginal zone histologies). Participants received 25 mg of lenalidomide for 21 days of a 28-day cycle, combined with rituximab at 375 mg/m^2 initiated on day 15 and repeated each week for 4 weeks. At the time of the analysis, 12 patients were evaluable for a response. The ORR was 83.3%, including a 41% CR rate and a 33% PR rate. After a median follow-up of 12 months, the median PFS had not yet been reached.

Although it is too early to draw definitive conclusions, this study suggests that there is impressive activity with the combination of lenalidomide and rituximab. There were, however, some issues with toxicity. Two of the first 4 patients developed tumor lysis syndrome. Consequently, the dose of lenalidomide was lowered to 20 mg daily, and a prophylactic dose of allopurinol was added to prevent this complication. Grade 3/4 neutropenia occurred in 25% of patients, and 16% reported grade 3/4 fatigue. Lymphopenia was reported in 33% of patients, and hyponatremia in 16%.

In a similar study, Wang and colleagues[7] studied the combination of lenalidomide and rituximab in patients with relapsed/refractory mantle cell lymphoma. In the phase I portion of the study, the researchers established the dose of lenalidomide at 20 mg/day, given for the first 21 days of a 28-day cycle, continued until disease progression or toxicity. Rituximab was given in its usual dose and schedule

(375 mg/m^2 weekly) for the first treatment cycle. In the phase II portion of the study, 45 patients received the 20 mg/day dose of lenalidomide. The median follow-up time was 11.4 months. The median age was 66 years, and patients had a median of 3 prior treatments with a fairly typical mantle cell demographic. The researchers observed an ORR of 53%, with minor responses or stability in a further 27%. They concluded that 80% of the patients received clinical benefit from the combination. The median PFS for patients in phase II was 12 months, and the median duration of response for responders was 25 months, indicating fairly impressive durability for this combination.

As in other trials of lenalidomide, however, this study found notable levels of toxicities. Investigators reported that 61% of patients had grade 3/4 neutropenia and 26% had grade 3/4 thrombocytopenia. Five percent of patients had grade 3/4 fatigue, which is quite profound fatigue. There was no report on the incidence of grade 2 fatigue or neuropathy, both of which can become a concern for patients on a prolonged course of therapy.

As in other trials, this study shows the promising activity of the combination of lenalidomide and rituximab. It would be particularly interesting to see more detail on the toxicity of this combination and to understand the details of dose adjustments and regimen modifications that are needed in patients who continue with therapy after an adverse event. The trial raises important questions: Could a lower dose of lenalidomide produce similar activity to the higher dose levels with less toxicity? Could remission duration be further enhanced with a prolonged rituximab schedule? These questions, and many others, will be examined in upcoming trials using combination rituximab/lenalidomide therapy in patients with mantle cell lymphoma.

Other Novel Agents for the Treatment of Non-Hodgkin Lymphoma

CAL-101 is a novel oral agent that is a selective inhibitor of class I phosphatidylinositol 3-kinase (P13K). This drug is unique because it targets the δ isoform, which is preferentially expressed in cells of hematopoietic origin. The specificity of CAL-101 may provide this drug with a better therapeutic window than other P13K isoforms.

Flinn and colleagues[8] presented findings from a phase I study that employed 3-by-3 dose escalations. During dose escalation, 3 patients per cohort were given 50, 100, 200, or 350 mg of oral CAL-101 twice daily. In the cohort expansion, 31 patients received 200 or 350 mg twice daily. At higher doses, issues with elevated transaminases emerged, so some cohort expansions were employed using lower doses. At the time of the analysis, the researchers had enrolled 57 evaluable patients with a mix of histologies, including

16 patients with indolent lymphoma, 13 with aggressive lymphoma, 18 with CLL, and 10 with AML. Patients had received a median of 5 prior therapies.

At the time of the analysis, most patients in the trial had received doses of 200 mg or 350 mg twice daily, for a median of 4 cycles. The drug did not demonstrate any activity in AML; of the 10 patients who received it, none showed a response. There were 4 objective responses out of 8 CLL patients, giving a response rate of 22%. Six of the 12 patients with aggressive lymphoma responded, and all of these responders were mantle cell lymphoma patients. Among the 15 patients with indolent lymphoma, 9 responded. None of the DLBCL patients responded.

The response rates for CAL-101 were fairly impressive in patients with follicular lymphoma and other indolent histologies. One interesting observation in CLL patients was that more than 50% of patients experienced an objective 50% reduction in their peripheral lymphadenopathy while on CAL-101. In addition, the researchers noted increasing peripheral blood lymphocytosis, as if there were a redistribution of tumor cells from one compartment to another. Although this phenomenon would preclude giving a classification of objective response in the trial results, it is clear that these CLL patients enjoyed substantial clinical benefit.

One issue with CAL-101 in this study is that increased levels of transaminases occurred at doses above 200 mg twice daily. Further study of the drug will focus on lower doses (100 mg and 150 mg twice daily) in an effort to find an effective dose with a lower rate of reversible transaminitis.

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Question and Answer Forum

Brad S. Kahl, MD Has recent research provided any insight into the optimal dosing and schedule of bendamustine?

Bruce D. Cheson, MD The problem with bendamustine is that the dose that was selected for the pivotal and supportive trials was 120 mg/m² days 1 and 2 every 21 days, which is probably too intensive. This dosing came from a German study without any pharmacokinetic background information. In clinical practice, when we give that dose, patients cannot tolerate it. There is a lot of dropout, and delays in therapy are common.

We had a consensus meeting a year and a half ago to discuss this issue, and we decided that the 120 mg/m² dose is probably fine if given every 4 weeks, but every 3 weeks is too intensive. When combined with rituximab, the dose should be lowered to 90 mg/m². For the first course, 6 cycles is fine, but in the relapse setting patients may not be able to tolerate it, so 4 cycles may be adequate. In the paper that came out of this meeting,[1] we provided guidelines for the optimal use of bendamustine in a variety of settings. It is important to know that if you give bendamustine at too high a dose, or too frequently, you will get high rates of hematologic toxicities, which may scare physicians away from using this effective agent.

BK One issue with the use of bortezomib is neurotoxicity, which can often manifest as painful peripheral neuropathy. In one trial[2] of its use in combination with rituximab and bendamustine, bortezomib was given on a once-weekly dosing schedule, while in another[3] it was used twice weekly. Can you make any comparison between those 2 trials and discuss what we may have learned from them about the optimal dosing of bortezomib?

BC We do not know the best way to use the drug. There are some data suggesting that as a single agent, it may not be as effective when given weekly instead of twice weekly. However, de Vos and colleagues tested bortezomib in a combination regimen, given weekly or twice weekly, and the results were quite comparable, except that there was much less neurotoxicity when the drug was given weekly.[4] So I would think that weekly dosing might be preferable to twice-weekly dosing in combinations.

Jonathan W. Friedberg, MD I agree that we do not really know the best dosing in combination therapy. Our motivation was based on the observation of the drug as a single agent that was made by the Memorial Group. Neither our study[5] nor the VERTICAL trial[6] found profound neurologic toxicity. We did have some grade 3 episodes in our study, but with the appropriate dose modification to bortezomib, I think they are manageable. And I think that the patient populations in these 2 trials tended to be reasonably heavily pretreated. If a bortezomib platform were to be moved upfront before patients are exposed to vinca alkaloids and other potential neurotoxic agents, my expectation is that bortezomib would be tolerated much better.

The other toxicity that we observed giving bortezomib twice weekly was varicella zoster reactivation. This effect has been described in myeloma and other lymphoma studies, and I think that if you are going to use this regimen, or similar regimens, prophylaxis with acyclovir is probably indicated.

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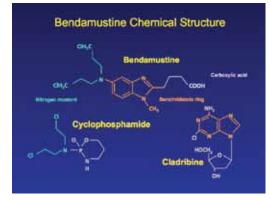2. Fowler N, Kahl BS, Rosen P, et al. Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: encouraging activity in the phase 2 VERTICAL study. *Blood*. 2009;114. Abstract 933.
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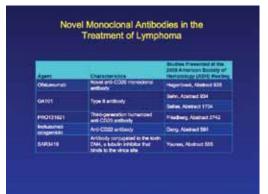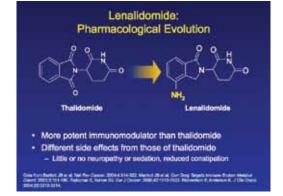
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