Recent Advances in NHL

Highlights from the 51st ASH Annual Meeting and Exposition, December 5–8, 2009, New Orleans, Louisiana

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Abstract

Current clinical trials evaluating new treatment options for non-Hodgkin lymphoma (NHL) are numerous. Studies are comparing traditional chemotherapy with high-dose regimens; various rituximab-based combinations for upfront therapy, many with newly developed drugs; new agents for rituximab-refractory patients; and other approaches. Several intriguing studies were presented at the 2009 annual meeting of the American Society of Hematology (ASH). The efficacy of bendamustine plus rituximab for the first-line treatment of advanced follicular, indolent, and mantle cell lymphomas was the most important finding presented. Other important results included the lack of superiority of high-dose chemotherapy plus rituximab compared with traditional chemotherapy plus rituximab for high-risk patients with aggressive B-cell lymphomas, and promising outcomes with the combination of lenalidomide plus rituximab for both rituximab-refractory and non–rituximab-refractory indolent NHL. The crucial data presented at the 2009 ASH annual meeting are discussed and evaluated by 2 leading experts in the treatment of NHL, Drs. Myron S. Czuczman and Mathias J. Rummel.
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Introduction

Non-Hodgkin lymphoma (NHL) comprises several disease subtypes, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma, and others. Among NHL malignancies, treatment regimens often overlap, but not always; therefore, novel agents and regimens need to be clinically evaluated in different NHL histologies and subgroups. DLBCL, an aggressive B-cell lymphoma, is the most common type of NHL, with a peak incidence among people in their 60s. FL and indolent B-cell lymphomas present serious therapeutic challenges, with no current regimen offering curative treatment. Rituximab-based therapy has vastly improved outcomes, but all patients eventually relapse. Maintenance regimens are numerous, but it is unknown whether any truly extend survival time. Mantle cell lymphoma is rare, and although recent advances have improved outcomes, the majority of patients relapse, and many become drug-resistant.

The monoclonal antibody rituximab has had a significant impact on outcomes. When added to chemotherapy—the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen, most commonly—rituximab improves survival for many NHL subtypes. However, relapse is common, and subsequent maintenance therapy is not proven to extend survival. Clinical trials to evaluate potentially effective maintenance regimens are under way. Maintenance following chemotherapy, immunotherapy, or chemoimmunotherapy has been found to improve time to disease progression but not survival.

Several new agents are showing promising results, with many already being integrated into the therapeutic armamentarium. Among patients with rituximab-refractory FL and indolent NHL, bendamustine is associated with a response rate of up to 80% and a median progression-free survival of 9.7 months. Rituximab plus bendamustine can achieve a response rate of up to 92%, with a median duration of 23.1 months, among patients not refractory to rituximab. As the following review of studies from the 2009 annual meeting of the American Society of Hematology (ASH) will show, bendamustine plus rituximab may be a viable frontline option for patients with advanced indolent B-cell lymphoma.

Other important agents for the treatment of NHL include lenalidomide, an immunomodulatory drug that has demonstrated single-agent activity in FL and, as will be discussed here, intriguing outcomes when given in combination with rituximab for the treatment of NHL. Romidepsin, a novel histone deacetylase inhibitor, was recently approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma patients who have received at least 1 prior systemic therapy. Pralatrexate, a novel antifolate, was FDA-approved for the treatment of peripheral T-cell lymphoma. Awaited data from clinical trials using novel second-generation anti-CD20 monoclonal antibodies (eg, ofatumumab) were presented at the ASH 2009 meeting. Studies are continuing with these novel agents to evaluate their full potential in the treatment of NHL.

Current clinical trials evaluating various approaches for the treatment of NHL are focusing on new agents and...
also alternative chemotherapy regimens, such as high-dose therapy. Several studies presented at the 2009 ASH annual meeting offered encouraging insights about treatment advances and will be reviewed in this monograph. Some advances appear to be ready for integration into clinical practice for appropriate patients. Others provide important indicators for the next step in research.

In this monograph, world-renowned NHL experts Myron S. Czuczman, MD, and Mathias J. Rummel, MD, PhD, discuss highlights from the 2009 ASH annual meeting presentations on NHL treatment. Their discussion provides useful insights for healthcare professionals who treat patients with NHL.

References

Q&A Discussion of Select Presentations With:

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Let’s begin with the phase III study comparing bendamustine plus rituximab versus CHOP plus rituximab for the first-line treatment of advanced follicular, indolent, and mantle cell lymphoma, presented as abstract 405. Dr. Rummel, could you describe this study?

Dr. Mathias J. Rummel  
This was a randomized study to compare the efficacy of these 2 treatment regimens, with a primary endpoint of proving progression-free survival (PFS) of bendamustine plus rituximab (BR) compared with the standard treatment of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) plus rituximab (CHOP-R). A total of 549 previously untreated patients were randomized to either treatment arm, with 513 patients evaluable for response and toxicity. Patient characteristics were well-balanced, and the median age was 64, thus representing a typical patient population for this disease entity. All of the patients who were enrolled in the study had advanced disease (Table 1).

With regard to efficacy, the response rate was similar between the 2 arms: 92.7% for patients randomized to the BR (n=221) regimen versus 91.3% for those randomized to CHOP-R (n=212; Table 2). The complete response rate was higher for the BR arm (37.6% vs 30.0%, respectively; *P*=.0262). This difference translated to a statistically significant longer median PFS (54.9 months vs 34.8 months, respectively; *P*=.00012). Importantly, this statistically significant difference in PFS was seen across all lymphoma subgroups included in the study.

In general, patients randomized to the BR treatment arm experienced comparatively less toxicity than those randomized to receive CHOP-R. The most commonly observed nonhematologic toxicities included infectious complications (127 patients on CHOP-R vs 96 patients on BR; *P*=.0025), paresthesias (73 vs 18 patients, respectively; *P*<.0001), and stomatitis (47 vs 16 patients, respectively; *P*<.0001). Among grade 3-4 hematologic toxicities, the most common were neutropenia, observed during 46.5% of treatment cycles among patients enrolled in the CHOP-R arm versus 10.7% of cycles in the BR arm (*P*<.0001), and leukocytopenia (38.2% vs 12.1%, respectively; *P*<.0001).

With regard to organ toxicity, again, the bendamustine-containing regimen was better tolerated. Skin toxicity was seen more often among patients randomized to the bendamustine-containing treatment arm compared with the CHOP-R arm (42 vs 23, respectively; *P*=.0122).

Based on these findings, we concluded that BR is a very effective treatment combination for non-Hodgkin lymphoma.

Table 1. BR vs CHOP-R for Frontline NHL: Inclusion Criteria

<table>
<thead>
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<th>Criteria</th>
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<tr>
<td>• B-symptoms</td>
</tr>
<tr>
<td>• Hematopoietic failure (hemoglobin &lt;11 g/dL, granulocytes &lt;1,500/μL,</td>
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<tr>
<td>thrombocytes &lt;100,000/μL)</td>
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<tr>
<td>• Large tumor burden (3 areas &gt;5 cm or 1 area &gt;7.5 cm)</td>
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<tr>
<td>• Rapid progression (increase of tumor mass &gt;50% within 6 months)</td>
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<tr>
<td>• Complications due to disease (eg, pain, infarction of spleen,</td>
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<td>hyperviscosity syndrome)</td>
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Table 2. BR vs CHOP-R for Frontline NHL: Response Rates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BR, %</th>
<th>CHOP-R, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>92.7</td>
<td>91.3</td>
</tr>
<tr>
<td>CR</td>
<td>39.6</td>
<td>30.0</td>
</tr>
<tr>
<td>SD</td>
<td>2.7</td>
<td>3.6</td>
</tr>
<tr>
<td>PD</td>
<td>3.5</td>
<td>2.8</td>
</tr>
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BR=bendamustine plus rituximab; CHOP-R=cyclophosphamide, vincristine, doxorubicin, prednisolone plus rituximab; CR=complete response; NHL=non-Hodgkin lymphoma; ORR=overall response rate; PD=progressive disease; SD=stable disease.
lymphoma (NHL) and could be the treatment of choice for this disease entity in the future.

**What is the next step for further evaluating this treatment combination for NHL?**

**MJR** Based on these positive findings, we have selected BR as the standard treatment for the next NHL study to be conducted by the Study Group for Indolent Lymphomas (StiL). This study will evaluate 2 different rituximab-based maintenance therapies, with all patients receiving BR as induction therapy.

In the opinion of StiL, the question of whether BR represents an advancement over CHOP-R for the first-line treatment of advanced NHL has now been answered: It does. The next step needs to focus on further improving outcomes in these disease entities by altering other aspects of treatment.

**Does BR offer an improvement in overall survival as well, or is more time needed in order to determine this important factor?**

**MJR** It is always very difficult to determine overall survival improvements for an indolent disease. In addition, many more patients who were randomized to receive CHOP-R then received salvage therapy with BR, compared to those who were initially randomized to the bendamustine-containing regimen (40% vs 13%, respectively). This difference further complicates the evaluation of overall survival strictly in terms of the 2-arm comparison because there is also a crossover effect. A longer observation time is needed in order to determine the benefit in terms of overall survival, but it may be difficult to gain a completely accurate reading because of the crossover aspect.

**Are there any cautions with regard to any changes in practice that this study might lead to?**

**Dr. Myron S. Czuczman** This presentation was one of the most interesting and important at the 2009 American Society of Hematology (ASH) annual meeting. It is very exciting to have a novel regimen that is less toxic but perhaps equally or more effective than CHOP-R. One caveat is that we do need to see the final publication if we are going to change our treatment practices in light of these findings, because the data need to be viewed in greater detail. For example, it is important to note that the study included patients with grades 1 and 2 follicular lymphoma (FL) but not patients with grade 3 FL. It is very possible that BR would be very effective in treating patients with grades 3A and 3B FL, but we have no data to support the use of this combination in this setting. There are limited data to date that support the current use of bendamustine in the treatment of aggressive B-cell lymphoma (eg, grade 3 FL, diffuse large B-cell lymphoma).

**MJR** Generally speaking, I would not use BR to treat an aggressive lymphoma because CHOP-R can be curative in this setting. The StiL study described above pertains only to grades 1 and 2 FL, and the authors provide no information about the use of BR in patients with grade 3A or 3B FL.

I agree, it is essential to see the final publication, where all the details will be clarified and transparent. Another important point is that it is difficult to compare this study with other studies of CHOP-R in the treatment of NHL because not that many have been done. There was a study by Czuczman and colleagues that evaluated CHOP-R in a young patient population with previously untreated indolent lymphoma, and another randomized study by Hiddemann and colleagues. In this latter study, patients received interferon consolidation therapy and had a younger median age than in the present BR study. In addition, 23% of the patients included in the study by Hiddemann and colleagues underwent autologous stem cell transplant following CHOP-R treatment. So it is very difficult to compare this new study with historic results.

**MSC** This is an important point. The multi-group study on which I was first author that you mentioned above was a phase II trial, and as noted, the patients had generally lower risk disease than those in the present study.

In that multi-group study, patients with a higher risk, in terms of the Follicular Lymphoma Independent Prognostic Index (FLIPI), fared worse than those with intermediate- or low-risk FLIPI scores. It would be interesting to make a formal comparison among higher-risk patients who received BR versus CHOP-R in the Rummel study.

In the trial by Hiddemann and colleagues, higher-risk patients also fared comparably worse than other risk groups, as did the higher-risk patients in the study by Press and coworkers evaluating CHOP followed by a single infusion of 131I-tositumomab. A US-intergroup phase III study evaluating R-CHOP versus CHOP followed by 131I-tositumomab was recently closed to accrual, and data continue to be gathered and monitored; a full analysis of this important trial is anticipated in the near future.

**Are there any data from the present BR vs CHOP-R study on high-risk FLIPI patients compared with low- and intermediate-risk patients?**

**MJR** The final publication will include these details; this particular analysis was not presented at the 2009 ASH meeting.
Looking at patients who experienced a complete response and those who experienced a partial response, was there any difference between these groups in terms of PFS?

MJR Among patients randomized to the CHOP-R arm, complete responders generally fared better than partial responders. However, among patients in the BR arm, that difference was not observed.

MSC That’s very interesting, because we have a general assumption that patients who experience a complete response, with no residual measurable disease, should do better than those with a partial response, who should in turn do better than those with stable disease—who of course do better than patients whose disease progresses during the study. So this finding is very intriguing and needs further evaluation and analysis.

Based on these findings, would you now treat NHL patients with BR as a first-line therapy?

MSC Based on the ASH presentation, without the final publication, there are definitely patients for whom I would recommend BR as a first-line treatment. These patients would include those who cannot handle an anthracycline due to a history of cardiac problems, and also elderly patients with other medical problems. CHOP chemotherapy is effective, but it takes a toll on the patient and carries significant side effects. BR is a very good alternative for these patients. It won’t be long before patients begin asking their doctors for this regimen, having read about it on the Internet, and so it is important that we know the population of patients for whom BR is an appropriate choice.

MJR Yes, I am already receiving e-mails from patients all over the world asking me about this regimen. In the end, if the clinician has concluded that BR is superior in efficacy to CHOP-R, then it should be given to any NHL patient whose disease subtype was included in the study, not only those who may have problems with an anthracycline or other similar challenges.

MSC CHOP-R has been around for many years, and that longevity adds weight when considering first-line treatment options for NHL. With BR, we don’t have the experience of having given it to our patients. It will take some time for oncologists to become comfortable with it—to learn when and how to adjust doses, how to use concurrent growth factor support, and when to monitor and treat drug-related side effects.

How were the skin rashes treated in the StiL study?

MJR The skin rashes, which were more common among patients receiving BR than among those receiving CHOP-R, were generally treated with systemic steroid therapy, often in combination with an antihistamine. With this approach, the rash was usually gone by the following day.

The study investigators wondered whether patients were reacting to rituximab and if this reaction was then leading to bendamustine toxicity. If this is the case, then it might be best to administer the rituximab alone on day 1, followed by bendamustine without rituximab on days 2 and 3. However, this approach is only hypothetical and has not yet been tested. It is also important to note that the skin reactions seen in the study were never life-threatening and generally were not very severe. It is extremely rare that a patient cannot tolerate bendamustine.

MSC That being said, the percentage of skin reactions among patients on the BR arm was fairly high, right?

MJR Yes, there were 40–80 reactions seen among 260 patients. This side effect was also seen among half of the patients in the CHOP-R arm, so the occurrence was about twice as high for patients receiving BR. In my experience outside of this study, I have seen this skin reaction in only 2% or 3% of patients who receive bendamustine.

MSC There was an important cautionary letter from Cephalon in the United States regarding the administration of allopurinol to patients before bendamustine. Clinicians have been giving allopurinol prior to bendamustine when there was a concern about the potential development of tumor lysis syndrome in patients with bulky disease and/or in leukemic phase of lymphoma. This approach was associated with at least 1 case each of Stevens-Johnson syndrome and toxic epidermal necrolysis, but the precise relationship to bendamustine is uncertain. Nevertheless, Cephalon recommended that allopurinol be avoided in patients being treated with bendamustine either alone or in combination.

MSC CHOP-R has been around for many years, and that longevity adds weight when considering first-line treatment options for NHL. With BR, we don’t have the experience of having given it to our patients. It will take some time for oncologists to become comfortable with it—to learn when and how to adjust doses, how to use concurrent growth factor support, and when to monitor and treat drug-related side effects.

MJR Allopurinol has never been recommended as a prophylactic treatment before bendamustine therapy, and so this approach was not addressed in the study protocol. Among patients without any circulating malignant cells, I have rarely seen any tumor lysis in a typical indolent lymphoma, and so we did not consider including allopurinol in the protocol. On the study’s Internet home page, we did include an instruction to avoid allopurinol unless it is specifically clinically recommended.
If a patient experiences a severe skin reaction with the first or second cycle of BR, would you continue premedication with hydrocortisone?

MJR Yes, but for the majority of patients who experience a skin reaction, this side effect occurs once during the first treatment cycle, and is already resolved by the next cycle.

MSC This insight is important, because as BR is integrated into NHL treatment practices, physicians should be aware that there may be a learning curve with regard to treating side effects, and that this skin reaction, for example, is easily treated and often does not last. Otherwise, if such problems occur, this potentially effective therapy could be left by the wayside because physicians may prefer to use drugs with which they are already comfortable.

The BR versus CHOP-R study was definitely the most important of the NHL studies presented at ASH 2009. We don’t yet have data on the long-term effects of bendamustine, and we need that extended follow-up so that we can better understand “life after bendamustine,” so to speak. But this is a very exciting advance for the first-line treatment of advanced-stage NHL.

Could you summarize the study presented by Schmitz and colleagues of CHOEP-14 plus rituximab versus mega-CHOEP plus rituximab for young, high-risk patients with aggressive B-cell lymphoma?

MJR The purpose of this study was to compare aggressive conventional chemotherapy plus rituximab versus repetitive high-dose chemotherapy also in combination with rituximab. Several such studies have already been done, but the results have not been very conclusive. Schmitz and colleagues escalated the chemotherapy doses to the highest possible level (Table 3). This increase in dose was made possible by also increasing the frequency of bone marrow stem cell support. This “mega” regimen was compared to the straightforward 8 cycles of CHOEP (CHOP plus etoposide 300 mg/m² given every 2 weeks).

The study results showed a higher mortality rate on the mega-CHOEP arm compared with the standard CHOEP arm (23% vs 16%, respectively; Table 4). Importantly, there were more lymphoma-associated deaths on the mega-CHOEP arm: 13 patients versus 8 patients, respectively. The mega-CHOEP arm also showed a higher rate of treatment-related deaths.

The complete response rate was 79% among patients randomized to the mega-CHOEP plus rituximab arm versus 72% among those on the standard CHOEP plus rituximab arm—the higher dose of chemotherapy did not induce a higher complete response rate. Conventional CHOEP plus rituximab was associated with a superior 3-year event-free survival (71.0% after 8 cycles of CHOEP-14 plus 6 cycles of rituximab vs 56.7% after mega-CHOEP plus 6 cycles of rituximab; \( P = .050 \)), as well as an improved (though not statistically significant) PFS (76.0% vs 64.6%, respectively; \( P = .119 \)).

Does this study answer the question of whether increasing the dose of CHOEP chemotherapy improves outcomes compared with standard chemotherapy, in rituximab-containing regimens?

MJR Yes, and this was another very important study presented at ASH. During the ASH presentation, the study’s first author noted that the oversight committee and the study group decided to close the mega-CHOEP plus rituximab arm early due to the increased mortality rate and lower efficacy. I think this study clearly indicates that patients undergoing treatment with chemotherapy plus rituximab are not better served by receiving a higher dose of CHOEP.
**MSC** The basic conclusion of this study is that more is not always better. It is important to keep in mind a couple of points that this evaluation demonstrated. First, patients on the mega-CHOEP arm experienced greater toxicity without improved outcomes.

Second, this study raises questions about what chemotherapy regimen is best. For example, some studies have found that younger patients are able to tolerate a higher dose of etoposide, such as that used in the CHOEP-14 regimen, whereas older patients may have more difficulty with CHOEP-14.9,10 But are there other chemotherapy regimens or schedules other than mega-CHOEP that would maximize the benefit from chemotherapy?

Also, could induction chemotherapy be optimized in individual patients based on risk stratification? If so, what regimen should be used? These questions remain unanswered and are important to address in future studies, especially for improving the treatment of younger high-risk patients who are able to tolerate aggressive therapies. Right now, treatment approaches vary around the world. For example, some investigators in Italy rotate different combinations of high-dose drugs that are not cross-resistant and/or are evaluating the benefit of autologous stem cell transplant in patients in first complete remission.11 More time is needed in order to determine if this approach improves outcomes.

For the most part, highly aggressive chemotherapy is restricted to younger patients. But we have not yet determined whether this approach increases treatment-related mortality. Do patients benefit in the long-term from this aggressive treatment? What are the long-term toxicities? Are these patients developing secondary malignancies, such as myelodysplastic syndrome or acute myeloid leukemia, as a result of aggressive chemotherapy? These questions need to be answered as we continue to improve the treatment of NHL.

**MJR** These are important questions. However, we also need to now adopt the findings of this study into our practice. The authors concluded that CHOEP-14 plus rituximab is associated with the best treatment results ever recorded for young, high-risk NHL patients.3 It is essential that we continue moving treatment forward and not go back to the past to look at questions that have already been answered.

**MSC** I don’t think any group has ever compared rituximab plus CHOEP-14 versus rituximab plus CHOEP-21. We do not yet know the standard of care for young, high-risk patients.

**MJR** True. The message of the study by Schmitz and colleagues6 is that mega-CHOEP plus rituximab does not achieve any improvements in outcome compared to standard CHOEP plus rituximab. This conclusion was unexpected and is very interesting. Additional work is needed to clarify the optimal regimen for young, high-risk NHL patients.

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**Table 5.** CORAL Study: Responses According to Prognostic Factors

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<th></th>
<th>N</th>
<th>Overall Response (CR + CRU + PR)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>All patients</td>
<td>245</td>
<td>63%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prior rituximab</td>
<td>124</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>No prior rituximab</td>
<td>122</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>Relapse/refractory &gt;12 months</td>
<td>140</td>
<td>88%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Relapse/refractory &lt;12 months</td>
<td>106</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>IPI score &lt;2</td>
<td>160</td>
<td>71%</td>
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<tr>
<td>IPI score &gt;1</td>
<td>76</td>
<td>52%</td>
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CORAL=Collaborative Trial in Relapsed Aggressive Lymphoma; CR=complete response; CRU=unconfirmed CR; IPI=International Prognostic Index; PR=partial response.

The CORAL study, which was presented as a joint symposium of ASH and ASCO, evaluated the treatment of patients with relapsed/refractory CD20-positive large-cell lymphoma with R-ICE versus R-DHAP. Could you discuss the results of this study?

**MSC** The CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study was a randomized trial in which patients received 3 cycles of R-ICE (rituximab, ifosfamide, etoposide, carboplatinum) or 3 cycles of R-DHAP (rituximab, dexamethasone, aracytine, cisplatinum).12 Although a joint venture between ASH and the American Society of Clinical Oncology (ASCO), with the abstract published through ASCO and not ASH, the study is important to include in this discussion.

After 3 cycles of salvage chemotherapy, all patients underwent autologous stem cell transplant. Patients that had achieved a complete or partial response were then randomized to maintenance rituximab versus observation. Patients with stable or progressive disease were taken off the study. It is too early to say whether there was any benefit to maintenance rituximab compared with observation.

What were the important findings here?
based therapy—CHOP-R or something similar—experienced a 51% response rate. By comparison, those who had received no prior rituximab showed an 83% response rate (Table 5).

Patients who had relapsed less than 12 months after initial induction therapy had a response rate of 46%, whereas those who had relapsed after more than 12 months following initial induction therapy had a response rate of 88%. Patients with no prior rituximab experienced a PFS rate of 62%, and those who had received prior rituximab had a PFS rate of 30% (Figure 1). Another interesting comparison is that patients with an International Prognostic Index (IPI) score of zero or 1 showed a 71% response rate, versus 52% among patients with an IPI score of 2 or 3. So with this study we are starting to see a new profile of patients: Those who have relapsed following rituximab therapy do not have as good of a response to rituximab-based salvage therapies as those patients who relapse following non–rituximab-containing induction regimens. Based on these findings, it’s clear that we need a better understanding of how to overcome this resistance in order to improve outcomes for patients who relapse after rituximab-based upfront therapy.

**MJR** I’m not sure I agree with this conclusion. The response rates seen among patients randomized to R-ICE versus those randomized to R-DHAP were fairly similar. The event-free survival and overall survival did not differ significantly. It is not possible to conclude from these findings which regimen is better for patients with relapsed large cell lymphoma.

**MSC** But a higher percentage of patients who had received prior rituximab-based upfront therapy and did not respond to salvage chemotherapy could not undergo subsequent transplant; these patients died from refractory disease.

**MJR** The core objective with regard to the randomization was to determine which chemotherapy regimen was more effective for these patients, and the data showed that there was no difference.

**MSC** Yes, this is true, but the underlying insight regarding patients who had received prior rituximab lends additional weight to this study. These data showed us, for the first time in relapsed/refractory diffuse large B-cell NHL, that prior rituximab is associated with poorer outcomes to second-line therapy. So we have to wonder whether a different regimen, not R-ICE or R-DHAP, would improve outcomes in these patients.

With regard to rituximab-refractory patients, another interesting NHL study was that presented by Hagenbeek and colleagues evaluating ofatumumab for FL patients who have relapsed following rituximab-based therapy. Could you describe this study?

**MSC** A total of 116 patients were treated in this study. Patients received 8 weekly infusions of ofatumumab, as follows: All patients received 300 mg for dose 1, followed by either 500 mg or 1,000 mg for doses 2–8. The overall response rate was 11%, which is not very promising. The results show that ofatumumab, a CD20 monoclonal antibody, as a single agent is not likely to be an effective treatment for this patient population. Adverse events observed in greater than 10% of patients included rash (15%), urticaria (14%), fatigue (14%), pruritus (13%), nausea (12%), pyrexia (11%), and cough (11%). The study authors noted that none of these were severe. Grade 3–4 hematologic toxicities included neutropenia (5%), anemia (3%), and thrombocytopenia (1%). Two patients experienced grade 3 infections.

![Figure 1. The Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study: progression-free survival (PFS) according to prior rituximab. Adapted with permission from Gisselbrecht C et al.](image-url)
It is disappointing that the use of a different anti-CD20 agent in rituximab-refractory FL patients did not show any major impact on outcomes.

Yes, and that really is the take-home message of this study. However, the findings also point to the need to better understand how to evaluate new CD20 monoclonal antibodies. For example, ofatumumab might be most effective in combination with other agents. Single-agent comparisons—upfront ofatumumab versus rituximab, for example—might be useful. But combination regimens also need to be tested. Do we gain anything by combining different biologic agents with chemotherapeutic or target-specific agents with varying activities and mechanisms of action? Studies to answer these questions are in the planning stages.

_lenalidomide is also being evaluated for the treatment of NHL. What is known about the mechanism of action of this agent in this disease setting?

_lenalidomide is an immunomodulatory drug with several potential mechanisms of action. Studies have found that this agent has direct activity against the tumor cell, affects cellular immunity, and also acts on the tumor microenvironment.14 The major mechanism at play may depend on the specific malignancy being treated.

There were 2 interesting studies of lenalidomide for NHL patients presented at ASH. Could you describe these?

One study, by Fowler and colleagues,15 evaluated lenalidomide plus rituximab as first-line therapy for patients with indolent B-cell NHL. This study was small, evaluating only 19 patients, but interestingly, the overall response rate was 84%, with 79% achieving either a complete response or unconfirmed complete response. The regimen was well tolerated in this patient population. The study gives us a glimpse into the potential efficacy of this combination for previously untreated patients, and indicates that there are non–cross-resistant novel agent combinations that could improve outcomes.

Dutia and colleagues16 reported a study of 15 patients with relapsed/refractory indolent NHL treated with lenalidomide plus rituximab. Here, lenalidomide was given every 20 days, and rituximab was given once a week for 4 weeks, an atypical schedule for rituximab. With 12 evaluable patients at the time of abstract submission, the overall response rate was 83.3% (n=10), with 5 patients achieving a complete response. The most common grade 3–4 adverse events included fatigue (16%), neutropenia (25%), lymphopenia (33%), and hyponatremia (16%). The authors noted that tumor lysis syndrome did not occur after prophylaxis was initiated, and they recommended that this approach be taken, particularly during the first few treatment cycles.

Is there currently one ideal regimen for the treatment of patients with FL?

No, it’s not possible to cure FL with any single agent or treatment approach at this time. Currently, we are hoping to identify regimens that provide a more durable remission duration. It may be possible to cure a subset of patients, but more alternatives are needed.

What are some of the promising regimens?

Well-tolerated unique combinations of novel agents, without the use of chemotherapy, such as lenalidomide plus rituximab, are promising. We will see as more data are gathered.

Yes, these are promising, but we must remember that these studies are phase II, and more follow-up is needed. Clearly, bendamustine is effective for these patients. Lenalidomide may play a role in the treatment of FL, but that role needs to be more defined.

What are other potentially effective agents, according to the ASH presentations?

There was an interesting study of pralatrexate presented by Savage and colleagues.17 Pralatrexate is a novel antifolate that has activity in peripheral T-cell lymphoma, as well as cutaneous T-cell lymphoma. In the study by Savage and colleagues, the overall response rate among 69 patients with highly refractory peripheral T-cell lymphoma who had not responded to their most recent prior therapy was 25% (36% according to investigator review). With this experimental agent, of course close attention was given...
to patients’ responses to prior therapies. Table 7 shows responses among patients with no evidence of response to their most recent therapy and no evidence of response to any prior therapy. Viewed in these terms, the results are certainly encouraging.

Another promising agent for NHL is romidepsin, a novel histone deacetylase inhibitor. Kim and colleagues presented a study of this agent in the treatment of cutaneous T-cell lymphoma, a disease for which few treatment options are available. The study found promising activity for this agent in this setting. The overall response rate was 41% among 27 evaluable patients with lower blood tumor burden, and 50% among the 8 evaluable patients with higher blood tumor burden. The authors noted that the safety profile among the evaluable patients was similar to the overall safety profile of romidepsin. It was very encouraging to see these 2 agents, pralatrexate and romidepsin, showing potential efficacy for the treatment of T-cell lymphomas.

References


Table 7. Pralatrexate for Highly Refractory Peripheral T-cell Lymphoma: Summary of Response According to Response to Prior Therapy

<table>
<thead>
<tr>
<th></th>
<th>Median No. Prior Systemic Therapies, n (range)</th>
<th>Response Rate by Central Review, n (%)</th>
<th>Response by Investigator Assessment, n (%)</th>
<th>Duration of Response by Central Review, range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of response</td>
<td>69 (63)</td>
<td>3 (1–11)</td>
<td>17 (25)</td>
<td>25 (36)</td>
</tr>
<tr>
<td>to most recent prior</td>
<td></td>
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<td></td>
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<tr>
<td>therapy</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No evidence of response</td>
<td>26 (24)</td>
<td>2 (1–6)</td>
<td>5 (19)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>to any prior therapy</td>
<td></td>
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