February 2008 www.clinicaladvances.com Volume 6, Issue 2, Supplement 4

Recent Advances in the Treatment of Lymphoma

A Review of Selected Presentations
From the 49th American Society of Hematology
Annual Meeting and Exposition
December 8–11, 2007
Atlanta, Georgia

With expert commentary by:
John P. Leonard, MD
The Richard T. Silver Distinguished Professor of
Hematology and Medical Oncology
Professor of Medicine
Clinical Director, Center for Lymphoma and Myeloma
Weill Cornell Medical College
New York Presbyterian Hospital

A CME Activity
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Supported through an educational grant from
Celgene Corporation.

PIM Postgraduate Institute for Medicine

Release date: February 15, 2008
Expiration date: February 15, 2009
Estimated time to complete activity: 1 hour

Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, hematologists, and oncology nurses involved in the management of patients with lymphoma.

Statement of Need/Program Overview:

In this time of accelerated development of biologics and other novel agents for treatment of lymphoma, it is imperative that clinicians treating patients with lymphoma have the latest information in order to achieve improved patient outcomes.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of lymphoma
- Review the results of these new study findings including current clinical trials evaluating therapy in the treatment of lymphoma
- Describe how to integrate into clinical practice the latest knowledge and methods for treating patients with lymphoma in an effort to improve current prognosis statistics
- Identify future research directions for all therapies in lymphoma

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Lymphoma describes a myriad of hematological malignancies with a lymphocytic origin. One of the leading types of cancer in both males and females, over 70,000 new lymphoma cases are diagnosed each year.[1] Lymphomas are traditionally classified as either Hodgkin's or non-Hodgkin's, distinguishable by various pathological features, epidemiology, sites of involvement, and clinical behavior.[2] Non-Hodgkin's lymphoma (NHL) is nearly eight times more prevalent than Hodgkin's lymphoma, and nearly 3% of all cancer deaths are due to NHL.[1,3]

NHL is primarily classified according to origin in either B or T cells. The majority (90%) of NHLs are of B-cell origin and the remaining 10% are of T-cell origin.[4] For many years, no standard classification system existed to easily classify NHL subtypes, causing a great deal of frustration for clinicians. As an increased understanding of the biology of NHL has occurred over time, many systems have been developed to classify the various types of disease.[5] The first of these was the Revised European-American Lymphoma (REAL) classification system, which was then used as a basis for the World Health Organization (WHO) classification system, now considered the standard for NHL classification worldwide.[6,7]

The most common subtypes of NHL are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), which together account for over half of all NHL cases.[8] Other less common forms of NHL include chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), and small lymphocytic lymphoma (SLL). Correctly identifying the NHL subtype is an important part of diagnosis, as various subtypes respond differently to therapy. Additionally, the aggressiveness of the NHL is a major factor when considering therapeutic strategies.

Treatment of Non-Hodgkin's Lymphoma

Cases of DLBCL make up the majority of aggressive NHL malignancies. Fortunately, this subtype responds well to therapy and is therefore generally considered to be curable. Most DLBCL patients present with advanced-stage disease and require intensive chemotherapy. A combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been the standard chemotherapeutic regimen used in these patients, although the cyclophosphamide, vincristine, and prednisone (CVP) regimen is also commonly used.[9] Recently, the addition of the monoclonal anti-CD20 antibody rituximab (CHOP-R or CVP-R) has been shown to dramatically increase the efficacy of these combination chemotherapeutic regimens, and this is now the gold standard of treatment for these patients.

Unlike aggressive NHL, where the goal of treatment is to achieve a cure, patients with indolent NHL are considered to be incurable. Therefore, the goal of therapy for patients with indolent NHL is long-term control of the disease and maintenance of quality of life. Treatment of asymptomatic indolent lymphoma patients is generally discouraged, as several studies have shown no clinical benefit over a watchful waiting approach.[10] Once symptomatic, the standard of therapy for these patients is CVP-R. Often patients with indolent FL experience a high rate of cellular transformation, leading to an elevated risk of developing resistance to treatment. As a result, these patients typically receive multiple sequential therapeutic regimens, leading to repeated cycles of relapse and remission over the lifetime of the patient.

Although several treatment options are active against NHL, many patients either do not respond well to first-line therapy or become refractory to treatment. Multiple agents are now under clinical investigation as a therapeutic alternative for these patients. One of these, the immunomodulatory drug lenalidomide, has shown promising activity in both phase I and II clinical trials. The results of several of these studies are summarized in the following abstract reviews. Other agents currently under development for NHL include the alkylating agent bendamustine, the proteasome inhibitor bortezomib, and the radioimmunotherapeutic drug ^{90}Y-ibritumomab tiuxetan.[11-15]

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3419 Durable Complete Responses Following Therapy With Epratuzumab Plus Rituximab: Final Efficacy Results of a Multicenter Study in Recurrent Indolent Non-Hodgkin's Lymphoma[1]

JP Leonard, SJ Schuster, C Emmanouilides, F Couture, N Teoh, WA Wegener, DM Goldenberg

Targeting NHL cells with monoclonal antibody therapies offers a potentially potent and active lymphoma treatment, often with a safety profile which is more favorable than standard chemotherapy regimens.[2] Epratuzumab is a novel monoclonal antibody directed against CD22, a molecule commonly expressed on the surface of NHL cells. Phase I and II clinical studies in NHL patients have shown that epratuzumab is active both as a single agent and in combination with rituximab.[3-7] Additionally, the results of a pilot study evaluating the addition of epratuzumab and rituximab to CHOP therapy were recently published, showing an overall response (OR) rate of 87%.[8] Here, Leonard and colleagues report a final analysis of a clinical study evaluating the safety and activity of the combination of epratuzumab and rituximab in patients with indolent NHL.[1]

This was an international, multicenter, open-label trial which followed patients for long-term responses over 4 years. All patients (N=49) had low-grade CD20-positive B-cell lymphoma, with measurable disease by CT scan and an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less. A total of 41 patients had low-grade FL and 7 patients had SLL or CLL. Patients were classified as having either recurrent or refractory NHL, and had failed at least one prior regimen of standard chemotherapy. Additionally, patients were either rituximab-naïve or had demonstrated a partial response (PR) or complete response (CR) to rituximab as a single-agent or in combination with chemotherapy, with a time to progression (TTP) of greater than or equal to 12 months. All patients received intravenous infusions of epratuzumab (360 mg/m^2) followed by rituximab (375 mg/m^2) weekly for 4 consecutive weeks.

Of the 49 enrolled patients, 48 completed the entire 4-week treatment regimen, with only 1 patient declining rituximab therapy after an infusion reaction. A safety analysis found that 88% of patients experienced at least one adverse effect.[9] The most frequently reported adverse effects included rigors, nausea, pyrexia, fatigue, vomiting, headache, cough, and dyspnea. All of the adverse events associated with epratuzumab therapy were grade 1 or 2, and usually occurred with the first infusion. Only 4 patients experienced a severe adverse event, 2 of which were considered to be related to the study treatment.

A total of 54.2% (95% confidence interval [CI], 39.2–68.6%) of patients had an objective response to the combination therapy, with 27.1% having a CR or unconfirmed CR (CRu). The epratuzumab plus rituximab combination was active in both FL (objective response: 53.7%) and SLL/CLL (objective response: 57.1%) histologies. FL patients with Follicular Lymphoma International Prognostic Index (FLIPI) scores of 0 or 1 responded better to the combination regimen than patients with FLIPI scores of 2 or more (objective response: 84.6% vs 39.3%, respectively). Prior exposure to rituximab did not significantly affect response to the epratuzumab plus rituximab combination, as individuals with a prior response to rituximab had an objective response rate of 64.3% compared to 50.0% of rituximab-naïve patients.

The median progression-free survival (PFS) for all patients was 11.1 months. The response in FL patients who achieved a CR or CRu was especially long-lived, with a median PFS of 35.1 months (range: 12.8–52.3 months). Importantly, 5 FL patients who experienced a CR remained in remission at the final study evaluation (median follow-up 44.3 months; range: 18.2–52.4 months). Future studies to evaluate this combination as first-line therapy for indolent NHL are both ongoing and planned.[10,11]

2572 Initial Results From an International Study in Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma to Confirm the Activity, Safety, and Criteria for Predicting Response to Lenalidomide Monotherapy[12]

M Czuczman, CB Reeder, J Polikoff, NM Chowhan, I Esseessee, R Greenberg, H Patel, D Vafai, PH Wiernik, A Ervin-Haynes, D Pietronigro, JB Zeldis, TE Witzig

The NHL-002 study is a phase II trial designed to evaluate the safety and efficacy of single-agent lenalidomide in patients with relapsed or refractory aggressive NHL. Data from a preliminary analysis of the study suggested that three prognostic factors may be predictive of patient response to lenalidomide monotherapy.[13] These three factors were tumor burden, time since last rituximab dose, and absolute lymphocyte count. The goal of this current study, presented by Czuczman and fellow investigators, was to evaluate the safety and efficacy of single-agent lenalidomide in an international cohort of NHL patients, as well as to confirm the previously reported predictors of response.[12]

A total of 79 patients were recruited into this single-arm phase II trial and 46 individuals were eligible for the preliminary assessment. Patients had either relapsed or refractory NHL of an aggressive nature with measurable disease (≥2 cm). Patients received daily oral lenalidomide (25 mg) on days 1–21 of a 28-day cycle, and continued treatment until disease progression or intolerance to therapy. The median time from diagnosis was 2 years (range: 0.2–12 years) and patients had a median of 3.5 prior therapeutic regimens (range: 1–13). Most patients (96%) had received prior rituximab therapy. Several NHL histologies were represented, including DLBCL (63%), MCL (28%), transformed lymphoma (7%), and FL (2%).

Lenalidomide monotherapy resulted in an objective response rate of 28%, with 26% of patients (n=12) having a PR and 2% (n=1) having a CR (Table 1). Additionally, 22% of patients (n=10) experienced stable disease (SD). Objective responses were observed in 21% of DLBCL patients, 38% of MCL patients, and 33% of transformed lymphoma patients, and in the 1 patient with FL. The only CR observed occurred in a patient with DLBCL. The most common grade 3 or 4 adverse events were neutropenia (24%), thrombocytopenia (16%), leukopenia (9%), and anemia (6%). Other grade 3 events included dehydration (5%) and fatigue (5%). The hematological adverse effects produced by lenalidomide were considered to be manageable.

Table 1. Objective Response of Patients Receiving Lenalidomide Therapy by Histology Type

		CR	PR	ORR	SD
	n	n (%)	n (%)	%	n (%)
Diffuse large B-cell lymphoma	29	1 (3)	5 (17)	21	5 (17)
Follicular center lymphoma	1	0	1 (100)	100	0
Mantle cell lymphoma	13	0	5 (38)	38	4 (31)
Transformed lymphoma	3	0	1 (33)	33	1 (33)

CR = complete response; ORR = overall response rate; PR = partial response; SD = stable disease.

This study confirmed that the individual prognostic factors previously identified were predictive of response to lenalidomide. Low disease burden, estimated by tumor size, was associated with a superior benefit from lenalidomide treatment (33% for tumors <50 cm^2 vs 17% for tumors ≥50 cm^2). Similarly, a longer time since the last rituximab dose also predicted a superior response (44% for ≥230 days vs 5% for <230 days), as did a higher absolute lymphocyte count (34% for >0.6 × 10^9/L vs 10% for ≤0.6 × 10^9/L). Significantly, patients with favorable values for both disease burden (<50 cm^2 tumor) and time since last rituximab dose (≥230 days) had a statistically higher objective response rate compared to patients with unfavorable values for both (50% vs 12%, respectively; *P*=.007).

2579 First Report of a Phase II Clinical Trial of Lenalidomide Oral Therapy for Peripheral T-Cell Lymphoma[14]

T Reiman, D Finch, N Chua, D White, DA Stewart, R van der Jagt, J Johnston, A Prasad, H Schwarz, JB Zeldis, AR Belch

Because of its demonstrated activity across several NHL histologies, Reiman and colleagues sought to determine the efficacy of lenalidomide in patients with PTCL.[13-17] This was the first analysis of a multicenter Canadian, phase II, open-label, single-arm study. All patients (N=10) had either relapsed or refractory disease (n=8) or were

untreated because of a comorbid illness that prevented standard chemotherapy (n=2). The median number of prior treatment regimens was 1 (range: 0–3). Patients were treated with oral lenalidomide (25 mg daily) on the first 21 days of a 28-day cycle, and continued treatment until disease progression, death, or unacceptable toxicity occurred. At the time of this analysis, a median of 2 (range: 1–8) treatment cycles had been delivered. Of the 10 patients, 1 was not evaluated, and therefore data from only 9 patients were included.

The OR rate to lenalidomide monotherapy in this first set of PTCL patients was 44% (n= 4; Table 2). All of these patients had a PR; an additional patient exhibited SD. The duration of response ranged from 2+ to 8+ months. Importantly, in the 2 patients with previously documented refractory disease, 1 patient had a PR that lasted 6 months and the second patient exhibited SD. Additionally, 1 patient died from pneumonia after the first treatment cycle and a second patient withdrew from the study following the first treatment cycle.

The authors determined that lenalidomide had an acceptable tolerability profile in this study. A total of 3 patients had a grade 3 or 4 hematological adverse effect, including pancytopenia, neutropenia, and thrombocytopenia. Additionally, besides the 1 patient who had a fatal pneumonia infection, 2 patients had grade 4 febrile neutropenia.

Table 2. Response to Lenalidomide in Patients With Peripheral T-Cell Lymphoma (n=9)*

Best Response	n
Complete response (CR)	0
Partial response (PR)	4
Stable disease	1
Progressive disease	2
Overall response rate (CR + PR)	4

* Intent-to-treat population; includes 1 patient who died from pneumonia in cycle 1 and 1 patient who withdrew by choice after cycle 1.

125 Durable Responses With Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma: Updated Time-to-Event Analyses of the Multicenter PINNACLE Study[18]

A Goy, S Bernstein, B Kahl, B Djulbegovic, M Robertson, S de Vos, E Epner, A Krishnan, J Leonard, S Lonial, E Stadtmauer, O O'Connor, H Shi, A Boral, R Fisher

The proteasome inhibitor bortezomib has shown promise as a novel therapy for NHL, and it is currently approved for patients with relapsed or refractory MCL.[19-21] This approval was primarily due to positive preliminary results from the PINNACLE trial, a prospective open-label phase II, international multicenter trial.[22] In the initial evaluation, 33% of relapsed or refractory MCL patients responded to bortezomib monotherapy, including a CR in 8% of patients. Here, Goy and colleagues present data from an extended time-to-event analysis of the PINNACLE trial.[18]

The PINNACLE study included 155 evaluable patients with pathologically confirmed progressive MCL. Most patients (77%) had advanced stage IV disease, and 44% of patients had an International Prognostic Index (IPI) score of 3 or greater. Patients had received up to two previous chemotherapy regimens, including anthracycline and rituximab–based therapies, but had no previous exposure to bortezomib. Bortezomib (1.3 mg/m^2) was administered to patients on days 1, 4, 8, and 11 of a 21-day cycle. Cycles were repeated until either a CR or CRu was reached, at which point 4 more cycles were administered, or for up to 17 cycles in the absence of a CR or CRu.

After an extended follow-up (median 26.4 months), 141 patients were evaluable for response. Although the median number of treatment cycles for all 155 patients was 4 (range: 1–21 cycles), the 141 responding patients received a median of 8 treatment cycles (range: 2–21 cycles). The OR rate in these evaluable patients was 32%; of these, 8% had a CR or CRu. Importantly, 29% of the patients with refractory disease had an OR, of which 6% were CR or CRu. These responses were durable, as the median duration of response in all of the evaluable patients was 9.2 months, and 5.9 months in the subgroup of refractory patients. The median duration of response was not reached in patients who achieved a CR or CRu.

Patients who responded to bortezomib therapy also had a prolonged median TTP of 12.4 months, and had a median overall survival (OS) of 35.4 months. The median TTP and OS were longer in patients with superior responses to bortezomib. Likewise, the 1-year OS was superior in responding patients compared to the total patients (91% vs 69%, respectively).

Importantly, these updated results of the PINNACLE trial confirmed the efficacy of single-agent bortezomib for patients with relapsed or refractory MCL. A predictable and manageable safety profile, combined with durable responses, has led to the continued approval of bortezomib for these patients. Future studies of bortezomib-based regimens are underway to study its activity as a first-line therapy.[23-26]

2563 Lenalidomide Oral Monotherapy Produces a 53% Response Rate in Patients With Relapsed/Refractory Mantle Cell Non-Hodgkin's Lymphoma[27]

JM Tuscano, IS Lossos, G Justice, JM Vose, K Takeshita, A Ervin-Haynes, D Pietronigro, JB Zeldis, TM Habermann

2570 High Response Rate to Lenalidomide in Relapsed/Refractory Aggressive Non-Hodgkin's Lymphoma with Prior Stem Cell Transplant[28]

JM Vose, JM Tuscano, G Justice, IS Lossos, A Ervin-Haynes, K Takeshita, D Pietronigro, JB Zeldis, TM Habermann

Table 3. Objective Responses of Patients With Mantle Cell Lymphoma Receiving Lenalidomide Therapy (n=15)

Response	n (%)
Complete response	1 (7)
Complete response, unconfirmed	1 (7)
Partial response	6 (40)
Stable disease	2 (13)
Progressive disease	5 (33)
Overall response rate	53%

Table 4. Objective Response of Patients With Prior Stem Cell Transplantation Receiving Lenalidomide Therapy (n=14)

Response	n
Complete response	0
Complete response, unconfirmed	1
Partial response	6
Stable disease	5
Progressive disease	2
Overall response rate	50%

The NHL-002 study is an ongoing, multicenter, single-arm, open-label phase II trial designed to assess the safety and efficacy of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL. A preliminary analysis of the NHL-002 study has previously been reported, showing 34% of patients achieved an objective response.[13] Here, two abstracts are presented, each of which further analyzes the activity of lenalidomide in specific subsets of the NHL-002 study population. In both reports, oral lenalidomide (25 mg daily) was administered on the first 21 days of a 28-day cycle, repeated up to 52 weeks.

In the first report, presented by Tuscano and colleagues, the subset of NHL-002 patients with MCL (n=15) were included.[27] All MCL patients had measurable disease (≥2 cm) and were relapsed or refractory to at least 1 prior treatment regimen. Patients received a median of 4 previous treatment regimens (range: 2–6) and had a median time from diagnosis of 5.1 years (range: 0.7–12.6 years).

The objective response rate in the MCL subset was 53% (n=8; Table 3). Of these, 1 patient had a CR, 1 patient had a CRu, and 6 patients had a PR. Importantly, all 8 of these responses occurred in patients with favorable prognostic factors, including a low tumor burden (<50 cm^2) and having 230 or more days since the time of their last rituximab dose. These prognostic factors were established to be predictive of lenalidomide response in a previously described analysis.[12] Progressive disease was observed in 5 patients and 2 patients had SD. At the time of this analysis, the estimated median duration of response for the MCL patients had not been reached.

The second report, by Vose and colleagues, sought to determine the efficacy of lenalidomide monotherapy following stem cell transplant using a subset of NHL patients who had received a stem cell transplant prior to initiating the study treatment.[28] Patients had a median time from stem cell transplant of 1.9 years (range: 0.5–11.7 years).

The objective response rate in this subset of patients was 50% (n=7), with a CRu in 1 patient and a PR in 6 patients (Table 4). Additionally, 5 patients experienced SD and 2 exhibited progressive disease. Again, the majority of responses occurred in patients with favorable prognostic factors; only patient with unfavorable prognostic factors exhibited a response. Importantly, of the 6 patients who had received a stem cell transplant as their last treatment prior to initiating the study regimen, 4 responded to lenalidomide therapy. For these 4 patients the median time from stem cell transplant to the start of lenalidomide therapy was 0.8 years (range: 0.5–4.8 years). At the time of this analysis, the estimated median duration of response had not been reached.

389 Phase II Study of R-CHOP Followed by ^{90}Y-Ibritumomab Tiuxetan in Untreated Mantle Cell Lymphoma: Eastern Cooperative Oncology Group Study E1499[29]

MR Smith, L Zhang, LI Gordon, J Foran, B Kahl, RD Gascoyne, R Advani, E Paietta, E Weller

^{90}Y-ibritumomab tiuxetan is a novel radioimmunotherapeutic comprised of the anti-CD20 monoclonal antibody ibritumomab connected to the radioactive isotope yttrium-90 with the linker tiuxetan.[30] Several phase I and II clinical trials have established the efficacy of ^{90}Y-ibritumomab tiuxetan in NHL patients, with OR rates of 74–83%.[31-34] Here, Smith and fellow authors report the results of a phase II study evaluating the safety and efficacy of ^{90}Y-ibritumomab tiuxetan administration following R-CHOP induction therapy.[29]

Previously untreated MCL patients with stage II–IV disease were included in this study. After 4 cycles of R-CHOP, patients with a CR, PR, or SD were treated with ^{90}Y-ibritumomab tiuxetan (0.4 mCi/kg) 4 to 8 weeks following completion of the induction therapy. Most of the participating patients received the entire treatment plan (n=51) and exhibited either a CR or CRu (42%), a PR (32%), SD (12%), or were not evaluable (4%). Importantly, 16 patients had an improvement in response following ^{90}Y-ibritumomab tiuxetan. At a median follow-up of 24.4 months, the median failure-free survival (FFS) was 27 months. The 18-month FFS was 71% and the estimated OS at 18 months was 93%. After 45 patients were followed for over 1.5 years, 33 individuals remained failure-free and 12 progressed; 4 of the patients who progressed died.

^{90}Y-ibritumomab tiuxetan following R-CHOP had a relatively safe toxicity profile. Although 55% of patients experienced grade 3 or 4 neutropenia and 45% had grade 3 or 4 thrombocytopenia, all but 1 patient with thrombocytopenia recovered by 12 weeks following treatment. The study authors suggested that because the addition of ^{90}Y-ibritumomab tiuxetan to R-CHOP produces prolonged FFS over that expected with R-CHOP alone, this is a potentially efficacious strategy for MCL patients with an otherwise poor prognosis.

2562 Lenalidomide in Combination With Rituximab Demonstrated Early Evidence of Efficacy in a Phase I/II Study in Relapsed/Refractory Mantle Cell Lymphoma[35]

M Wang, L Fayad, F Hagemeister, S Neelapu, B Samuels, F Samanigo, B Pro, Q Yi, N Bell, C Byrne, P Weaver, K Hartig, R Knight, J Zeldis, L Kwak, J Romaguera

Because both lenalidomide and rituximab have activity in MCL, Wang and colleagues examined the efficacy of combining the two agents in a phase I/II clinical trial.[35] The phase I portion of the study evaluated the safety of this combination, and further determined the maximal tolerated dose (MTD) of lenalidomide when combined with rituximab. A total of 15 patients were enrolled in the phase I single-center portion of this trial. All patients had either relapsed or refractory MCL after having received a median of 2 (range: 1–4) prior treatment regimens. Prior rituximab exposure was permitted, but no patients had any therapy for at least 1 month prior to initiating the study. All patients received prior rituximab therapy. Patients were administered oral lenalidomide on the first 21 days of a 28-day cycle; rituximab (375 mg/m^2) was administered once weekly for the first 4 weeks of treatment during the first cycle.

To determine the MTD of lenalidomide, defined as the dose prior to the level in which 1 of 3 or 2 of 6 patients had a dose-limiting toxicity during cycle 1, a standard 3 + 3 dose escalation was performed (10, 15, 20, or 25 mg lenalidomide). Dose-limiting toxicities included grade 3 or 4 nonhematological adverse events or grade 4 hematological adverse events. The MTD of lenalidomide within this combination was determined to be 20 mg. Dose-limiting toxicities occurred in 2 patients at the 25 mg dose, with one patient having grade 3 hypercalcemia, hyperuricemia, and acute renal insufficiency, and an additional patient having grade 4 nonneutropenic fever, hypotension, and sepsis. Despite treatment for the hypotension, this patient, with a previous history of coronary artery disease, died.

The most frequently reported nonhematological adverse events included fatigue, pruritus, rash, and nonneutropenic infection. Neutropenia, thrombocytopenia, lymphopenia, and febrile neutropenia were the most common grade 3 or 4 hematological adverse events.

In the initial phase I portion of the trial, an OR rate of 67% was achieved in the 6 patients who were adminis-

tered the MTD. Of these, 3 patients had a CR, 1 patient had a PR, 1 patient exhibited SD, and 1 patient had progressive disease. No responses occurred in the patients receiving lenalidomide at doses of 10 or 15 mg. To date, 3 patients have been enrolled in the ongoing phase II portion of this trial, which administered lenalidomide at the previously determined MTD of 20 mg. A PR was achieved by 2 of these patients. When all of the patients who were administered 20 mg lenalidomide in both the phase I and II portions of the trial were combined (n=10), the total OR rate was 70% (30% CR and 40% PR).

This early report reveals promising efficacy of the combination of lenalidomide with rituximab, and a further analysis of the ongoing phase II portion of this study will be used to confirm these results in a larger population of MCL patients.

3473 Lenalidomide Displays Direct Anti-Non-Hodgkin's Lymphoma Cell Activity in Association With Enhanced SPARC Expression but Independent of its Ability to Strongly Inhibit NHL Cell VEGF Production In Vitro[36]

LH Zhang, PH Schafer, G Muller, DI Stirling, JB Bartlett

Zhang and colleagues used several cell-based assays to investigate key mechanisms in the activity of lenalidomide against NHL.[36] A cell proliferation assay, which measured the cellular incorporation of ^{3}H-thymidine into replicating DNA, was used to determine the proliferative effect of lenalidomide. Interestingly, lenalidomide inhibited to various degrees the proliferation of several cell lines representing various NHL histologies. Namalwa cells, a Burkitt's lymphoma cell line, were found to be the most sensitive to lenalidomide of the cells tested, followed by the MCL cell lines REC-1, Jeko-1, Granta-519, and JVM-2. The proliferation of DB cells, a large B-cell lymphoma cell line, was not inhibited by lenalidomide.

In search of the mechanism for its antiproliferative action, lenalidomide was also shown to inhibit the production of the proangiogenic factor vascular endothelial growth factor (VEGF). The inhibition of VEGF occurred posttranscription, as lenalidomide was unable to inhibit the production of VEGF mRNA expression. Lenalidomide-induced VEGF inhibition only occurred in those cell lines that were sensitive to lenalidomide and at lenalidomide doses that were lower than those required

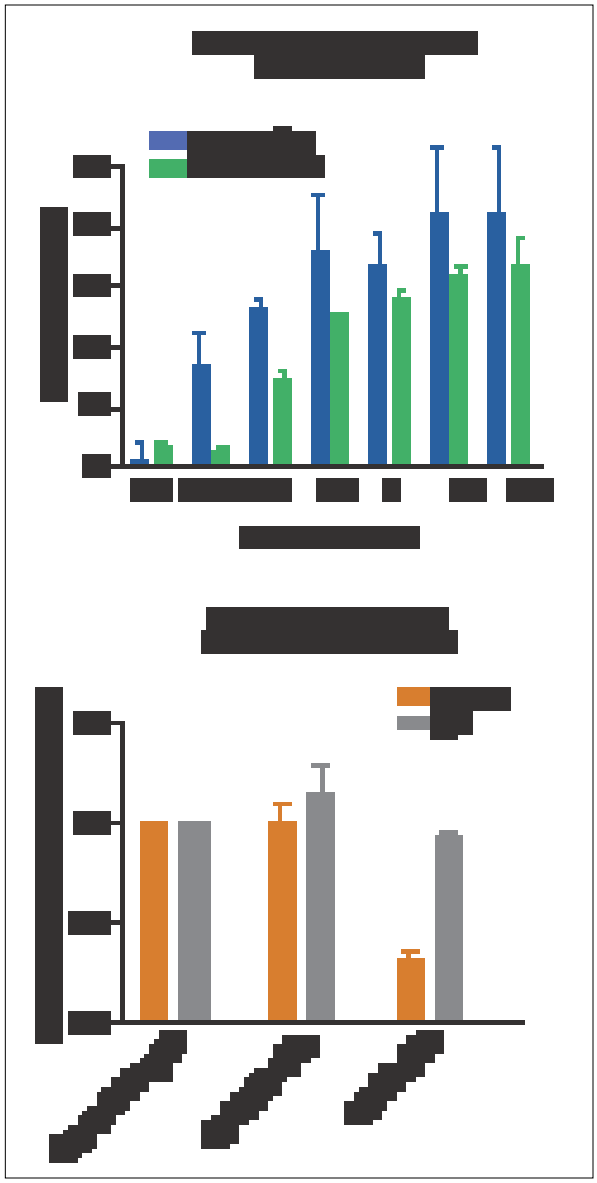

Figure 1. *SPARC* knockdown impairs the antiproliferative effect of lenalidomide on Namalwa cells.

for its antiproliferative effects. However, VEGF inhibition was determined to not be required for the antiproliferative effect of lenalidomide, because adding excess VEGF to the cells to overcome the VEGF inhibition did not affect cell proliferation in the presence of lenalidomide.

Lenalidomide treatment did lead to an increase in the expression of several tumor suppressor genes, including p21(Cip/Kip) and SPARC. Although p21(Cip/Kip) gene expression was upregulated in both lenalidomide-sensitive and -resistant cell lines, upregulation of SPARC gene expression was limited to cells that were sensitive to lenalidomide. Interestingly, Zhang and colleagues further showed that the antiproliferative effect of lenalidomide

may be dependent on the increased expression of SPARC, as genetically induced downregulation of SPARC by small interfering (si)RNA-mediated knockdown limited the antiproliferative effect of lenalidomide (Figure 1).

1351 Bendamustine Is Safe and Effective in Patients With Rituximab-Refractory, Indolent B-cell Non-Hodgkin's Lymphoma[37]

BS Kahl, NL Bartlett, JP Leonard, K Ganjoo, ME Williams, MS Czuczman, KS Robinson, R Joyce, RH van der Jagt, BD Cheson

385 Bendamustine Plus Rituximab Versus CHOP Plus Rituximab in the First-line Treatment of Patients With Indolent and Mantle Cell Lymphomas—First Interim Results of a Randomized Phase III Study of the StiL (Study Group Indolent Lymphomas, Germany)[38]

MJ Rummel, U von Gruenhagen, N Niederle, F Rothmann, H Ballo, E Weidmann, M Welslau, G Heil, H Duerk, M Stauch, C Losem, A Matzdorff, C Balser, K Schalk, D Kofahl-Krause, U Kaiser, W Knauf, A Banat, D Hoelzer, W Brugger

Bendamustine is an alkylating agent with established activity in several malignancies.[39] Single-agent bendamustine produced OR rates of 73% and 82.5% in two clinical studies of relapsed or refractory NHL patients.[40] Here, two studies evaluated bendamustine activity in NHL in both first-line and salvage therapy settings.

Kahl and colleagues conducted a phase III multicenter trial designed to determine the efficacy and safety of single-agent bendamustine in patients with relapsed or refractory NHL.[37] In this study of 100 patients, the majority had FL (62%); other lymphoma histologies included SLL (21%), extranodal marginal zone (9%), nodal marginal zone (7%), and lymphoplasmacytic (1%). Of the patients with FL, 29% were low risk, 42% were intermediate risk, and 29% were high risk, according to FLIPI score. All patients had received prior rituximab, and the median number of previous treatment regimens was 2 (range: 0–6). Patients received bendamustine (120 mg/m^2) on days 1 and 2 of a 21-day cycle, for 6 cycles.

Table 5. Response Rates to Bendamustine in Previously Treated Indolent B-Cell Non-Hodgkin's Lymphoma (N=100)

Measure	Response rate (%)
Complete response	14
Complete response, unconfirmed	3
Partial response	58
Stable disease	16
Progressive disease	7
Overall response rate	75

In all patients, an OR rate of 75% was achieved. Of these, 14% were a CR, 3% were a CRu, and 58% were a PR (Table 5). With a median follow-up of 11.8 months, the median duration of response to therapy was 9.2 months (95% CI, 7.1–10.8 months) and median PFS was 9.3 months (95% CI, 8.1–11.9). Patients who had previously been sensitive to their last chemotherapy regimen had a better OR rate to bendamustine therapy (88%) compared to patients who had been refractory (64%) or unknown (50%). Similarly, patients who were previously sensitive had a longer median PFS (11.8 months; 95% CI, 9.0–13.1 months) compared to those who were refractory (7.5 months; 95% CI, 4.4–12.0 months).

In the second study, Rummel and colleagues reported the first interim analysis of the StiL study, a phase III prospective, multicenter trial.[38] This ongoing trial is comparing bendamustine plus rituximab versus CHOP plus rituximab as first-line therapy for patients with indolent NHL or MCL. A total of 463 stage III/IV patients with previously untreated CD20-positive lymphoma were randomized to receive bendamustine plus rituximab or CHOP plus rituximab. At a median follow-up of 18 months, 315 patients were eligible for evaluation.

Both treatment combinations had similar activity, with a 93% OR rate in each treatment group. Of these, a CR was achieved in 47% of the bendamustine-receiving group and 42% of the CHOP-receiving group. Similarly, each treatment regimen produced similar outcomes among each lymphoma histology. The median PFS between the two treatment arms was not statistically different.

A similar number of patients died in the bendamustine arm (n=13) and the CHOP arm (n=12). However, the bendamustine combination proved to be less toxic than the CHOP combination, with lower incidences of alopecia (0% vs 94%, respectively), grade 3 or 4 leucocytopenia (16% vs 41%), and infectious complications (23% vs 41%). These results were similar to a previously reported phase III study comparing a bendamustine-based

combination regimen with an established cyclophosphamide-based combination in NHL patients.[41] In that study, although both treatment regimens were equally efficacious, the bendamustine-receiving group had a significantly improved toxicity profile.

Taken together, these trials show that bendamustine is a safe and effective therapy for NHL patients. Future studies are planned to determine the efficacy of bendamustine as long-term maintenance therapy for patients with FL and other NHL malignancies.

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Commentary

John P. Leonard, MD

The Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Professor of Medicine
Clinical Director,
Center for Lymphoma and Myeloma
Weill Cornell Medical College
New York Presbyterian Hospital

Therapy for NHL has significantly evolved over the last decade. While systemic treatments consisted primarily of cytotoxic chemotherapy for many years, the development of the anti-CD20 antibody rituximab has ushered in the era of targeted therapy. Since about 90% of NHL cases are of B-cell origin and therefore express the CD20 antigen, use of this agent is applicable across a broad array of lymphoma subtypes. Numerous clinical trials have demonstrated the efficacy of rituximab, as a single agent or in combination with chemotherapy, for first-line treatment, in relapse, and as maintenance therapy.[1-5] Patients with DLBCL appear to benefit through an increase in the cure rate, while patients with follicular and other histologies can have enhanced response rates and durations to treatment, as well as improved overall survival in some settings. However, despite these enhanced patient outcomes, a substantial fraction of DLBCL patients still die of their disease, while patients with indolent lymphoma still generally are not cured and frequently become resistant to standard treatments, including rituximab. Therefore, there are clearly unmet needs of lymphoma patients, and much ongoing work is focused in these areas. Reports from the 2007 American Society of Hematology meeting highlighted several new and important avenues of exploration. While some involved agents with well-defined targets, other agents have broader effects but nonetheless offer the potential to make a significant impact on the lives of lymphoma patients.

While targeting CD20 with unlabeled antibodies does show activity, it is clear that radiolabeled antibodies offer the potential for augmented activity through targeted radiation. Two such agents, ^{90}Y ibritumomab tiuxetan and ^{131}I tositumomab, are approved for use in patients with recurrent indolent lymphoma.[6,7] An additional strategy beyond single-agent use is to employ radiolabeled antibodies after chemotherapy in an attempt to extend remission and enhance survival. Several efforts have been undertaken in this fashion in indolent lymphoma. Smith and colleagues in the Eastern Cooperative Oncology Group have pursued this strategy in MCL.[8] Standard therapies for this difficult lymphoma subtype include CHOP chemotherapy with rituximab. While some advocate more intensive treatments such as R-HyperCVAD or high-dose chemotherapy and autologous stem cell transplant in first remission, these approaches do not appear to be curative and are not applicable to patients of older age, which is the norm in MCL. The approach presented at ASH included CHOP-R treatment followed by ^{90}Y ibritumomab tiuxetan in initial treatment of MCL. Therapy was well tolerated and response rates were high, but additional follow-up will be needed to determine whether long-term outcomes are enhanced by the consolidative therapy.

Another direction in targeted treatment is combination antibody therapy, where multiple antibodies directed against different antigens are employed together with the hope of additive or synergistic effects. Epratuzumab is a humanized, anti-CD22 monoclonal antibody with single-agent preclinical and clinical activity in a variety of B-cell malignancies.[9] Extended follow-up data from a long-term study of epratuzumab plus rituximab demonstrated that the combination was well tolerated and that extended remissions (some >3 years) could be achieved.[10] This combination is currently being studied with CHOP chemotherapy in DLBCL and will soon be evaluated as initial therapy for FL by the Cancer and Leukemia Group B (CALGB).

Proteasome inhibition with bortezomib has been validated as a therapeutic target in multiple myeloma and NHL, with antilymphoma effects likely due to perturbation of protein degradation.[11] Recently, bortezomib was FDA approved for the treatment of recurrent MCL and recent data demonstrated that remission duration can be substantial in a subset of patients.[12] Ongoing studies, including those that combine bortezomib with rituximab in recurrent indolent lymphoma and with CHOP-R in upfront DLBCL and MCL, as well as other trials evaluating bortezomib maintenance, seek to define the best setting for its use.

Several studies from ASH 2007 reported on exciting data exploring the activity of lenalidomide, an immunomodulatory agent, in the treatment of various lymphoma subtypes. This drug, which is FDA approved for use in myeloma and myelodysplastic syndrome, has a variety of purported mechanisms of action, including direct antitumor effects, enhanced effector cell function, and antivascular effects, and also appears to alter the tumor cell microenvironment.[13] Recent trials have shown that lenalidomide is well tolerated as therapy in both indolent and aggressive lymphoma, with overall response rates as high as 53% in the latter subtype. Notable activity has been noted in patients with recurrent DLBCL, MCL,

and T-cell histologies.[14-17] These difficult to treat subtypes are typically challenging settings to test new agents, and this early activity is quite encouraging. Because of overlapping myelosuppression with chemotherapy, in the future lenalidomide might be combined at low doses, in sequence as maintenance, or in combination with rituximab without cytotoxics. This latter approach is under evaluation by Wang and colleagues in MCL and is currently being studied in recurrent FL by CALGB.[18] One can anticipate an extensive evaluation of lenalidomide in lymphoid malignancies in the near future, and it appears that this agent may have a potentially significant impact in these settings.

Recently, several trials have evaluated the use of bendamustine, a bifunctional alkylating agent, in lymphoid malignancies. Kahl and colleagues demonstrated that this drug, with its principal toxicity being myelosuppression, has a high response rate in rituximab-refractory indolent lymphoma.[19] These data suggest that this agent offers a potentially useful new option for patients with disease that has become resistant to other cytotoxics and rituximab. A very interesting report was provided by Rummel and colleagues, with preliminary data of a trial of bendamustine + rituximab versus CHOP-R as initial treatment for indolent lymphoma.[20] Toxicity results appeared to favor the bendamustine + rituximab arm, and efficacy appeared comparable with the available follow-up. This study warrants close attention, and if efficacy data hold up in the longer term, one can envision that this may be a very useful option for the initial treatment of indolent lymphoma, in particular with respect to the favorable safety profile and allowance to defer anthracycline treatment (and its associated toxicity).

Overall, ASH 2007 demonstrated several exciting new approaches for the treatment of NHL. While we continue to explore treatment options that appear to have targeted or specific mechanisms of action, it is clear that some agents with generalized effects will continue to have important therapeutic roles. Considerable challenges remain in determining the optimal setting for the use of novel agents, including their combination and sequence with standard therapies. Accrual to ongoing and future clinical trials should remain a priority so that we may rapidly sort out the best use of these new strategies.

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18. Wang M, Fayad L, Hagemeister F, et al. Lenalidomide in combination with rituximab demonstrated early evidence of efficacy in a phase I/II study in relapsed/refractory mantle cell lymphoma. Presentation at the 49th American Society of Hematology Annual Meeting and Exposition; Atlanta, GA. December 8-11, 2007:Abstract 2562.
19. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is safe and effective in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma. Presentation at the 49th American Society of Hematology Annual Meeting and Exposition; Atlanta, GA. December 8-11, 2007:Abstract 1351.
20. Rummel MJ, von Gruenhagen U, Niederle N, et al. Bendamustine plus rituximab versus CHOP plus rituximab in the first-line treatment of patients with indolent and mantle cell lymphomas - first interim results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). Presentation at the 49th American Society of Hematology Annual Meeting and Exposition; Atlanta, GA. December 8-11, 2007:Abstract 385.

Recent Advances in the Treatment of Lymphoma

CME Post-Test: *Circle the correct answer for each question below.*

1. In a multicenter study reported by Leonard and colleagues, the combination of _____ with rituximab produced an objective response rate of 54.2%.
   a. bortezomib
   b. bendamustine
   c. lenalidomide
   d. epratuzumab

2. An international study presented by Czuczman confirmed that _____ of patients having the favorable prognostic factors of low tumor burden and increased time since last rituximab dose had an objective response, compared to _____ of patients with unfavorable values for both.
   a. 50%; 12%
   b. 50%; 44%
   c. 33%; 12%
   d. 34%; 17%

3. Lenalidomide monotherapy was shown to be efficacious in patients with PTCL, producing an OR rate of _____ in a study presented by Reiman and fellow investigators.
   a. 25%
   b. 33%
   c. 44%
   d. 72%

4. Updated results of the PINNACLE trial found that the 1-year OS rate in patients responding to bortezomib therapy was _____
   a. 38%
   b. 52%
   c. 64%
   d. 91%

5. An analysis of the subset of MCL patients from the NHL-002 study, presented by Tuscano and colleagues, showed that single-agent lenalidomide therapy produced an objective response rate of _____.
   a. 53%
   b. 58%
   c. 62%
   d. 84%

6. In a second subset analysis of the NHL-002 study, reported by Vose and colleagues, a 50% objective response rate to lenalidomide was observed in patients who had previously received _____.
   a. bendamustine
   b. stem cell transplant
   c. CHOP
   d. rituximab

7. The novel radioimmunotherapeutic agent ^{90}Y-ibritumomab tiuxetan produced a CR or CRu in _____ of MCL patients.
   a. 4%
   b. 12%
   c. 32%
   d. 42%

8. The MTD of lenalidomide, administered in combination with rituximab, was determined to be _____ in a phase I study reported by Wang and fellow authors.
   a. 10 mg daily
   b. 15 mg daily
   c. 20 mg daily
   d. 25 mg daily

9. A cell-based study performed by Zhang and colleagues found that the antiproliferative effect of lenalidomide in NHL cells may be dependent on increased expression of the _____ gene.
   a. SPARC
   b. VEGF
   c. p53
   d. Akt

10. True or false: the StiL study showed that bendamustine plus rituximab had a more favorable safety profile compared to CHOP plus rituximab in NHL patients, despite a lack of increased efficacy.
    a. True
    b. False

CERTIFICATE REQUEST FORM

First name MI Last name

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Certificate type: ☐ Physician ☐ Other

May we contact you in the future to participate in a short post-activity evaluation? Yes No

Approximately how many minutes did it take you to complete this CME activity, including the post-test and evaluation? _____

I certify that I have completed this CME activity as designated.

Signature Date

Evaluation Form—Recent Advances in the Treatment of Lymphoma

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
(1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree)

1. Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

- Describe the importance of new study findings in the form of selected abstracts/poster summaries in the natural history of lymphoma — 1 2 3 4 5
- Review the results of these new study findings including current clinical trials evaluating therapy in the treatment of lymphoma — 1 2 3 4 5
- Describe how to integrate into clinical practice the latest knowledge and methods for treating patients with lymphoma in an effort to improve current prognostic statistics — 1 2 3 4 5
- Identify future research directions for all therapies in lymphoma — 1 2 3 4 5

2. Overall Effectiveness of the Activity

The content presented:

- Was timely and will influence how I practice — 1 2 3 4 5
- Enhanced my current knowledge base — 1 2 3 4 5
- Addressed my most pressing questions — 1 2 3 4 5
- Provided new ideas or information I expect to use — 1 2 3 4 5
- Addressed competencies identified by my specialty — 1 2 3 4 5
- Avoided commercial bias or influence — 1 2 3 4 5

3. Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity: _____

Please list any topics you would like to see addressed in future educational activities: _____

_____

Additional comments about this activity: _____

_____

4. Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the posttest by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Posttest Answer Key

1	2	3	4	5	6	7	8	9	10

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I certify my actual time spent to complete this educational activity to be: _____

☐ I participated in the entire activity and claim 1.0 credit. ☐ I participated in only part of the activity and claim _____ credits.