Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

July 2010 www.clinicaladvances.com Volume 8, Issue 7, Supplement 13

B-cell Non-Hodgkin Lymphoma: A Case-based Discussion of Recent Advances in Patient Management

Moderator

Myron S. Czuczman, MD
Professor of Medicine
and Oncology
Chief, Lymphoma/
Myeloma Service
Department of Medicine
Head, Lymphoma Translational
Research Laboratory
Department of Immunology
Roswell Park Cancer Institute
Buffalo, New York

Discussants

Stephanie A. Gregory, MD
Head, Section of Hematology
Elodia Kehm Professor
of Medicine
Professor, Department of
Internal Medicine
Rush University Medical
Center/Rush University
Chicago, Illinois

Richard van der Jagt, MD
Associate Professor of
Clinical Haematology
Department of Medicine
The Ottawa Hospital
University of Ottawa
Ottawa, Ontario
Canada

Supported through funding from Cephalon Oncology

Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Abstract

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders. In the United States, an estimated 65,980 patients were newly diagnosed with NHL in 2009, and 19,500 deaths were attributed to this disease. NHLs are classified according to the current World Health Organization system, a modification of the Revised European-American Classification of Lymphoid neoplasms. According to this system, lymphomas are classified according to the cell of origin (B, T, or natural killer cells), subclassified as to whether they are derived from precursor or mature lymphocytes, and further subclassified based on immunophenotype and genetic markers. Some B-cell lymphomas (eg, follicular lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma) are classified as indolent, others (eg, diffuse large B-cell lymphoma, mantle cell lymphoma) are classified as aggressive, and others (eg, Burkitt lymphoma, AIDS-related B-cell lymphoma) are highly aggressive. Chemotherapy is the treatment of choice, although treatment of individual patients is dependent on accurate diagnosis and classification. Many new drugs and new drug combinations are being developed to treat these patients. Drs. Richard van der Jagt, Stephanie A. Gregory, and Myron S. Czuczman discuss several patients with B-cell NHL they have recently encountered.

Case Presentations

Richard van der Jagt, MD

Case 1

The patient was a 68-year-old man with mantle cell lymphoma. He presented with night sweats, a 20-pound weight loss, lymphadenopathy in his neck, and bilateral axillary nodes, mediastinal nodes, and abdominal nodes up to 3 cm. His lactate dehydrogenase (LDH) was twice the normal level. The patient had a history of diabetes and chronic obstructive pulmonary disorder and an Eastern Cooperative Oncology Group (ECOG) score of 2. He was given 6 cycles of rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP). His Ki-67 index was 90%. Given the combination of his high LDH, his performance status, and his Ki-67 characteristics, he was considered to have high-risk disease.[1] Because of his age and comorbidities, he was not considered to be a transplant candidate.

Seven months later, the patient relapsed with significant abdominal disease, with lymph nodes up to 3 cm in 4 different locations and 2 enlarged mediastinal nodes up to 2.5 cm. He reported night sweats, fevers, a bloated abdomen, and another weight loss of 10 pounds. After a discussion of the therapeutic options available, the patient opted to participate in a phase II study of bendamustine and rituximab (BR).

Discussion

Richard van der Jagt, MD (RvdJ) Bendamustine is a bifunctional mechlorethamine alkylator that leads to DNA damage, apoptosis, and mitotic catastrophe. It is as effective as but less toxic than other alkylating agents, including cyclophosphamide, melphalan, and carmustine, with low cross-resistance with these other agents.[2] Bendamustine monotherapy and the combination of bendamustine plus rituximab have shown activity in patients with various hematologic malignancies, including chronic lymphocytic leukemia (CLL) and multiple myeloma, as well as in patients with non-Hodgkin lymphoma (NHL).[3-8] Bendamustine has also shown activity in patients with breast cancer and small cell lung cancer.[2]

Several clinical trials have assessed the efficacy and safety of BR in patients with relapsed mantle cell and indolent B-cell NHL. In a 2005 study by Rummel and colleagues, 63 patients received bendamustine (90 mg/m^2) on days 1 and 2 and rituximab (375 mg/m^2) on day 1 every 4 weeks for a maximum of 4 cycles (total cycles, 245).[9] Of

the 63 patients, 57 (90%; 95% confidence interval [CI], 80–96%) responded, with 38 (60%; 95% CI, 47–72%) showing a complete response (CR). Median progression-free survival (PFS) was 24 months (range, 5–44+ months), and the time to progression was not reached. In the 16 patients with mantle cell lymphoma, the response rate was 75% (95% CI, 48–93%), and the CR rate was 50%. Myelosuppression was the major toxicity, with 16% of patients experiencing grade 3/4 leukopenia; only 3% experienced grade 3/4 thrombocytopenia.

Another study by Rummel and coworkers for StiL (the Study Group Indolent Lymphomas, Germany) presented at the 2009 American Society of Hematology (ASH) meeting compared treatment with rituximab (375 mg/m^2 on day 1) plus bendamustine (90 mg/m^2 on days 1 and 2) every 28 days or the standard CHOP regimen every 21 days for a maximum of 6 cycles as first-line treatment in patients with follicular, indolent, and mantle cell lymphoma.[10] Of the 513 evaluable patients, 260 were treated with BR and 253 with R-CHOP; with a median observation time of 32 months. Although overall response rates (ORRs) were similar (93.8% vs 93.5%), patients treated with BR had a significantly higher CR rate (40.1% vs 30.8%; *P*=.0323) and significantly longer median PFS (54.8 vs 34.8 months; *P*=.0002), event-free survival (54 vs 31 months; *P*=.0002), and time to next treatment (not reached vs 40.7 months; *P*=.0002).

The toxicities of the 2 regimens also differed, with 49 serious adverse events in the BR group and 74 in the R-CHOP group. Rates of grade 3/4 neutropenia were lower in the BR group (10.7% vs 46.5%; *P*<.0001), as were rates of leukocytopenia (12.1% vs 38.2%; *P*<.0001) and use of granulocyte colony stimulating factor (4.0% vs 20.0%; *P*<.0001). The BR group also had a significantly lower rate of alopecia (15% vs 62%) and lower incidences of infectious complications, peripheral neuropathy, and stomatitis. The BR regimen was, however, associated with a significantly higher rate of drug-associated erythematous skin reactions (*P*=.0122).

Myron S. Czuczman, MD (MC) It is important to remember that these exciting results have been presented at national/international meetings, but they have yet to be published in the academic literature. I would like to see more details about these patients. Also, time to next treatment is dependent on both the physician and the patient and may be quite variable and subjective. It is largely dependent on the physician's therapeutic approach and beliefs and/or the patient's input.

Of note, in the StiL trial, patients were not started on treatment until they demonstrated significantly progressive and/or symptomatic disease. Indications that were necessary prior to initiation of therapy on trial required one of the following conditions: rapid progression, B symptoms, hematopoietic failure, large tumor burden, or complications due to disease. Also, all of these patients had follicular grades 1 and 2 disease; those with grades 3A/3B were excluded.

I personally believe that it is also important to perform subanalyses of the data in the StiL trial. Although the 2 regimens had similar response rates and overall survival, subsets of patients may be identified that may benefit from one regimen compared to the other. For example, a patient with bulky disease and an elevated LDH level may do better on R-CHOP than on BR.

I would also like to mention that first-line treatment with BR may theoretically alter the natural history of the disease in these patients. For example, the impact of this regimen on responsiveness to subsequent therapies at the time of relapsing disease and long-term outcome cannot be determined at this time.

RvdJ In a phase II trial from Robinson and coauthors, 67 patients received rituximab (375 mg/m^2) on day 1 and bendamustine (90 mg/m^2) on days 2 and 3 every 4 weeks for 4–6 cycles, plus single doses of rituximab 1 week before the first cycle and 23 weeks after the last cycle (total cycles, 245).[11] The ORR was 92%, including a CR rate of 41%. Median duration of response was 21 months, and median PFS was 23 months. Outcomes were similar in patients with indolent and mantle cell lymphoma. Of these patients, 92% completed at least 4 cycles of therapy, and 62% completed 6 cycles. Of the 6 patients who discontinued before 4 cycles, only 2 did so due to adverse events. Myelosuppression was the major toxicity, with 36% of patients experiencing grade 3/4 neutropenia and 9% experiencing grade 3/4 thrombocytopenia.

My personal experience has been similar to that described above regarding the relatively low incidence of grade 3/4 neutropenia (ie, grade 4 febrile neutropenia occurring in 2–14% of treated patients). The fact that this patient was a mantle cell patient made him a particularly good candidate, given that published experience has demonstrated response rates using bendamustine plus rituximab in up to 92% of patients previously treated with standard rituximab-containing regimens.

MC Did you use growth factors for this patient initially?

RvdJ In Canada, where I practice, we do not use growth factors for primary prophylaxis. Also, in the recent trial presented by Rummel and colleagues, only 4% of patients receiving bendamustine required the use of growth factors.[10]

MC I routinely administer pegfilgrastim, beginning with the first chemotherapy cycle, to elderly patients—those in their late 70s or early 80s—who are being treated with bendamustine. Although they may not experience grade 3/4 myelosuppression, most of these patients experience

some degree of myelosuppression due to limited bone marrow reserve related to advanced age and other factors. Administration of pegfilgrastim can help avoid infectious complications, which are poorly tolerated by elderly patients with comorbid medical conditions. Although significant neutropenia is especially common in patients receiving the 120 mg/m^2 bendamustine dosing schedule, it is also observed in patients who receive the 90 mg/m^2 bendamustine (on days 1 and 2 every 28 days) dosing schedule. Although bendamustine has shown good short-term safety profiles, long-term safety data are not yet available, especially in patients with NHL. For example, there may be risks for secondary myelodysplastic syndrome or acute myeloid leukemia. Also, there may be problems collecting stem cells from patients for autologous stem cell transplantation, especially patients with low CD34-positive counts or prolonged bone marrow suppression.

Stephanie A. Gregory, MD (SG) Another option in patients such as this one, with a first relapse of mantle cell lymphoma, especially a quick relapse, is rituximab plus bortezomib. Preliminary results from the VERTICAL (A Phase II Study of VELCADE [Bortezomib] in Combination With Bendamustine and Rituximab in Subjects With Relapsed or Refractory Follicular Lymphoma) study were presented at the 2009 ASH meeting.[12] In that trial, patients were treated with up to five 35-day cycles of bortezomib (1.6 mg/m^2 on days 1, 8, 15, and 22), bendamustine (90 mg/m^2 on days 1 and 2), and rituximab. Grade 3/4 neutropenia, thrombocytopenia, and anemia occurred in 25%, 6%, and 3% of patients, respectively.

A study from ECOG has examined abbreviated chemotherapy (4 cycles of R-CHOP), followed by consolidative radioimmunotherapy with ^{90}Y ibritumomab tiuxetan, but that was primarily in a frontline setting in patients with mantle cell lymphoma.[13]

MC Until long-term data are published, I think we have to be cautious. But there is interesting potential in this way of treating patients. I would say that we are not quite sure what advantage there is in giving a dose of radioimmunotherapy to these patients at this time. And this innovative approach is not approved by the US Food and Drug Administration (FDA) in patients with mantle cell lymphoma. It is approved for frontline therapy of follicular NHL.[14]

SG Yes, I agree. Some other options that are not yet approved for patients with relapsed mantle cell lymphoma include temsirolimus and everolimus—which are being tested in ongoing trials in patients with mantle cell lymphoma—and the combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM). And fludarabine, either alone or in combination with other agents, has been included in many studies of mantle cell lymphoma patients.

MC Another "off-label" (ie, non–FDA-approved indication) therapeutic option is lenalidomide. A trial presented at the 2009 ASH meeting described results of lenalidomide monotherapy in patients with relapsed/refractory aggressive NHL.[15] In that trial, 217 patients, including 57 with mantle cell lymphoma, received 25 mg of oral lenalidomide once daily on days 1–21 of each 28-day cycle until disease progression or unacceptable toxicity. The ORR was 35%, with 13% achieving CR and 22% achieving partial response (PR). The response rate was 42% in patients with relapsed/refractory mantle cell lymphoma. Grade 3/4 neutropenia, thrombocytopenia, anemia, and leukopenia occurred in 41%, 19%, 9%, and 7% of patients, respectively. The dosing is oral, and dosage adjustments usually need to be made during the course of therapy.

RvdJ One of the things I like about the bendamustine combination is that it is easy to deliver and well tolerated, as demonstrated in clinical trials in North America and Germany.[3,9-11]

MC I have found that a significant percentage (eg, 15–20%) of my patients experience variable degrees of drug-induced rash, similar to that found in the trial by Rummel and colleagues.[10]

RvdJ That would be in accordance with the data published in the randomized R-CHOP versus BR study, in which there were more skin rashes in the BR group (16% vs 9%; *P*=.0122).[12] However, allopurinol may have contributed to some of those skin reactions.

MC I have now been avoiding the use of allopurinol, but I still have some patients who develop skin reactions, which may be quite symptomatic in a small percentage. It should be kept in mind that therapy need not be discontinued. If the patient needs treatment for the rash, I often try topical steroids, typically triamcinolone cream if the rash is diffuse. Occasionally, symptomatic patients might need a methylprednisolone dose pack, but usually that need is limited to the first and/or second cycles of bendamustine. The rash seems to get much better or to resolve with subsequent cycles.

SG I have treated several patients with bendamustine, and I have not seen the skin reaction.

RvdJ I have seen very mild skin rash, maybe grade 1.

MC I think the main point is that if allopurinol is prescribed, the patient should be instructed to call the office

immediately if he or she develops any significant or worsening rash.

RvdJ Another potential adverse event is myelodysplasia. Bendamustine is both an alkylator and has some resemblance to a purine analog, and both of these types of agents have been associated with myelodysplasia.

SG In some of the US studies, there have been about 3 or 4 cases of myelodysplastic syndrome, but they were all in patients who were heavily treated.

MC It could be cumulative toxicity exposure over a prolonged period of time. I think as we gain more knowledge and have larger numbers of patients being treated with bendamustine around the world, we may see reactions that previously were not identified or described in the current drug database.

RvdJ Patients being treated with bendamustine should be registered in a central registry to collect as much information as possible about adverse events.

MC Any atypical and/or severe toxicities possibly or probably related to bendamustine exposure, especially in patients who are not part of a clinical trial study, should be reported to the FDA and also to Cephalon, the manufacturer of bendamustine.

Case 2

The patient was a 71-year-old man newly diagnosed with grade 2 follicular lymphoma. He had a 6-month history of gradually developing painless adenopathy in his axilla and groin, and a 3-month history of night sweats, but no weight loss. Computed tomography (CT) revealed adenopathy in 4 areas above and below the diaphragm, and his LDH was elevated. He enrolled in a clinical trial in which he was randomized to treatment with BR. He had a Follicular Lymphoma International Prognostic Index (FLIPI) score of 3. He achieved CR after 6 cycles of BR and is now on maintenance rituximab given once every 3 months for 2 years.

Discussion

SG Tumor burden, as assessed by FLIPI, is very important in determining patient treatment or in deciding whether to just observe a patient. We must realize, though, that some patients with a high-risk FLIPI score may be asymptomatic and do not necessarily need immediate treatment.

RvdJ What we do not know yet is what happens when a patient who receives BR fails this therapy. For instance, what is the best means of rescuing them?

MC We have some data indicating that most of those patients received R-CHOP if they progressed after BR. There may be subsets of patients who may have a greater benefit from BR; maybe there are other patients who derive a greater benefit from an anthracycline-containing regimen.

SG For example, if a patient has very bulky disease and an elevated LDH level, treatment might not be with BR, but with R-CHOP. However, recent data presented at the 2010 Annual Meeting of the American Society of Clinical Oncology showed efficacy of bendamustine in aggressive NHL.[16]

RvdJ Although bendamustine has been very effective in patients previously treated with purine analogs or alkylating agents, the proper rescue therapy for patients who fail first-line BR is not clear. However, you are both right. We need to look at the FLIPI-2 score, and we need the final data from the StiL trial. Based on a more recent publication,[17] the FLIPI should be modified and can be improved by the FLIPI-2, especially in its abilities to predict risk of transformation and outcome.

Case 3

The patient was a 60-year-old man with stage 3B, bulky follicular NHL and an ECOG score of 2. He was treated with 6 cycles of BR and achieved a CR. He was subsequently placed on rituximab maintenance therapy, administered every 3 months for 2 years. His FLIPI was 3 pre-therapy.

Discussion

RvdJ In addition to BR and R-CHOP, other possible first-line therapies for patients with follicular lymphoma include rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP), and R-FCM.

The results of the PRIMA (Primary Rituximab and Maintenance) phase III trial testing the efficacy of rituximab maintenance therapy in patients with follicular lymphoma were recently presented at the 2010 ASCO meeting.[18] Of the 1,217 patients enrolled and treated with R-CHOP, R-CVP, or R-FCM, 1,018 who responded to induction therapy were stratified by regimen and response to induction and randomized to observation (n=513) or maintenance with 375 mg/m^2 rituximab every 8 weeks (n=505). Patients receiving rituximab maintenance showed significant improvements in PFS and 2-year PFS rate (stratified log-rank; P<.0001), time to next treatment, and response rate. The rates of grade 3/4 adverse events (22% vs 16%), neutropenia (4% vs 1%), and infections (4% vs 1%), however, were higher in the rituximab maintenance group. A new trial is testing the efficacy and tolerability of rituximab maintenance therapy extending beyond 2 years, but these results are not yet available.

Maintenance therapies to date have shown significant extension of PFS, but not of overall survival. Also, with all the new and emerging agents and combination therapies available, it is difficult to determine the best treatment options, including first-line and second-line therapies, therapies that target selected patients, and dosing schedules.

MC Certain good-risk subsets of patients may do well without receiving any post-induction rituximab maintenance. Importantly, systematic evaluation (preferably on a clinical study) of post-immunochemotherapy consolidation with targeted novel agents (other than rituximab) following first-line therapy in advanced-stage indolent NHL patients is needed.[19]

SG An ECOG trial, RESORT (Rituximab Extended Schedule or Treatment Trial), has finished accrual and is comparing rituximab administered every 3 months with retreatment at relapse after frontline therapy of 4 weeks of rituximab in patients with low tumor burden, indolent NHL.[20] I am currently treating 5 of the patients in the rituximab arm; after 5 years of maintenance treatment, all are still in remission.

RvdJ So far, there has been improvement in PFS but not in overall survival.

SG That is correct. And that is the problem with all of the maintenance therapies.

MC I have a theoretical concern that I have been working on in the laboratory. It may not be consistent with all types of lymphoma, but using positive selection pressure by repeatedly exposing NHL cell lines to rituximab can render these cells rituximab-resistant.[21] The extent to which similar repeated rituximab exposure in patients affects the development of in vivo rituximab resistance in individual patients is currently unknown, but it may potentially become a major clinical concern in the future.

RvdJ Recent research describes 2 emerging concepts in the treatment of indolent NHL: the excellent antilymphoma activity of BR as upfront treatment of grade 1 and 2 follicular lymphoma and the ability to prolong PFS following upfront rituximab-chemotherapy with rituximab maintenance therapy. However, many promising new agents are emerging and/or are in clinical trials and will likely be associated with further improvements in therapeutic outcomes in the future.

References

1. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008;111:558-565.
2. Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. *J Clin Oncol*. 2009;27:1492-1501.
3. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. *J Clin Oncol*. 2008;26:204-210.
4. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2009;27:4378-4384.
5. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. *Cancer*. 2010;116:106-114.
6. Cheson BD, Wendtner CM, Pieper A, et al. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma: treatment recommendations from an international consensus panel. *Clin Lymphoma Myeloma Leuk*. 2010;10:21-27.
7. Fischer K, Stilgenbauer S, Schweighofer CD, et al. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): a multicentre phase II trial of the German CLL Study Group (GCLLSG). *Blood*. 2008;112. Abstract 330.
8. Fischer K, Cramer P, Stilgenbauer S, et al. Bendamustine combined with rituximab (BR) as first-line therapy of advanced CLL: a multicenter phase II trial of the German CLL Study Group (GCLLSG). *Blood*. 2009;114. Abstract 205.
9. Rummel MJ, Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23:3383-3389.
10. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). *Blood*. 2009;114. Abstract 405.
11. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:4473-4479.
12. 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.
13. ClinicalTrials.gov. Rituximab, Combination Chemotherapy, and Bortezomib in Treating Patients With Untreated Mantle Cell Lymphoma. Identifier: NCT00433537. Available at: clinicaltrials.gov/ct2/show/NCT00433537. Accessed June 15, 2010.
14. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008;26:5156-5164.
15. Witzig TE, Vose JM, Zinzani PL, et al. Durable responses after lenalidomide oral monotherapy in patients with relapsed or refractory (R/R) aggressive non-Hodgkin's lymphoma (a-NHL): results from an international phase 2 study (CC-5013-NHL-003). *Blood*. 2009;114. Abstract 1676.
16. Vacirca JL, Acs PI, Shimkus BJ, Bendamustine/rituximab in relapsed or refractory diffuse large B-cell lymphoma. Abstract presented at: American Society of Hematology Annual Meeting. Chicago, IL: June 4-8, 2010. Abstract 8041.
17. Relander T, Johnson NA, Farinha P, Connors JM, Sehn LH, Gascoyne RD. Prognostic factors in follicular lymphoma. *J Clin Oncol*. 2010;28:2902-2913.
18. Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. *J Clin Oncol*. 2010;28. Abstract 8004.
19. Cortazar P, Keegan P, Justice RL, Johnson JR, Pazdur R. Targeted cancer therapies: FDA approval overview. *J Clin Oncol*. 2010;28. Abstract 2537.
20. In focus: ECOG 4402: Rituximab Extended Schedule or Retreatment Trial (RESORT). *Clin Adv Hematol Oncol*. 2004;2:152.
21. Czuczman MS, Olejniczak S, Gowda A, et al. Acquirement of rituximab resistance in lymphoma cell lines is associated with both global CD20 gene and protein down-regulation regulated at the pretranscriptional and posttranscriptional levels. *Clin Cancer Res*. 2008;14:1561-1570.

Case Presentations

Stephanie A. Gregory, MD

Case 1

The patient was a 49-year-old man with several enlarged lymph nodes in his neck, including the anterior and posterior cervical lymph nodes and bilateral supraclavicular nodes. His FLIPI score was 3, and his bone marrow was not involved initially. He was diagnosed with grade 1 follicular lymphoma treated with 6 cycles of R-CHOP, followed by rituximab maintenance therapy administered every 3 months for 2 years.

Three years after rituximab maintenance was stopped, the patient relapsed with progressive disease that was symptomatic. He had diffuse lymphadenopathy, some fatigue, some weight loss, and 35% bone marrow involvement. A lymph node biopsy showed follicular grade 2 disease. His calcium and LDH levels were normal. Although this patient was a candidate for bone marrow transplantation, because he was young and had had a relapse of follicular lymphoma, he chose not to go on to transplant. This patient never showed resistance to rituximab, and he therefore was treated with bendamustine plus rituximab.

Discussion

Stephanie A. Gregory, MD (SG) Among the other options that should be considered for this patient are various rituximab-based combinations, including the R-CVP, R-FCM, and rituximab, fludarabine, mitoxantrone, and dexamethasone (R-FND) regimens. Radioimmunotherapy could be entertained for therapy in this patient who does not want a stem cell transplant. The earlier use of radioimmunotherapy gives higher overall responses, CRs, and longer duration of responses.[1] Other possibilities include the combination of bortezomib, bendamustine, and rituximab, currently being tested in the VERTICAL trial, and the combination of bortezomib and fludarabine.[2] The design of a phase II clinical trial comparing bortezomib plus fludarabine with rituximab plus fludarabine in patients heavily pretreated with rituximab was presented at the 2010 ASCO meeting.[3] Researchers aim to enroll 110 subjects, and 17 months of accrual are expected.

In a recent study by Kahl and associates, 100 patients with rituximab-refractory, indolent NHL received bendamustine at a dose of 120 mg/m^2 by intravenous infusion on days 1 and 2 every 21 days for 6–8 cycles.[4] The ORR was 75%; CR was seen in 14% of patients, with unconfirmed CR seen in 3%. A PR was seen in 58% of patients. The median duration of response was 9.2 months, and the median PFS was 9.3 months. The authors concluded that use of single-agent bendamustine produced a high rate of objective responses, with an acceptable level of toxicity, in patients with recurrent, rituximab-refractory indolent B-cell lymphoma.

As previously discussed, data from Rummel and colleagues demonstrated that the bendamustine/rituximab combination appeared to be as effective as R-CHOP and was associated with less toxicity.[5] In the phase II study of patients with NHL by Robinson and associates, the ORR was 92%, with a CR of 41%, an unconfirmed CR of 14%, and a PR of 38%. The median duration of response was 21 months, and median PFS was 23 months (95% CI, 20–26 months).[6]

A novel agent for the treatment of these patients is ofatumumab, which is a humanized anti-CD20 monoclonal antibody currently in clinical trials for NHL and CLL. In a study by Österborg and colleagues, patients received 8 weekly infusions of ofatumumab followed by 4 monthly infusions (dose 1: 300 mg; doses 2–12: 2,000 mg).[7] The ORR was 58% in CLL patients refractory to both fludarabine and alemtuzumab and 47% in patients with bulky lymphadenopathy who were refractory to fludarabine. Ofatumumab was well tolerated, with no unexpected toxicities. Lenalidomide might be another option for patients with relapsed or refractory disease. As previously mentioned, data from Witzig and associates showed that lenalidomide monotherapy achieved an ORR of 35%, with 13% of patients achieving CR and 22% achieving PR.[8]

Another possibility for this patient is radioimmunotherapy. Although he did initially have 35% of his bone marrow involved with lymphoma, we do not know how much marrow was involved at relapse. I frequently administer radioimmunotherapy after abbreviated immunochemotherapy to patients who do not want to go on to bone marrow transplant. However, because this patient is young and has experienced a relapse of follicular lymphoma, he would certainly be a candidate for bone marrow transplantation.

Myron S. Czuczman, MD (MC) I would be cautious about administering radioimmunotherapy to this patient for another reason, the potential future risk for treatment-related myelodysplastic syndrome and acute myeloid leukemia. A study found that 19 of 756 (2.5%) patients with NHL treated with ibritumomab tiuxetan radioimmunotherapy developed treatment-related myelodysplastic syndrome and acute myeloid leukemia.[9] Most of these patients had multiple cytogenetic abnormalities, however, suggesting an association of myelodysplastic syndrome and acute myeloid leukemia with previous exposure to chemotherapy.

Did you perform a positron emission tomography (PET) scan on this patient?

SG No. I do not routinely do PET scans in follicular NHL unless I suspect transformation. This patient had a re-biopsy and had no evidence of transformation, and he still remained with a follicular histology.

Richard van der Jagt, MD (RvdJ) Once a patient has had a relapse and has elevated LDH levels, I would re-biopsy a bulky node from that patient to determine if transformation occurred.

MC But what area would you biopsy? The PET scan would guide us to where the area of highest suspicion for transformation was located in the body.

SG Because the point is, as they say, "Don't biopsy just any node because it is available; try to go for the bulkier mass."

RvdJ Of course, and that is what I would do.

References

1. Gregory SA, Leonard JP, Vose JM, et al. Superior outcomes associated with earlier use: experience with tositumomab and iodine I 131 tositumomab in 1,177 patients (pts) with low-grade, follicular, and transformed non-Hodgkin's lymphoma (NHL). *J Clin Oncol*. 2005;23(16 suppl):575s. Abstract 6561.
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.
3. Theocharous P, Shpilberg O, Elsayed YA. A randomized, open-label, multicenter phase II study of bortezomib with fludarabine in comparison to rituximab with fludarabine in follicular lymphoma subjects previously treated with rituximab. *J Clin Oncol*. 2010;28(15S). Abstract TPS303.
4. Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. *Cancer*. 2010;116:106-114.
5. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). *Blood*. 2009;114. Abstract 405.
6. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:4473-4479.
7. Österborg A, Kipps TJ, Mayer J, et al. Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: results from the planned interim analysis of an international pivotal trial. *Blood (ASH Annual Meeting Abstracts)*. 2008;112. Abstract 328.
8. Witzig TE, Vose JM, Zinzani PL, et al. Durable responses after lenalidomide oral monotherapy in patients with relapsed or refractory (R/R) aggressive non-Hodgkin's lymphoma (a-NHL): results from an international phase 2 study (CC-5013-NHL-003). *Blood*. 2009;114. Abstract 1676.
9. Czuczman MS, Emmanouilides C, Darif M, et al. Treatment-related myelodysplastic syndrome and acute myelogenous leukemia in patients treated with ibritumomab tiuxetan radioimmunotherapy. *J Clin Oncol*. 2007;26:4285-4292.

Case Presentations

Myron S. Czuczman, MD

Case 1

The patient was a 49-year-old white man who had noticed progressive left neck adenopathy 1 month previously. He was examined by his primary care doctor, who referred him for an ultrasound examination, which showed extensive left-sided neck adenopathy. He was referred for a CT scan, which demonstrated extensive adenopathy above and below the diaphragm, along with splenomegaly. A needle biopsy of an enlarged left cervical lymph node revealed diffuse large B-cell lymphoma (DLBCL). A multigated acquisition (MUGA) scan showed a normal left ventricular ejection fraction. The patient was referred to our cancer center. A staging PET scan showed an extensive fluorodeoxyglucose-positive mediastinal mass measuring 7 × 3 cm, and additional disease above and below the diaphragm. Bone marrow studies demonstrated extensive (40%) involvement, and he was classified as stage 4A. His International Prognostic Index (IPI) score was intermediate-high risk. He was eligible for a Cancer and Leukemia Group B/intergroup clinical trial, in which patients with de novo DLBCL are being randomized to either R-CHOP or rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH). This patient was randomized to R-EPOCH. After 4 cycles, he converted to PET negative and completed a total of 6 cycles of therapy. After a year and a half, he remains in complete remission.

Discussion

Stephanie A. Gregory, MD (SG) Immunohistochemical analysis should show whether a DLBCL is of the germinal center B cell (GCB) or non-GCB phenotype. (Patients with the GCB phenotype may do better on rituximab plus EPOCH than on R-CHOP.) A recent phase II trial in 72 patients with untreated de novo DLBCL who were treated with rituximab plus EPOCH showed that PFS was higher in patients with the GCB than with the non-GCB phenotype and higher in patients with tumors positive for BCL6.[1] Moreover, comparison of these patients with EPOCH-treated historical controls showed that rituximab benefited only those patients positive for the apoptosis inhibition marker BCL2.

Myron S. Czuczman, MD (MC) Repeat needle biopsies can be taken from accessible tumors for immunohistochemical analysis and/or gene profiling by microarray testing. My colleagues and I recently presented the results of a retrospective study from Roswell Park Cancer Institute, in which de novo DLBCL patients were classified as GCB versus non-GCB via the Hans immunohistochemical technique.[2] Clinical responsiveness to upfront anthracycline-based therapy (ie, R-CHOP or rituximab plus EPOCH) was evaluated. Of the 192 patients, 57 (29.7%) were classified as GCB, 55 (28.6%) as non-GCB, and 80 (41.7%) as undetermined. Although remission rates were equivalent in GCB and non-GCB patients, 5-year PFS (75.4% vs 56.4%; *P*=.017) and 5-year overall survival (84.2% vs 70.9%; *P*=.037) were significantly better in the GCB subtype than in the non-GCB subtype. These data (along with others) suggest that clinical trials in which DLBCL patients with a non-GCB phenotype receive the addition of a targeted agent either concurrent with induction therapy and/or in a post-induction consolidation/maintenance approach may show improved outcomes in this subgroup of patients with DLBCL.

Richard van der Jagt, MD (RvdJ) One important prognostic marker in these patients is rearrangement of the *Myc* oncogene. A recent study included 303 patients with previously untreated DLBCL who were assayed for rearrangements of the *Myc*, *BCL6*, and *BCL2* genes and subsequently treated with R-CHOP.[3] Evaluable biopsies from 245 patients showed *Myc* rearrangements in 35 (14%). Moreover, these rearrangements were prognostic of poor survival, with 2-year survival probabilities of 0.35 and 0.61 in patients with rearranged and nonrearranged *Myc*, respectively.

SG Another factor that should be pointed out is that this patient had diffuse, large B cells in his lymph nodes and small cells in his bone marrow. Usually, patients with large cells in bone marrow receive intrathecal therapy, whereas patients with small cells do not. Some hematolo-

gists will administer intrathecal therapy only to patients with extensive large B cells in bone marrow, as well as in other, extranodal, sites.

MC Also, some DLBCL patient subsets may be at greater risk of central nervous system involvement (eg, patients with involvement of marrow with large cell lymphoma; those with testicular, epidural, paranasal sinus, or, possibly, breast involvement; those with HIV-associated DLBCL; those with ≥2 extranodal sites of disease). I believe that intrathecal therapy is certainly warranted for these patients. However, the issue of which patients should receive central nervous system prophylaxis is somewhat controversial, and the optimal dosing regimen needs further investigation and clarification.

RvdJ There are pros and cons of using prophylaxis in a patient who does not currently have central nervous system involvement. A recent study determined how many patients must receive prophylaxis treatment in order to prevent 1 event. It is an inordinately high number.

MC A recently published retrospective analysis performed at the British Columbia Cancer Agency evaluated the incidence and risk factors for central nervous system relapse in DLBCL in 435 patients. In a multivariate analysis, the use of rituximab (ie, R-CHOP compared to CHOP alone) significantly reduced the risk of central nervous system relapse.[4]

Case 2

The patient is a 60-year-old man with stage 3B DLBCL diagnosed 4 years ago. He originally presented with night sweats and was diagnosed with disease above and below the diaphragm. He also was found to have idiopathic thrombocytopenic purpura. His primary oncologist started him on R-CHOP, but, after 8 cycles, his disease was found to have initially responded, but then to have progressed. He then received 2 cycles of rituximab plus etoposide, carboplatin, and etoposide (RICE). Although he did well on this regimen for a few months, an attempt at autologous stem cell collection was unsuccessful. A few months after completing the RICE regimen, the patient demonstrated disease progression. A PET scan again showed disease above and below the diaphragm. His bone marrow was not involved, and he was treated with 2 cycles of R-DHAP without significant response.

At the time this patient was referred to me, he had a reasonable performance status. Although he had extensive disease, his bone marrow function was acceptable. He was found to be eligible for a phase II lenalidomide trial. He was started on oral lenalidomide (25 mg/day for days 1–21 every 28 days). During the first treatment cycle, however, he developed a severe rash, necessitating a decrease to 20 mg/day lenalidomide. At this dose, he also developed a rash, which may have indicated a possible tumor flare (ie, primarily described in patients with CLL receiving lenalidomide).[5] Due to the limited treatment options, we elected to continue treatment with lenalidomide, which resulted in an excellent response (near CR), although his dose was slowly decreased over a period of approximately 2 years to 5 mg/day for 21 days every 28 days. After a total of 25 cycles, he eventually demonstrated evidence of progressive adenopathy. A lymph node biopsy demonstrated active disease. Fortunately, the patient underwent another attempt at autologous stem cell collection several months into lenalidomide therapy that—although it required 6 days of collections—provided an adequate quantity of stem cells for future transplantation if he can demonstrate therapy-sensitive disease to additional salvage treatment.

Discussion

SG In addition to studies showing that the combination of bendamustine and rituximab is effective in patients with relapsed mantle cell and indolent B-cell lymphoma,[6,7] results presented at the ASH and ASCO meetings suggest that this combination is effective in patients with heavily pretreated, relapsed DLBCL.[8-11]

RvdJ Were other stem cell mobilizing agents used in this patient?

MC Originally, the patient failed his initial stem cell collection at another cancer center. They had tried to mobilize him with granulocyte colony stimulating factor but were unsuccessful. After the patient had been off of chemotherapy (and on lenalidomide) for about 9 months, he was able to be successfully collected with use of granulocyte colony stimulating factor and plerixafor. He was lucky.

References

1. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol.* 2008;26:2717-2724.

2. Chavez J, Walsh M, Hernandez-Ilizaliturri FJ, Elefante A, Czuczman MS. Classification of newly diagnosed diffuse large B-cell lymphoma (DLBCL) according to the Han's criteria defines two groups of patients with different clinical outcomes following systemic rituximab-multi agent anthracycline-based therapy. *Blood.* 2009;114. Abstract 623.

3. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. *J Clin Oncol.* 2010;28:3360-3365.

4. Villa D, Connors JM, Shenkier TN, Gascoyne RD, Sehn LH, Savage KJ. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: the impact of the addition of rituximab to CHOP chemotherapy. *Ann Oncol.* 2010;21:1046-1052.

5. Andritsos LA, Johnson AJ, Lozanski G, et al. Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2008;26:2519-2525.
6. Rummel MJ, Al-Batran SE, Kim SZ, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23:3383-3389.
7. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26:4473-4479.
8. Rigacci L, Puccini B, Orciuolo E, et al. Safety and efficacy of bendamustine with or without rituximab for the treatment of heavily pretreated CLL and lymphoma patients: a multicenter retrospective study. *Blood*. 2009;114. Abstract 1662.
9. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany). *Blood*. 2009;114. Abstract 405.
10. Vacircal JL, Acs PI, Shimkus BJ, Rosen PJ. Bendamustine/rituximab in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol*. 2010;28. Abstract 8041.
11. Sanchez-Gonzalez B, Penalver F, Guillen H, et al. Clinical experience of bendamustine/rituximab in relapsed or refractory diffuse large B-cell lymphoma subjects previously treated with rituximab. *J Clin Oncol*. 2010;28. Abstract e18526.

Conclusion

Myron S. Czuczman, MD (MC) Various new drugs and combinations for patients with NHL are being tested in clinical trials. Patients with newly diagnosed DLBCL should be staged and treated as quickly as possible before he or she deteriorates clinically or develops disease-associated complications, and/or before treatment delay results in disease progression.

The incorporation of novel therapy approaches and agents into well-designed clinical trials is critical to continue to improve current success rates. Which patients will benefit most from novel treatment approaches? What are the biomarkers, chromosomal abnormalities, or other indicators that can determine which patients will respond best to each therapeutic option? Subgroup analyses of current and future clinical trial results are therefore critical.

Another critical issue is long-term follow-up, especially to identify the type of relapse and begin treatment as soon as possible. In treating patients who relapse, what is the optimal sequence of salvage therapies? How can these sequences be tailored to individual patients?

Richard van der Jagt, MD Profiling the patient upfront may allow us to determine the best sequence. Such profiling may be partly based on pharmacogenetics or tumor profile. The question becomes how much of this approach can be applied in daily clinical practice in the community doctor's office.

MC Currently, prognostic profiling should be based on something simple, such as a relatively easily determined prognostic score based on readily accessible information (eg, IPI, FLIPI) and, possibly, incorporation of an immunohistochemical test (eg, Hans criteria) that is standardized, can be reproduced easily, and has a high concordance between different groups.

Advances in biotechnology will likely permit a relatively quick and efficient way to determine gene expression profiles of patient's lymphomas and result in risk-adapted and tumor-specific therapies in the foreseeable future.

Stephanie A. Gregory, MD As with all therapeutic decisions, one has to look carefully at the age of the patient, his or her comorbid conditions, and his or her personal preferences. A decision should then be made with both the doctor and patient exploring all possible options. Novel approaches and clinical trials should always be a part of the discussion.

MC In conclusion, the important message deduced from these cases and the associated roundtable discussion is that there are more options now to treat NHL than ever existed before, and our patients are not only living longer, but also living better.

Slide Library

B-cell Lymphomas

- Indolent
  - Follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma
- Aggressive
  - Diffuse large B-cell lymphoma, mantle cell lymphoma
- Highly aggressive
  - Burkitt lymphoma, AIDS-related B-cell lymphoma

FLIPI Scoring

Prognosis	Number of Factors	Patients	5-Year Overall Survival	10-Year Overall Survival
Good	0–1	36%	91%	71%
Intermediate	2	37	78%	51%
Poor	≥3	27	59%	36%

FLIPI 2: Risk Group Versus Progression-free Survival and Overall Survival

Risk Group	Number of Factors	Patients/ Group (n=832)	3-Year Progression-free Survival	3-Year Overall Survival	5-Year Progression-free Survival
Low	0	20%	91%	99%	80%
Intermediate	1–2	53%	69%	96%	51%
High	3–5	27%	51%	84%*	19%

Bendamustine Plus Rituximab as First-line Therapy

Bendamustine Plus Rituximab Is Superior in Respect of Progression Free Survival and CR Rate When Compared to CHOP Plus Rituximab as First-Line Treatment of Patients with Advanced Follicular, Indolent, and Mantle Cell Lymphomas: Final Results of a Randomized Phase III Study of the StiL (Study Group Indolent Lymphomas, Germany).

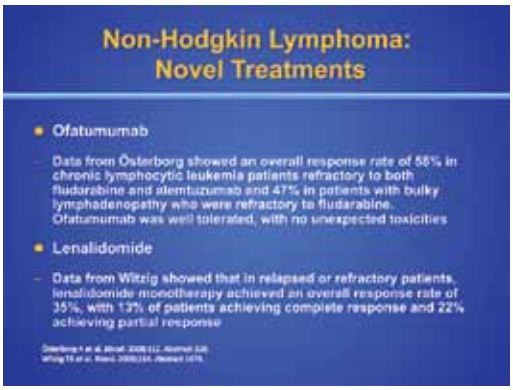
- Multicenter, randomized phase III study
- Initiated in October 2003
- Compared efficacy and safety of bendamustine plus rituximab vs R-CHOP as first-line therapy for patients with follicular, indolent, or mantle cell lymphoma

DLBCL: GCB Versus Non-GCB Subtypes

- Retrospective study examined clinical responsiveness to upfront anthracycline-based therapy (ie, R-CHOP or rituximab plus EPOCH)
- Of the 192 patients, 57 were classified as GCB, 55 as non-GCB, and 80 as undetermined
- 5-year progression-free survival and 5-year overall survival were significantly better in the GCB subtype than in the non-GCB subtype
- Remission rates were equivalent in GCB and non-GCB patients

Follicular Lymphoma: Treatment Options

- R-CHOP, followed by rituximab maintenance therapy
- Bendamustine plus rituximab
- Rituximab, cyclophosphamide, vincristine, and prednisolone
- Rituximab, fludarabine, cyclophosphamide, and mitoxantrone
- Rituximab, fludarabine, mitoxantrone, and dexamethasone
- Bortezomib, bendamustine, and rituximab
- Bortezomib and fludarabine



For a free electronic download of these slides, please direct your browser to the following web address:

http://www.clinicaladvances.com/index.php/our_publications/hem_onc-issue/ho_july_2010/


H&O