Management of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Survey of 100 Practicing Medical Oncologists and 25 Clinical Investigators on Issues Related to the Treatment of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

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Patterns of Care in Medical Oncology

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Access PowerPoint slides from this program at ResearchToPractice.com/POCNHL111.
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**ABOUT THIS SURVEY**

This survey was completed in September 2010 by 100 community-based medical oncologists and 25 hematologic oncology clinical investigators (see list on page 3) who treat non-Hodgkin lymphomas in the United States. The community-based oncologists were selected from a proprietary database used by Research To Practice for distribution of its CME activities, and the specialists included physicians who have participated in education programs with Research To Practice and others referred for this project.

OVERVIEW OF ACTIVITY
It is important for medical oncologists, hematologists, and fellows to be aware of similarities and differences among their patterns of cancer care and those of other community practitioners and non-Hodgkin lymphoma (NHL) clinical investigators. Additionally, the recognition that heterogeneity exists within the treating oncology community underscores the existence of clinical situations for which the research evidence to support a single definitive approach may be suboptimal.

This program focuses on the self-described treatment approaches used by randomly selected community medical oncologists and hematologists in a variety of key clinical scenarios in NHL. Also included are the parallel treatment approaches used by clinical investigators in academic practices, commentary from lymphoma experts and references addressing these topics. This CME program will provide medical oncologists, hematologists and hematology-oncology fellows with information on national cancer patterns of care to assist with the development of best-practice clinical management strategies for NHL.

LEARNING OBJECTIVES
• Compare treatment strategies employed by community oncologists and cancer clinical investigators, and apply this knowledge to the routine management of NHL, including chronic lymphocytic leukemia.
• Evaluate clinical issues for which relative agreement and heterogeneity exist in patterns of NHL care, and make treatment decisions considering this information.
• Counsel patients with diverse subtypes of NHL about the benefits and risks of multiple acceptable treatment options when they exist.
• Summarize common toxicities associated with the systemic treatment of NHL, and identify current approaches to reduce or ameliorate these side effects.

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COMMERCIAL SUPPORT
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Dr. Fisher — Consulting Agreements: Millennium — The Takeda Oncology Company; Dr. Horwitz — Consulting Agreements: Allos Therapeutics, Celgene Corporation, Millennium — The Takeda Oncology Company; Dr. Kantarjian — Paid Research: Bristol-Myers Squibb Company, Genzyme Corporation, Novartis Pharmaceuticals Corporation.

Dr. Kahl — Advisory Committee: Celgene Corporation, Cephalon Inc, Genentech BioOncology; Consulting Agreements: Celgene Corporation, Roche Laboratories Inc.


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RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.
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Progress in NHL/CLL may be viewed as rapid and promising, glacier-like and depressing or somewhere in between. You be the judge after reviewing the enclosed report of a national survey of 25 clinical investigators specializing in the field and 100 community-based medical oncologists, all of whom see many patients with these diseases (Figure 1).

After much discussion with our faculty, Mitchell Smith and Jonathan Friedberg (who helped plan the survey and contributed teaching cases), as well as other investigators and oncologists in practice, here are our top five (well, six) stories/issues/trends illuminated via the survey findings.

1. “Watchful waiting” in indolent lymphoma is to a great extent being replaced by rituximab (R) monotherapy (page 7, Figure 5).

We’ve been hearing for years from urologists about how difficult it is to follow a man with prostate cancer off treatment, but in follicular lymphoma this age-old concept is beginning to change. As commented on by our faculty (pages 6-7), clinicians are now more regularly turning to the anti-CD20 antibody rituximab for these patients because of its relatively low risk and potential for long-term anticancer benefit.

A landmark presentation just given at the ASH meeting in December of a trial demonstrating a delay in the need for chemotherapy for patients who received rituximab monotherapy compared to watchful waiting is likely to further increase this practice trend.

2. Patients with follicular, indolent and mantle-cell lymphomas now often have a new alternative to R-CHOP and R-CVP, namely BR (bendamustine/rituximab).

Yes, it’s one trial that is only now about to be formally published in a peer-reviewed journal, but there can be no doubt that the German research group in indolent and mantle-cell lymphoma shocked the rest of the world (ROW) at the 2009 ASH meeting when their study evaluating BR versus R-CHOP demonstrated less toxicity — including minimal alopecia — and apparent greater efficacy in terms of progression-free survival, and these data are now leading many physicians to choose this option outside a protocol setting (page 8, Figure 7 and page 31, Figure 45).

The BR story reminds many general oncologists of a similar tale in breast cancer — Steve Jones’ classic TC versus AC trial that surprised us when it demonstrated that a nonanthracycline (docetaxel) was superior in both efficacy and toxicity to doxorubicin. Most breast cancer mavens were pretty conservative when they first saw the TC data, but physicians in the clinic moved quickly and, five years later, practice has changed (as they say).

3. Two years of R maintenance after R/chemo offers a positive benefit-risk ratio to patients with follicular lymphoma (PRIMA study; page 9, Figure 11).

Although oncologists in practice and some investigators have been using this strategy for at least two to three years, the ASCO presentation of the PRIMA trial has clearly had a major impact on how people view this intervention (page 9, Figure 10).

The Germans — again, light years ahead of the ROW — are already almost two years into a trial evaluating two versus four years of R maintenance that is reminiscent of the old days of adjuvant endocrine therapy studies in breast cancer.

4. R offers significant benefit to patients with CLL (although not as much as it does for B-cell lymphomas), but there are a lot of questions about which chemo partner to use, particularly for older patients or those with comorbidities (page 22, Figure 31).

A host of new agents — including bendamustine and lenalidomide — seem to be gentler than F or FC, but the current clinical research database needs to rapidly
expand to properly determine how these and other emerging therapies like the new CD20 antibody ofatumumab best fit into the treatment algorithm.

5. Effective clinical trials focused on T-cell lymphomas are finally being completed in spite of the relative rarity of these diseases.

It is impressive that in recent years enough high-quality clinical research has been completed that two new agents (pralatrexate and romidepsin) were recently approved for T-cell lymphoma and are increasingly on the radar of oncologists in practice (page 35, Figure 51 and page 36, Figure 53). Hopefully, this is just the beginning and many more new approaches for patients will be available in the future for this often relentless set of diseases.

(5A) Radioimmunotherapy (RIT) in community practice.

This is sort of a nonstory that deserves mention — namely, the current relative lack of use of RIT in community-based practice and what seems to be a movement toward making this option more accessible very soon (page 12, Figure 14).

For years, investigators have gotten red in the face telling me how important it is to include this treatment as part of the armamentarium. RIT is not a miracle cure, but clearly it is efficacious, less toxic and much less life disturbing than almost any form of chemotherapy.

With the evolution of data demonstrating the value of this strategy as consolidation after induction (Morschhauser 2008), there is awareness of and interest in bringing this option to more patients (page 13, Figure 16). We will see if this really is about to happen. If not, patients will be forced to wait as we get our logistical act together to solve perhaps the most embarrassing story in oncology.

Other key nuggets in this issue relate to management of diffuse large B-cell lymphoma, including patterns of use of dose-dense R-CHOP and interim PET scanning. And then there is mantle-cell, in which novel agents such as bortezomib and lenalidomide are being incorporated into trials of earlier-stage disease but not often used in nonprotocol practice in the up-front setting.

Clearly a lot is happening in clinical research in these diseases, and oncologists are being remarkably effective in staying up to date, but 42 percent of the community-based physicians surveyed had not enrolled a single patient with any of these cancers on a clinical trial in the past year (Figure 2) either directly or by referral. In the long run, this is one statistic more than any other that somehow needs to change.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
March 3, 2011

SELECT PUBLICATIONS


FIGURE 2

In the past year, how many patients with non-Hodgkin lymphoma (NHL) have you enrolled on a clinical trial, either directly or through a referral?

Number of patients enrolled

<table>
<thead>
<tr>
<th>% of physicians</th>
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<tr>
<td>Number of patients enrolled</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2-5</td>
</tr>
<tr>
<td>6-10</td>
</tr>
<tr>
<td>11-20</td>
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<tr>
<td>&gt;20</td>
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<tr>
<td>0</td>
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</table>

0 10 20 30 40 50 60 70 80

0% 10%

FIGURE 2

In the past year, how many patients with non-Hodgkin lymphoma (NHL) have you enrolled on a clinical trial, either directly or through a referral?
Follicular Lymphoma

CASE 1

A 72-year-old man with multiple comorbidities including COPD/asthma presents with slowly progressive cervical adenopathy. Bone marrow biopsy is positive and the patient is diagnosed with Stage IV Grade I follicular lymphoma (FL) with a FLIPI score of 3 (nodal sites, age and stage).

The patient receives weekly rituximab (R) x 4, achieves a complete response and subsequently receives R maintenance every 2 months for 4 cycles (SAKK regimen). Treatment is well tolerated.

Three years later, CT reveals new adenopathy in his chest, at which point he again receives rituximab weekly x 4, which results in a complete response. He then receives maintenance rituximab, again on the SAKK schedule.

— Jonathan W Friedberg, MD, MMSc Rochester, New York

FIGURE 3

Of your patients with newly diagnosed FL, approximately what percent present with few or no symptoms? (Median)

<table>
<thead>
<tr>
<th>% of patients</th>
<th>0 10 20 30 40 50 60 70</th>
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<tr>
<td></td>
<td>60%</td>
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<tr>
<td></td>
<td>50%</td>
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</table>

FIGURE 4

Of your patients with FL for whom you recommend observation, approximately what percent have a difficult time accepting the approach? (Median)

<table>
<thead>
<tr>
<th>% of patients</th>
<th>0 10 20 30 40 50</th>
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<tr>
<td></td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>40%</td>
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Observation versus treatment for asymptomatic newly diagnosed follicular lymphoma (FL)

DR FRIEDBERG: In the management of FL, which is an incurable disease, a number of factors should be considered when deciding on the initiation and type of therapy. One group of patients needs a quick response because either they are symptomatic or have a risk of FL-related organ dysfunction. These patients will definitely need immunochemotherapy.

In the other group of patients with FL, who are relatively asymptomatic and eligible for observation, my threshold to initiate therapy has become lower than it used to be.

Long-term results with single-agent rituximab have demonstrated a large benefit in progression-free survival even after 10 years of follow-up. Ten years later, as many as 40 percent of patients are in remission with essentially no significant toxicities with single-agent rituximab.

For me, this has changed the threshold for initiating treatment with single-agent rituximab versus observation in the group of relatively asymptomatic patients. Although I do observe some patients, a moderate lymph node growth now triggers me to consider single-agent rituximab as treatment.

DR SMITH: It is interesting that a slightly higher proportion of patients seen by clinical investigators had few or no symptoms (Figure 3). I am surprised by this because I would have thought that the patients who are seen at referral centers might be the patients who are actually more symptomatic. However, one explanation for this observation could be that the patients being offered the “watch and wait” strategy because of the fact that they are asymptomatic might be more likely to seek a second opinion from a clinical investigator.

When determining whether to initiate therapy for asymptomatic patients with newly diagnosed FL, my approach is to try to establish the risk that the patient might “get into trouble” within the next three to six months in terms of his or her disease. If this is a possibility, then it is not worth “watching and waiting” for such patients.

If the patient can be actively observed for a year or longer, then the watch and wait strategy is reasonable. The discussion on watch and wait is generally a prolonged one. Patients must be...
approach. However, within a few visits they feel more comfortable with the fact that the disease is quiet and that they still feel well. Many of these patients become more accepting of this approach within the first six to 12 months.

Based on the survey data, it appears as though some of the community physicians are starting to lean toward rituximab monotherapy a little more versus observation (Figure 5). Again, these are usually long discussions with the patient, and it is generally more comforting to the patient on the initial visit to hear that we are starting treatment with single-agent rituximab rather than to accept the concept of watch and wait. Additionally, single-agent rituximab is tolerated well and works well.

So some of opting to go with rituximab monotherapy versus observation is ease, and some of it is the patient having real trouble dealing with watch and wait. With rituximab monotherapy, patients are receiving an active treatment without experiencing the side effects associated with many combination chemotherapies. So as the treatment becomes more tolerable, I believe it is reasonable to say that we are going to initiate active therapy earlier.

Having said that, it is important to note that no treatment regimen has been shown to prolong survival for patients with FL, and early initiation may or may not be beneficial. In the long run, a selection resistance could be seen earlier, which may not be in the best interest of the patient. Therefore, in the absence of studies showing a survival advantage, I have not changed my treatment strategy for patients with asymptomatic FL and continue to use the watch and wait approach.

However, I can understand the rationale behind physicians changing theirs. It is difficult to argue with patients when they want a well-tolerated, relatively nontoxic and effective treatment.

**Selection of initial induction therapy for FL**

**DR SMITH:** My approach to initial induction therapy for FL is different today informed of the indolent and incurable nature of the disease, and it should be carefully explained that if their disease is not causing trouble then it is reasonable to not actively treat until they become symptomatic.

Initially, patients often have a hard time with the watch and wait treatment

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**FIGURE 5**

Which of the following statements applies to you as it relates to your approach to FL during the past 2 to 3 years?

- Recommend observation a lot less, R monotherapy more
- Recommend observation somewhat less, R monotherapy more
- No change
- Recommend observation somewhat more, R monotherapy less
- Recommend observation much more, R monotherapy less
- I have not recommended R monotherapy

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**FIGURE 6**

How would you compare your approach to initial induction therapy for FL today to your approach 2 to 3 years ago?

- Somewhat different
- About the same
- Very different
The two issues I consider when addressing this question are the choice of induction regimen and use of rituximab maintenance. In the up-front setting, a recent switch has occurred to administering bendamustine/rituximab (BR) as induction therapy. I didn’t use much R-CHOP previously. Rather, I used mostly R-CVP.

Because the data indicate that BR is at least as good as or potentially better than R-CHOP, I can extrapolate that BR will be better than R-CVP. If the same results or better can be attained with BR with less toxicity, we have no need to debate on R-CHOP versus R-CVP and can settle on the BR regimen (Figures 8-9). I am using BR up front in addition to more rituximab maintenance.
DR FRIEDBERG: These are interesting results because in the short period of time since the Rummel data were presented, BR has largely displaced R-CVP as an option (Figure 7). The fact that BR has penetrated not only the clinical investigators who may have had experience with it but also the community physicians to this degree is pretty remarkable.

It is interesting that treatment with rituximab monotherapy is so low, especially among the clinical investigators. I believe that in clinical practice, a lot of 75-year-olds may end up receiving rituximab monotherapy, and the relatively small uptake of that approach reflected in the survey results may be related to the wording of the question. The physicians participating in the survey may have presumed that a patient who requires treatment might be in need of a relatively rapid response. Additionally, many physicians are now developing experience treating elderly people with bendamustine-based regimens with reasonable tolerance.

I believe that the data presented at ASH 2009 by Rummel and colleagues suggest that BR may be more efficacious for progression-free survival with less toxicity (Figures 8-9). Until the data are published, at least we can tell a patient that the regimens have equivalence. I don't believe any evidence states that R-CHOP is more efficacious or that R-CHOP will beat BR clinically. In my view, the top three answer choices are all reasonable responses, given that differ-

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### FIGURE 9

**Safety data from the Phase III study comparing bendamustine/rituximab (BR) to R-CHOP in the front-line treatment of indolent lymphomas**

<table>
<thead>
<tr>
<th>Grade 3/4</th>
<th>Leukopenia</th>
<th>Neutropenia</th>
<th>G-CSF administration</th>
<th>Anemia</th>
<th>Thrombocytopenia</th>
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<tr>
<td>BR (n = 1,450) (% of cycles)</td>
<td>12.1%</td>
<td>10.7%</td>
<td>4.0%</td>
<td>1.4%</td>
<td>0.7%</td>
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<td>R-CHOP (n = 1,408) (% of cycles)</td>
<td>38.2%</td>
<td>46.5%</td>
<td>20.0%</td>
<td>1.9%</td>
<td>1.2%</td>
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<tr>
<td>p-value</td>
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<td>Not reported</td>
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</tbody>
</table>


### FIGURE 10

**How would you compare your approach to maintenance rituximab therapy after R/chemotherapy induction for FL today to your approach 2 to 3 years ago?**

<table>
<thead>
<tr>
<th>CI</th>
<th>PO</th>
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<tr>
<td>More likely to use</td>
<td>68%</td>
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<tr>
<td>About the same</td>
<td>28%</td>
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<tr>
<td>Less likely to use</td>
<td>4%</td>
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</table>

### FIGURE 11

**Phase III PRIMA study: Efficacy results with rituximab maintenance after induction R/chemotherapy in previously untreated FL**

<table>
<thead>
<tr>
<th>Observation (n = 513)</th>
<th>Rituximab maintenance (n = 505)</th>
<th>Hazard ratio</th>
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<tbody>
<tr>
<td>Two-year PFS</td>
<td>66%</td>
<td>82%</td>
<td>0.50</td>
</tr>
</tbody>
</table>

PFS = progression-free survival
FOLLCULAR LYMPHOMA

Which one of the following R maintenance regimens do you generally use?

- 1 dose every 3 months for 2 years: 39%
- 1 dose every 8 weeks for 2 years: 35%
- 1 dose every 2 months for 4 cycles: 13%
- 4 weekly doses every 6 months for 2 years: 9%
- 1 dose every 3 months until disease progression: 4%

Which of the following best describes how long you generally recommend that R maintenance be administered?

- 2 years: 83%
- 1 to <2 years: 9%
- <1 year: 4%
- Indefinitely (until disease progression): 4%
- Other: 1%

ent people might think differently about the same data. I also find the treatment selection data for the 75-year-old patient remarkable. The clinical investigators have clearly moved toward BR for the elderly population, and the community

is following suit. I believe an additional advantage of bendamustine is that it is easier to combine with new agents than CHOP.

For example, if a drug that could cause neurotoxicity is being evaluated in this setting, then it might be easier to combine with bendamustine than with vincristine-containing CHOP.

DR SMITH: Currently, my usual preferred treatment for both a 58-year-old and a 75-year-old is BR (Figure 7). It appears that a fair proportion of physicians, both in academia and the community, prefer using R-CHOP for a younger patient, such as the 58-year-old. I believe for a young patient some concern persists about the effect of BR on bone marrow and ability to harvest stem cells at a later point.

I am not sure what proportion of patients with FL undergo a transplant. It is likely a small proportion, probably young healthy patients with short remissions. So I don’t believe that we should tailor our treatment based on the potential for a future transplant because so few patients really receive the transplant, although I understand the rationale of not using bendamustine for a younger patient, as the goal may be a more aggressive approach.

I can argue that you might achieve that goal with less toxicity by avoiding doxorubicin and administering R-CVP rather than R-CHOP.

I have seen patients with transformed lymphomas who received R-CHOP as initial therapy and now the disease has become more aggressive. In these situations, treatment of the transformed disease becomes more challenging as the patient might already have reached the limit of anthracyclines. It is not that I do not recommend R-CHOP in this setting, but for someone with slowly progressive disease who reaches the point of needing treatment, I believe those patients would be better served with BR.

Another observation related to the survey data regarding initial induction treatment is that approximately one quarter of community oncologists would
recommend rituximab monotherapy for the 75-year-old patient. I believe I am using less rituximab monotherapy, but the community physicians might be correct in using it more. I don’t believe anything is lost by using rituximab monotherapy up front and saving rituximab/chemotherapy for later lines.

**Use of maintenance rituximab in FL**

**DR FRIEDBERG:** The PRIMA study, which was presented at ASCO 2010, clearly shows that the progression-free survival benefit is substantial two years after rituximab maintenance (Figure 11).

These patients initially received immunochemotherapy, with 75 percent of patients having received R-CHOP and almost all of the remaining patients having received R-CVP. Patients who experienced a response were randomly assigned to rituximab maintenance or observation.

A significant improvement was seen in the primary endpoint of progression-free survival — for rituximab maintenance two-year progression-free survival was 82 percent versus 66 percent for observation. I was surprised at the magnitude of the benefit because R-CHOP alone has shown median progression-free survival in the range of four to five years in some data sets. Therefore, it was surprising to see that two years of rituximab maintenance early on would show that degree of benefit.

Because of the PRIMA data set, use of rituximab maintenance has been the biggest change in my practice recently. Prior to the PRIMA study, I did not recommend rituximab maintenance after initial immunochemotherapy.

**DR SMITH:** I individualize maintenance therapy, using it when concerned that remission may be short. The PRIMA trial may change practice, although we have no data for prolonged survival yet. Physicians need to discuss the risks of maintenance therapy — which are low but include infection and, theoretically, resistance — versus the potential benefit, which is prolonging progression-free survival but probably not changing survival in the long run (Figures 10-11). Community physicians may be ahead of the clinical investigators in adopting rituximab maintenance.

The rationale for every six months is that B cells start to recover after that time. The rationale for a single dose every three months is to maintain adequate trough levels, but for many patients a two-month schedule is needed to maintain that level. Data do exist for every two months for four doses. The PRIMA trial rituximab maintenance regimen is every two months for two years, so that is a reasonable choice for single-dose maintenance after initial immunochemotherapy.

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**CASE 2**

A 70-year-old man initially diagnosed in 2002 with FL achieves remission with R-CHOP x 6. One year later, he receives rituximab monotherapy for recurrent disease. Over the subsequent 6 years he experiences multiple relapses and receives immunotherapies and IMiD® therapies on and off protocol. Six months after receiving lenalidomide he experiences disease recurrence and receives ibritumomab tiuxetan.

Radioimmunotherapy leads to a 1-year complete response. The patient then receives bendamustine with good partial remission.

— Mitchell R Smith, MD, PhD
Philadelphia, Pennsylvania

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**FIGURE 13**

In your practice, is a nuclear medicine specialist or radiation oncologist with expertise in delivering radioimmunotherapy accessible to you for patient referral/consultation?

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Follicular Lymphoma (Continued)

Radioimmunotherapy (RIT)

DR FRIEDBERG: At our institution, we use both tositumomab and ibritumomab. Most of our SWOG studies have used tositumomab, so the study team is more accustomed to tositumomab. In my view, the two agents are relatively interchangeable.

Based on the data from the survey, the community physicians rarely use radioimmunotherapy (RIT), and the median number of times the oncologists in the academic setting use RIT is also low (Figures 14 and 16). I believe some physicians underappreciate the potential role of RIT, although these agents are available at every major academic center and many community-based practices have tositumomab.

A number of explanations exist as to why RIT has not been used more, and I believe part of the reason is potentially the fact that the oncologists don’t control the administration and partially the way the data sets have been generated. The data sets don’t address how to incorporate these agents into the treatment algorithm for FL. The other issue is the success of rituximab. Many physicians use rituximab-based regimens early and reserve RIT for much later in the disease course, frequently rendering the patients ineligible for the treatment.

An ongoing trial may answer the question regarding RIT as initial therapy for FL. The Intergroup study SWOG-S0016 compares R-CHOP to CHOP followed by tositumomab for patients with newly diagnosed FL (Figure 15). Results of this study will be available in the next few months and will likely be presented at ASCO 2011. If the trial is positive, this data set may give physicians more insight as to what RIT has to offer. The one big asterisk is that no maintenance rituximab was administered.

DR SMITH: According to the survey data, little uptake of RIT has occurred in the community-practice setting (Figures 14 and 16). Both of these agents have been available for quite some time. However, the usage is low. In terms of administration logistics, patients receive two infusions a week apart with intermediate scans, so it is an easy treatment. In relapsed disease, response rates with these agents are in the 70 to 80 percent range, which is high. Short-term toxicity is minimal, and it is easy on the patient. So RIT should be used much more widely than it has been.

The practical issues for the oncologists include collaboration with either
FOLLICULAR LYMPHOMA

A nuclear medicine expert or a radiation oncologist. Radiation safety issues in addition to cost and reimbursement must be considered (Figures 13-14). Admittedly, licensing is rigorous and site setup can be difficult, so barriers to RIT administration exist. However, once licensing and setup are complete administration of RIT is straightforward.

The one clinical consideration is that RIT can only be used if the patient’s bone marrow is still adequate and not replaced with lymphoma. Bone marrow must be less than 25 percent involved with the malignant clone. So by the time community oncologists are ready to incorporate RIT into later lines of therapy, many patients are not eligible either because of relatively high bone marrow involvement or because of coexisting cytopenias. For a patient to be truly eligible for RIT, this treatment option should be considered earlier in the disease course.

In terms of the choice of the agent, both ibritumomab tiuxetan and I 131 tositumomab are effective. I don’t believe they will ever be compared head to head in a clinical trial. In similar patient populations, the response rates and longer efficacy outcomes are similar.

I generally recommend ibritumomab because, from a radiation safety point of view, it is somewhat better. Ibritumomab is a pure beta emitter, meaning it does not radiate the nearby people and surroundings. This makes the logistics better because the patient doesn’t need to worry about avoiding contact with people.

Tositumomab is a gamma emitter, so it does emit radiation, and one needs to be a little more careful with radiation safety. Tositumomab can also cause hypothyroidism because of radiation to the thyroid.

The FIT trial shows benefit with ibritumomab consolidation after initial response to chemotherapy (Figure 17). The issue with the FIT trial is that only 14 percent of patients received rituximab as part of initial therapy.

It was not a design flaw — simply that rituximab was not a standard part of initial treatment when the study was conducted. With the PRIMA trial and...
rituximab maintenance, the immediate question is where consolidation with RIT might fit in the initial treatment algorithm for FL. We are missing these critical data. For a patient who might have residual disease after rituximab/chemotherapy, for whom the remission needs to be consolidated and it is not really maintenance, I believe it may be reasonable to consider RIT.

Hematologic Oncology Update Special Edition, 2010

DR STEPHANIE GREGORY: I have continued to embrace the use of RIT, both as consolidation after initial induction in FL and for the treatment of relapsed FL. In the relapsed setting, patients tend to prefer it as they don’t have to go through six cycles of chemotherapy and they don’t lose their hair.

Hematologic Oncology Update Issue 1, 2010

DR PETER MCLAUGHLIN: At ASH 2008, we reported interim results from a Phase II study for patients with high-risk FL according to FLIPI. The induction regimen in this study included rituximab, fludarabine, mitoxantrone and dexamethasone (R-FND).

After induction, patients received consolidation RIT with ibritumomab tiuxetan and then maintenance rituximab for one year. The complete remission rate was 83 percent, and the Kaplan-Meier curve showed a 20 percent improvement compared to the expected three-year disease-free survival.

We also have Phase III data with RIT consolidation after initial therapy in FL, and ibritumomab is FDA approved in this setting. It is surprising that despite these data the strategy is not embraced by the community.

One of the issues is that only a small proportion of patients received rituximab as part of initial therapy in the FIT trial. My hunch is that RIT consolidation likely confers a benefit in patients receiving rituximab chemotherapy as upfront induction, at least among patients who only had a partial remission for whom the job of induction therapy is not completely done.

Dosing and schedule of bendamustine in combination with rituximab
(see next page, Figures 18 and 19)

DR FRIEDBERG: Despite the fact that the approved dose of bendamustine is 120 mg/m² for two days every 21 days, it is widely accepted that this is not a tolerable dose for most patients (Figure 18).

Bendamustine is almost always administered with rituximab, and all of the data in combination with rituximab are with a dose of 90 mg/m² for two days every 28 days. A recently published article has a consensus discussion with uniform agreement that when administering with rituximab, the bendamustine dose should be 90 mg/m² for two days every 28 days.

As far as the number of cycles, the data in the up-front setting are for six cycles and the data in the relapsed setting are for four cycles. How much you have to administer in the relapsed setting is individualized.

However, in the up-front setting, six cycles should be enough for most patients, and I believe eight cycles of bendamustine may be unnecessary (Figure 19). I also want to add that I am not sure what additional benefit a patient would obtain from cycles beyond the six cycles for an indolent histology.

DR SMITH: The pivotal trial in relapsed FL used the 120-mg/m² dose of bendamustine on days one and two every 21 days. This trial was with single-agent bendamustine without rituximab. Many patients had treatment delays, and investigators involved with the trial tell us that dosing every 21 days is just not feasible in the majority of patients and that the every 28-day schedule is more reasonable.

The data on rituximab with 90 mg/m² of bendamustine on days one and two every 28 days show good efficacy. In view of all this, most oncologists have elected to move toward 90 mg/m² on days one and two every 28 days (Figure 18). Regarding the number of cycles, I lean...
then I would not hesitate to stop at four or five cycles.

**Hematologic Oncology Update Issue 2, 2010**

**DR JOHN LEONARD:** The Phase III data presented by Prof Rummel at ASH 2009 basically showed that the BR combination has less toxicity than R-CHOP (page 9, Figure 9). Patients receiving BR experienced less myelosuppression and almost no alopecia. BR does cause a little rash and nausea. With regard to efficacy, the response rates were high in both arms, but the progression-free survival was improved with BR compared to R-CHOP (page 8, Figure 8). The study certainly suggests that efficacy is at least comparable with better safety.

The dosing of bendamustine has been quite variable in different studies. Like some other drugs, when you administer it with rituximab you see a little more hematologic toxicity. We typically use 90 mg/m² on days one and two every four

![Figure 18](image1)

**When administering bendamustine either alone or with rituximab for the treatment of FL, what dose and schedule do you generally use?**

**Patients age 65 or younger**

- 90 mg/m² IV on days 1 and 2 every 28 days: 76%
- 90 mg/m² IV on days 1 and 2 every 21 days: 24%
- 120 mg/m² IV on days 1 and 2 every 21 days: 8%
- 120 mg/m² IV on days 1 and 2 every 28 days: 8%
- I have not administered bendamustine for patients with FL: 10%

**Patients older than age 65**

- 90 mg/m² IV on days 1 and 2 every 28 days: 45%
- 120 mg/m² IV on days 1 and 2 every 21 days: 26%
- 120 mg/m² IV on days 1 and 2 every 28 days: 8%
- I have not administered bendamustine for patients with FL: 10%

![Figure 19](image2)

**When using bendamustine alone or with rituximab for FL, how many cycles do you generally administer?**

- 6 cycles: 96%
- Until disease progression or development of unacceptable side effects: 77%
- 8 cycles: 19%

![Figure 19](image3)

**When using bendamustine alone or with rituximab for FL, how many cycles do you generally administer?**

- 6 cycles: 96%
- Until disease progression or development of unacceptable side effects: 77%
- 8 cycles: 19%

more toward six cycles of therapy in the up-front setting (Figure 19). However, in later lines of therapy, for which the goal is mainly palliation, I don’t necessarily push to six cycles. If a patient is older and is having prolonged myelosuppression, then I would not hesitate to stop at four or five cycles.
Follicular Lymphoma (Continued)

How would you compare the efficacy and safety of R-bendamustine and R-CHOP in the front-line treatment of FL?

- R-bendamustine is less toxic and more efficacious: 52%
- R-bendamustine is equally efficacious: 36%
- R-CHOP and R-bendamustine have comparable efficacy and toxicity: 16%
- R-CHOP is more toxic and more efficacious: 4%
- Other: 0%

Role of biopsy and PET in relapsed FL

DR FRIEDBERG: I believe that we frequently don’t know what’s going on in patients with relapsed FL without having a tissue confirmation. Biopsy results at the time of relapse can be helpful in choosing subsequent therapies.

The PET scans and other attempts to try to figure out if transformation is happening or not are not always accurate, so I try to perform a biopsy to determine whether transformation is present. The biopsy also helps determine whether the grade might have changed. I find that patients are willing to undergo a surgical biopsy once they know that the results might affect their treatment.

In the LymphoCare study we did not have good data on the issue of biopsy at the time of relapse. We are capturing this now. In viewing the NCCN database, we are seeing that the majority of patients are undergoing biopsies, similar to what the clinical investigators have reported here (Figure 22).

From my perspective, the role of PET scans in FL is much less clear than in curable lymphomas. In Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL), PET scans can be helpful if the results are negative, at least at the end of treatment.

In a disease such as FL, which is incurable, it is not clear to me how PET scans assist in the management of this disease. I believe a lot of people perform PET scans in FL because that’s how they follow patients (Figure 23). But in FL, no strong data indicate that PET scans assist in management. In an international consensus conference in 2007, the opinion was that outside of clinical protocols, PET scans are not recommended in FL.

weeks, although some of the published data and package insert data suggest that higher doses at a shorter interval can be reasonable. I believe 90 mg/m² on days one and two every 28 days is tolerable for most patients and can be highly effective, and this is the dose I have used.
DR LEONARD: The role of PET scans in FL is rather limited. One situation in which they could definitely be useful is for patients with limited-stage FL, for whom a PET scan may alter the staging and thus treatment recommendations. The other clinical scenario, which is more common, is when progression of FL has occurred and the concern is that there might be transformation. SUV values from a PET scan can be extremely helpful because higher SUV values tend to correlate with the presence of a large cell transformation. If the SUV value is lower, it provides reassurance that transformation is less likely. High SUV values increase the concern regarding transformation and consideration of a biopsy.

**Hepatitis screening for patients receiving rituximab**

**DR SMITH:** Cases of fulminant hepatitis have occurred among patients with lymphoma receiving rituximab therapy. It is now in the NCCN guidelines that patients should be screened for hepatitis B. Even if subclinical infection is present, patients should receive hepatitis B therapy before starting treatment for their lymphoma. I tend to obtain a hepatitis panel and if anything is positive, then I involve a gastroenterologist or hepatologist in the care of the patient (Figure 24).

The issue of hepatitis C reactivation with rituximab is not as clear as it is for hepatitis B. Overall, we are not as concerned about hepatitis C, but it is good information to have. Hepatitis C has been associated with marginal zone lymphoma. Interferon has activity against both hepatitis C and lymphoma. Sometimes the patient just needs to receive interferon without additional chemotherapy, particularly for indolent lymphomas.

**DR FRIEDBERG:** In the laboratory screening for hepatitis B in patients starting a rituximab-containing regimen, the core antibody is important, and more and more data are coming out suggesting that antihepatitis B core antibody (HBc Ab) should be tested (Figure 24). NCCN guidelines now also include testing for HBc Ab before starting a patient on a rituximab-based regimen.

At my institution, which is not in an inner-city area and does not have much ethnic diversity, we started doing the core antibody routinely last year. We did find a few patients who screened positive, so it clearly needs to be used as a screening tool.

**Hematologic Oncology Update**

**Issue 2, 2010**

**DR ANDREW ZELENETZ:** At Memorial, all patients are now tested prospectively...
for hepatitis if they’re receiving immunosuppressive chemotherapy. We now consider it the standard approach, and we’ve identified a number of patients in this setting with positive hepatitis B test results — 22 cases with three deaths — so clearly this is an important issue.

SELECT PUBLICATIONS


Ghielmini M et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. *Blood* 2004;103(12):4416-23.


Rummel MJ 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 randomised phase III study of the StiL (Study Group Indolent Lymphomas, Germany). *Proc ASH* 2009; Abstract 405.


Indications for initiation of therapy in chronic lymphocytic leukemia (CLL)

DR SMITH: No absolute white blood cell (WBC) count should be a trigger to initiate treatment in CLL (Figure 26). I have seen patients who have been told that if the WBC count reaches 100,000/mm$^3$, then treatment should be initiated. This absolute count comes from acute myeloid leukemia, in which an absolute blast count of 100,000/mm$^3$ increases the risk for hyperviscosity. The initiation of treatment in CLL should be based on symptoms or cytopenias, and usually in my practice treatment is initiated for fatigue, enlarging nodes, progressive anemia or thrombocytopenia that are either clinically relevant or bothersome to the patient.

DR FRIEDBERG: The classic indications for initiating therapy for CLL are development of symptoms or cytopenias. A rapid lymphocyte doubling time of less than six months is a relative indication for treatment, in which case the physician is trying to get a sense of whether for a given patient the pace of disease progression needs to be slowed down.

Biomarker assessment in CLL

DR SMITH: It is interesting that we believe

--- Dr Friedberg

**CASE 3**

A 74-year-old woman is diagnosed with asymptomatic CLL in 2000 with a white blood cell count of 15,000/mm$^3$ and is initially observed. After 7 years of active surveillance, at age 81 she develops progressive fatigue and anemia (Hb 8.0 g/dL). Cytogenetic testing shows CLL with 17p deletion.

The patient undergoes transfusion and receives R-CVP x 4 with a near-complete response and becomes transfusion independent. Consolidation alemtuzumab is administered x 6 weeks. She fares well for approximately 2 years and then develops progressive lymphocytosis and anemia. She is being considered for treatment with rituximab/bendamustine followed by alemtuzumab consolidation.

--- Dr Friedberg

**Figures 26-27**

For a patient with CLL who is asymptomatic without bulky disease, anemia or thrombocytopenia and has a slow lymphocyte doubling time, is there an absolute white blood cell count that you use to initiate treatment?

**Do you routinely order cytogenetic testing for your patients with CLL...**

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<th>At first diagnosis?</th>
<th>At time of first relapse?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, usually</td>
<td>Yes, usually</td>
</tr>
<tr>
<td>Yes, occasionally</td>
<td>Yes, occasionally</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

---
**FIGURE 28**

In otherwise healthy younger patients with CLL, which of the following cytogenetics or biomarkers do you consider when making your initial treatment decision?

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Consider</th>
<th>Less Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(17p)</td>
<td>76%</td>
<td>75%</td>
</tr>
<tr>
<td>del(11q)</td>
<td>40%</td>
<td>39%</td>
</tr>
<tr>
<td>ZAP-70</td>
<td>36%</td>
<td>52%</td>
</tr>
<tr>
<td>CD38 antigen</td>
<td>32%</td>
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</tr>
<tr>
<td>del(13q)</td>
<td>32%</td>
<td>41%</td>
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<tr>
<td>IgVH gene status</td>
<td>28%</td>
<td>45%</td>
</tr>
<tr>
<td>t (11q;v)</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>I do not consider cytogenetics/biomarkers</td>
<td>24%</td>
<td>17%</td>
</tr>
</tbody>
</table>

In otherwise healthy younger patients with CLL (Figures 27-28), we have to know all these biomarkers in patients with CLL. We obtain FISH to look for cytogenetic abnormalities, we conduct flow cytometry to examine CD38 and we also frequently do ZAP-70. However, the bottom line is that these biomarkers are rarely factored in when making treatment decisions. It is the clinical course of the patient that dictates when and if they need treatment. In my view, the only biomarker that will affect any treatment choices is deletion of chromosome 17p.

**DR FRIEDBERG:** I believe we have more biomarkers in CLL than we have data on how to interpret them (Figure 28). One of the biggest frustrations is that sometimes these biomarkers provide conflicting information, and then what to do with the information is unclear. I believe we should bank all this information, and perhaps five years from now we will understand it better.

Among the specific biomarkers of more utility I would say that deletion of 17p could have an effect on treatment choice. Fludarabine as a single agent doesn’t appear to perform well in patients with deletion of 17p. Similarly, with the 11q deletion, many physicians try to include cyclophosphamide in the regimen. I believe that these two probably should have the biggest effect on treatment. I am not certain how markers such as ZAP-70 are affecting the therapeutic decision-making of physicians outside of the academic institutions.

**Impact of adverse cytogenetics on initial treatment decision-making for CLL**

**Hematologic Oncology Update**

**Think Tank 2011**

**DR FRIEDBERG:** Assuming a patient with an 11q deletion is in good health and hasn’t acquired additional abnormalities, I would probably recommend FCR because a benefit does seem to be apparent in adding cyclophosphamide for those patients.

Depending on the patient’s performance status, another consideration would be treatment with BR. We have less experience with that combination up front, but I have used BR for older patients with the 11q deletion.

**DR BRUCE CHESON:** For patients in their seventies with an 11q deletion, I would recommend BR because older patients don’t tolerate FCR as well, with myelosuppression and perhaps some age-related renal compromise. Based on the available indirect data in the up-front setting, response rates are comparable between BR and FCR. The response rates are over 90 percent with BR and FCR, and the CR rates are high with both regimens. That’s why the CLL-10 study (Figure 30) evaluating BR versus FCR is so important.

**DR ZELENETZ:** Patients who have the 11q deletion clearly have a different response rate with fludarabine-based regimens with or without an alkylator included. The reports are from retrospective studies, but we have consistently seen that cyclophosphamide dramatically increased response rates for patients with the 11q abnormality.

Of course, the big question is, FCR or BR? That brings us back to, what are the supporting data? We’ve had an evolution of trials: F versus FC and FC versus FCR. The FC versus FCR trial is important and has now been published.
older patient. Unequivocally, we want to see the results of the BR versus FCR trial, which is an essential study (Figure 30). The long-term follow-up of the bendamustine versus chlorambucil trial, which was presented at ASH, continues to confirm the benefit of bendamustine over chlorambucil.

**DR CHESON:** In the study by Wendtner and colleagues, which produced the only first-line data for BR in CLL, patients with the 11q deletion had a 91 percent response rate, with 43 percent complete remissions, which was even better than the response rate in trisomy 12. So BR is active in those patients with the 11q deletion.

**DR SMITH:** It is interesting that alemtuzumab use in the initial regimen is increased for a 60-year-old patient with CLL if the biomarkers reveal 17p deletion (Figure 29). The long-term follow-up of the bendamustine versus chlorambucil trial, which was presented at ASH, continues to confirm the benefit of bendamustine over chlorambucil.

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zero, and the response rate is still reasonable. We have a sense that we should incorporate alemtuzumab in the initial treatment algorithm for patients with deletion 17p CLL. But the data for that are not that strong. Further, a study with alemtuzumab consolidation after initial rituximab/chemotherapy has shown significant toxicities, and the trial was halted because of deaths of patients in complete response. So we need to be careful using such an approach.

Another issue with deletion 17p is that it usually does not come as either 100 percent or zero percent. Many times we get 10 percent or 18 percent of cells with deletion 17p, and we don’t know the cutoff. So it is an unsettling situation at the moment — we have all this information and we don’t know what to do with it.

In terms of the 75-year-old patient, a bit of a shift appears to BR as up-front treatment when compared to the use of BR for the 60-year-old patient (Figure 31). I believe we all get nervous about administering FCR to patients in their upper sixties and certainly to patients older than age 70. FCR is probably a toxic regimen in such settings, so most of us would go to something less toxic. I believe either FR or BR is a reasonable choice. For older patients I prefer BR because I worry about fludarabine-related immunosuppression.

DR FRIEDBERG: In terms of up-front treatment of CLL, the classic Hallek study evaluating the addition of rituximab to fludarabine and cyclophosphamide indicated that a clear benefit existed — perhaps a smaller benefit than what we see in FL — both for progression-free survival and overall survival when rituximab was included with up-front chemotherapy (Figure 32). This has also been demonstrated in the relapsed setting, so if one is considering FC, these data suggest adding rituximab for patients with CLL.

Hematologic Oncology Update Issue 1, 2011

DR CHESON: A number of options are now available for patients with CLL, several of which are approved by the FDA. Of course, fludarabine-based regimens revolutionized how we treated CLL in the 1990s. Several randomized studies indicated that fludarabine was better than alkylating agent-based therapy. With the availability of rituximab, FR and related regimens became the standard, and whether you believe FR or FCR to be the preferred regimen, those two regimens have dominated the field for a number of years.

More recently, two other drugs have been approved for the initial treatment of CLL. One of them is alemtuzumab, which is an anti-CD52 monoclonal antibody that beat up on chlorambucil in
subcutaneously, it’s better tolerated. Whether this route of administration is as effective as intravenous administration is a bit controversial. The absorption is a little slower, so it takes a little longer to obtain the blood levels needed.

More recently, bendamustine has been widely studied in a variety of tumor types, including CLL, other NHL subtypes and even some solid tumors and multiple myeloma. Based on studies from Germany, a Phase III trial in CLL was launched against chlorambucil, and bendamustine resulted in higher overall and complete response rates, but more importantly, the primary endpoint was progression-free survival, which was significantly longer with bendamustine compared to chlorambucil, leading to its approval by the FDA. We’ve seen data with bendamustine and rituximab from the German CLL Study Group, with an overall response rate up front of approximately 90 percent and complete remissions in approximately 50 percent of cases, which is comparable to FR and FCR in patients at similar risk. Bendamustine is not renally excreted, and you don’t need to modify the dose in the setting of mild to moderate renal failure. The package insert says you can use it safely with creatinine clearances as low as approximately 40. We’ve used it in cases in which creatinine clearance was lower than that, and it has been administered safely to patients with myeloma undergoing dialysis for renal failure. So it’s a good drug. Fludarabine, on the other hand, requires dose modification in patients who have renal insufficiency. Bendamustine is also less immunosuppressive than fludarabine and probably less myelosuppressive than FCR.

Hematologic Oncology Update
Issue 4, 2010

**DR HAGOP KANTARJIAN:** The studies evaluating BR in the front-line CLL setting are showing a high overall response rate of approximately 90 percent, with a complete response in one third of patients. Clearly, this combination is effective in front-line CLL. The issue is whether BR is as good as FCR or

---

**FIGURE 32**

*Effect of the addition of rituximab (R) to fludarabine (F) and cyclophosphamide (C) on survival for patients with CLL: A Phase III trial*

<table>
<thead>
<tr>
<th></th>
<th>FCR (n = 408)</th>
<th>FC (n = 409)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year PFS</td>
<td>65%</td>
<td>45%</td>
<td>0.56</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3-year OS</td>
<td>87%</td>
<td>83%</td>
<td>0.67</td>
<td>0.01</td>
</tr>
<tr>
<td>Grade 3/4 neutropenia</td>
<td>34%</td>
<td>21%</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3/4 leukocytopenia</td>
<td>24%</td>
<td>12%</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


**FIGURE 33**

*When administering rituximab up front either alone or with chemotherapy for a patient with CLL, what dose and schedule do you generally use?*

- **375 mg/m² q four-weekly**: 41%
- **375 mg/m² initially followed by 500 mg/m² q four-weekly**: 32%
- **375 mg/m² q weekly**: 18%
- **500 mg/m² q four-weekly**: 8%
- **Other**: 4%

I have not administered rituximab up front alone nor with chemotherapy for patients with CLL: 4%
whether it can rescue patients who have failed on FCR therapy.

I believe that the question of bendamustine treatment for elderly patients with CLL is important because although the FCR data have shown a significant advantage for progression-free survival and survival, most of the FCR studies enrolled patients younger than age 75. In fact, at least one German study compared fludarabine to chlorambucil and did not show an advantage with fludarabine in patients older than age 65. So, among this patient subset, BR might have equivalent efficacy to FCR and might be a gentler regimen. We should conduct comparative studies of BR versus FCR for patients with CLL who are older than age 70. In general, among patients who are older than the age range accrued in the FCR studies, BR is a reasonable approach in the up-front setting.

**Dose and schedule of up-front rituximab in CLL**

**DR FRIEDBERG:** My background is mainly in treating lymphomas, and I am more used to the 375-mg/m² dose and I don’t go up to the 500-mg/m² dose, which is what the majority of people do. The data, though, at least with FCR, are with 500 mg/m², so that is not an incorrect answer.

**Monday Night with Research To Practice NHL/CLL, November 1, 2010**

**DR BRAD KAHL:** The approved dose of rituximab in lymphoma is 375 mg/m², but in virtually all of the CLL trials the dose administered has been 500 mg/m². Frankly, I doubt that we’ll ever see a randomized clinical trial comparing the 375-mg dose to the 500-mg dose. Therefore, given that the advantage with rituximab is with the 500-mg/m² dose, that’s what we’ve adopted for the treatment of CLL at our institution.

**Treatment of relapsed/refractory CLL**

**DR FRIEDBERG:** I believe for a patient who experiences disease progression after FR, I would virtually always choose BR now. As far as ofatumumab is concerned, I usually stick to the labelled indication for CLL refractory to both fludarabine and alemtuzumab.

**Hematologic Oncology Update Think Tank 2010**

**DR CHESON:** We have had a number of patients with CLL whose disease has progressed on fludarabine-based therapy, R-CHOP and hyper-CVAD who still experience responses to bendamustine. In terms of new treatment regimens for CLL, a number of important ongoing trials, mostly developmental, are building on other active drugs, such as lenalidomide, which has been shown to be effective in the relapsed/refractory setting. We are conducting a Phase I study at our institution evaluating the combination of bendamustine, lenalidomide and rituximab for patients with...
Phase II study of lenalidomide as initial treatment for CLL in elderly patients (N = 60)

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients, n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>CR with incomplete blood cell count recovery</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Nodular PR</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>37</td>
<td>62</td>
</tr>
</tbody>
</table>

Badoux X et al. Proc ASCO 2010; Abstract 6508.

Phase II study of lenalidomide for patients with relapsed or refractory CLL (N = 45)

<table>
<thead>
<tr>
<th>Response</th>
<th>Patients, n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td>Complete response</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Partial response</td>
<td>17</td>
<td>38</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Not assessable</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>Early for assessment response</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>


**Hematologic Oncology Update**

**Think Tank 2010**

**DR CHESON:** Lenalidomide is an interesting agent. We don’t know how it works, but it seems to work in CLL. Two major studies have been published with lenalidomide in CLL. Asher Chanan-Khan and the Roswell Park group demonstrated a 45 percent response rate with lenalidomide for patients with relapsed or refractory CLL, starting at a high dose of 25 mg with subsequent dose reductions. In the MD Anderson study, they started at a low dose and worked their way up and achieved a 30 to 35 percent response rate. Lenalidomide is also active in the front line, and surprisingly the response rates aren’t much different from those observed in the relapsed setting.

Complete remissions with lenalidomide are rarely observed, so it is being used in combination with other agents or as sequential therapy. We have an ongoing trial of FR followed by lenalidomide. We also have a Phase I trial of bendamustine/lenalidomide in the relapsed setting. When we get to the maximum tolerated dose, we will add rituximab to the doublet. I believe lenalidomide is also being combined with rituximab or ofatumumab.

When combined with cytotoxic therapy, lenalidomide is frequently used as consolidation or maintenance therapy because it can compromise the dose of cytotoxic agents.

**DR KAHLE:** Maintenance lenalidomide could be an attractive strategy in CLL, analogous to the experience with indolent lymphomas, especially in the relapsed setting.

Getting patients into remission isn’t difficult, but keeping them in remission can be a challenge. So an oral therapy with a favorable toxicity profile is an attractive maintenance strategy. A num-
Chronic Lymphocytic Leukemia (Continued)

**FIGURE 38**

*During the past year, have you administered any of the following treatments to your patients with CLL? (Check all that apply)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + chemotherapy</td>
<td>100%</td>
</tr>
<tr>
<td>Bendamustine +/- rituximab</td>
<td>97%</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>92%</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>88%</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>68%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>50%</td>
</tr>
<tr>
<td>Rituximab monotherapy</td>
<td>48%</td>
</tr>
<tr>
<td>Bendamustine +/- rituximab</td>
<td>21%</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>40%</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>34%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>32%</td>
</tr>
<tr>
<td>Rituximab monotherapy</td>
<td>67%</td>
</tr>
</tbody>
</table>

For patients who require additional treatment, as they all eventually do.

**SELECT PUBLICATIONS**


Fischer K et al. Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter Phase II trial of the German CLL Study Group (GCLLSG). *Proc ASH* 2009; Abstract 205.


Smith MR et al. Increased incidence of therapy related myeloid neoplasia (t-MN) after initial therapy for CLL with fludarabine-cyclophosphamide (FC) vs fludarabine-cyclophosphamide (FC) vs fludarabine (F): Long-term follow-up of US Intergroup study E2997. *Proc ASH* 2010; Abstract 924.


Varghese AM et al. Long term survival report of the UKCLL02 Trial: A Phase II study of subcutaneous alemtuzumab in patients with fludarabine refractory CLL (on behalf of the NCRI CLL Trials Sub-Group). *Proc ASH* 2010; Abstract 922.


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**Oraftumab in CLL**

**Hematologic Oncology Update Issue 1, 2011**

**DR CHESON:** A number of interesting drugs are being developed for CLL. Fortunately, most are biologic and targeted agents, with approximately 10 anti-CD20 monoclonal antibodies available or in clinical trials. Ofatumumab is approved by the FDA for patients with fludarabine- and alemtuzumab-refractory CLL.

The response rates in that patient group were approaching 50 percent, but some concerns have arisen about ofatumumab. I’ve had a lot of experience with ofatumumab and found that the infusion reactions seem to be greater than with rituximab. Whether a novel anti-CD20 antibody will replace rituximab will be determined by one of two factors — either it needs to be more effective or it needs to work when rituximab doesn’t.

Bill Wierda from MD Anderson presented data evaluating the combination of FC and ofatumumab — instead of FCR — and the overall response rate was approximately 75 percent, with about 40 percent complete remissions, which is lower than has been reported with FR, FCR and even BR.

Whether the patient groups match with respect to prognostic factors remains to be seen, but ofatumumab is an interesting drug. I’ve had some patients for whom many prior therapies had failed who experienced excellent responses to ofatumumab. So it’s a reasonable option for patients who require additional treatment, as they all eventually do.
**Diffuse Large B-Cell Lymphoma**

**CASE 4**

A 55-year-old woman is diagnosed with Stage III DLBCL with a low-intermediate IPI score. She has bulky abdominal adenopathy and receives R-CHOP-21 x 8 followed by consolidation iodine I 131 tositumomab on the SWOG-S0433 study. The patient achieves a CR, but her disease recurs after 6 months with biopsy-proven DLBCL. She receives salvage chemotherapy with R-DHAP and initially responds. After stem cell collection and within 6 weeks of her documented response to R-DHAP, she experiences significant disease progression and recurrence of B symptoms, at which point she enrolls on a clinical trial.

— Dr Friedberg

**FIGURE 39**

**SWOG-S0433 Phase II open-label trial**

<table>
<thead>
<tr>
<th>Eligibility (target accrual = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulky Stage II to Stage IV DLBCL, previously untreated</td>
</tr>
<tr>
<td>CD20 antigen-positive</td>
</tr>
<tr>
<td>Age ≥ 18 years; PS 0 to 2</td>
</tr>
<tr>
<td>Adequate sections and a paraffin block OR ≥10 unstained sections from original diagnostic specimen</td>
</tr>
<tr>
<td>No CNS involvement</td>
</tr>
<tr>
<td>No histologic transformation</td>
</tr>
</tbody>
</table>

R = rituximab; CHOP = cyclophosphamide/doxorubicin/vincristine/prednisone
* Patients undergo gamma scans over a one-week period to determine the correct treatment dose of I 131 tositumomab. After a dosimetric dose, patients receive tositumomab IV followed by a treatment dose of I 131 tositumomab.


**FIGURE 40**

**Do you generally use R maintenance for patients with DLBCL who have received R-containing front-line therapy?**

<table>
<thead>
<tr>
<th>% responding no</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 10 20 30 40 50 60 70 80 90 100</td>
</tr>
<tr>
<td>100%</td>
</tr>
<tr>
<td>80%</td>
</tr>
</tbody>
</table>

**Treatment of newly diagnosed DLBCL**

**DR FRIEDBERG:** R-CHOP remains the standard in the United States in the management of DLBCL. It could be administered every 21 days or every 14 days, and you could offer arguments on both sides. Two randomized studies are trying to determine whether R-CHOP-14 might be better. Preliminary results from both studies do not suggest a benefit with R-CHOP-14, but some flaws may be present in the design of the studies. At my institution we don’t feel that any reason exists to move away from R-CHOP-21 at this time.

No evidence suggests that rituximab maintenance in DLBCL is appropriate and therefore I don’t use it (Figure 40).

**Role of interim PET scans in DLBCL**

**DR FRIEDBERG:** These survey results surprise me a bit because it appears that the majority of physicians perform interim PET scans in DLBCL (Figure 41). Multiple studies suggest disagreements on how interim PET scans are interpreted, and a lot of discordance exists regarding whether the PET scan is positive or negative. Even if the PET scan is positive, frequently the biopsies are negative and no data set tells us what to do with an interim positive scan. So outside of a clinical trial, I don’t see any indication for an interim PET scan. In fact, I believe that a positive interim PET scan can often be distracting.

Of note, 75 percent of the investigators and 69 percent of the practicing oncologists indicated that they would change the course of therapy on the basis of a positive interim PET scan. I am surprised by that because outside of a clinical trial I don’t know what you would do differently.

**Hematologic Oncology Update**

**Issue 4, 2010**

**DR RICHARD FISHER:** I am not convinced that interim PET scans need to be done. If the question is, “Is it better for an...
interim PET scan to be negative than to be positive?" then it is an easy question to answer. I would want it to be negative. The real question in my mind is what to do for patients whose interim PET scans are positive if performed. We don’t have any good prospective data on this clinical scenario, and my concern is twofold. One issue is whether some of these scans are false positives, and the other issue is whether administering up-front high-dose chemotherapy with stem cell rescue to patients with true interim PET scan-positive results changes the natural course for those patients. In my practice, I don’t make decisions, off protocol, on the basis of an interim PET scan. The scenario is definitely different from that of a patient with clinically progressive disease, for whom we would change therapy.

Hematologic Oncology Update Issue 2, 2010

DR LEONARD: I believe the issue of PET scanning is complicated in DLBCL. I have no doubt that in the initial staging a PET scan can be helpful in aggressive lymphomas and is standard. Documenting a remission with PET scanning at the end of treatment is also well established.

Two questions in my mind are follow-up PET scans when a patient is in remission and interim PET scans during treatment. I believe the questions remain largely in those areas. A paucity of data are available in follow-up, and concern exists about both radiation exposure and cost, which are important issues.

Regarding interim PET scans, a huge amount of interobserver variability occurs, and published data show that experts differ as much as a third of the time on whether a scan is positive or negative. In my view, the answer should be to minimize interim PET scanning and not act on it unless a biopsy is being performed because both false-positive and false-negative results occur.

Hematologic Oncology Update Issue 2, 2010

DR STEVEN HORWITZ: The ECOG-E3404 study brought out some of the same issues that we have experienced, primarily that it is a bit difficult to identify and then know what to do with a positive interim PET scan. Also quite a bit of operator dependence or interoperator variation is involved. Basically this study demonstrated that it is difficult to obtain universal agreement on what a positive interim PET scan is.

With the use of interim PET scanning — at least in our hands in a study for patients receiving R-CHOP-14 — a number of false positives emerge. So we’ve evolved the dogma that we biopsy residual PET avidity and then either it’s a false-positive PET scan, in which case we continue with our planned therapy, or it’s a true-positive PET scan, and then we label that case potentially primary refractory and switch course at that point.

Right now, I generally don’t perform interim scans outside of a protocol setting for patients with DLBCL. However, sometimes it is difficult to resist doing it because you would like to give the patient good news.
I think it’s interesting that in practice use of interim PET scanning is frequent — even among clinical investigators it’s frequent, but in practice even more so. And I believe it’s that sense of wanting to be able to tell the patient “Yes. You’re doing great and we’re going to push on.”

**Molecular phenotyping of DLBCL**

**DR FRIEDBERG:** In terms of molecular phenotyping of DLBCL, I don’t believe that it has substantial relevance in clinical practice at this time (Figure 43). However, some hints exist that in the future determining molecular phenotype will be relevant to practice. For example, preliminary data on combining the EPOCH regimen with bortezomib suggested a benefit for patients with the nongerminal-center — or activated B-cell — phenotype versus the germinal-center phenotype.

In addition, data presented at ASCO 2010 suggested that patients who harbor the nongerminal-center phenotype derive a greater benefit from lenalidomide than do those with the germinal-center phenotype.

Clearly, these are two different diseases that should be approached differently in trials moving forward. We don’t evaluate DLBCL phenotype for all patients right now, but perhaps we should consider doing so.
Another discussion that has developed directly from the identification of molecular subtypes in DLBCL is whether we can determine which genes are upregulated or downregulated in each of the subtypes and treat them accordingly.

One example of this phenomenon is that the less favorable subtype, the non-germinal-center subtype, has been associated with chemoresistance. One known target of the proteasome inhibitor bortezomib is NF-kappa-B.

This led our group to conduct a study in which bortezomib was added to R-CHOP chemotherapy in DLBCL and in mantle-cell lymphoma. From this small study, it appears that by adding bortezomib to the R-CHOP regimen, we may be improving the outcome for the poorer-prognosis nongerminal-center subtype.

That has all led to a prospective study that is enrolling patients with newly diagnosed DLBCL who have the non-germinal center subtype, determined by immunophenotyping, and randomly assigning them to R-CHOP with or without bortezomib. The goal is to be able to address the question, does adding bortezomib in this particular subtype improve outcomes?

### SELECT PUBLICATIONS

- Coiffier B et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: A study by the Groupe d’Etudes des Lymphomes de l’Adulte. *Blood* 2010;116(12):2040-5.
- Donor K et al. Rapid prospective identification of non-germinal center B cell-like (GCB) diffuse large B-cell lymphoma (DLBCL) patients for targeted trials: Early results from PYRAMID, a Phase 2 randomized study of R-CHOP ± bortezomib in newly diagnosed non-GCB DLBCL. *Proc ASH* 2010; Abstract 1792.
- Hernandez-Hizilaliturri FJ et al. Response of relapsed-refractory diffuse large B-cell lymphoma (DLBCL) with nongerminal center B-cell phenotype to lenalidomide (L) alone or in combination with rituximab (R). *Proc ASCO* 2010; Abstract 8038.
- Sehn L et al. FDG-PET scan guided consolidative radiation therapy optimizes outcome in patients with advanced-stage diffuse large B-cell lymphoma (DLBCL) with residual abnormalities on CT scan following R-CHOP. *Proc ASH* 2010; Abstract 854.

### FIGURE 44

*During the past year, have you administered any of the following treatments to your patients with DLBCL?*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Your Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem cell transplant</td>
<td>55%</td>
</tr>
<tr>
<td>R-CHOP-21</td>
<td>96%</td>
</tr>
<tr>
<td>R-EPOCH</td>
<td>80%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>15%</td>
</tr>
<tr>
<td>R-CHOP-14</td>
<td>40%</td>
</tr>
<tr>
<td>Radioimmunotherapy</td>
<td>25%</td>
</tr>
<tr>
<td>CNS prophylaxis</td>
<td>48%</td>
</tr>
<tr>
<td>Intrathecal chemotherapy</td>
<td>45%</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>36%</td>
</tr>
</tbody>
</table>

During the past year, have you administered any of the following treatments to your patients with DLBCL?
A 66-year-old man is diagnosed with biopsy-proven MCL in the duodenum and colon and is initially watched in the absence of any symptoms. After 2 years, he develops progressive adenopathy with bilateral renal and left orbital masses and involvement of the bone marrow. The patient receives R-CHOP x 4 followed by consolidation ibritumomab tiuxetan on an ECOG protocol and achieves a CR. After a further 4 years, the disease recurs with periorbital subcutaneous masses and is unresponsive to a combination of bortezomib and rituximab. The patient subsequently receives rituximab/bendamustine and achieves a second CR.

— Dr Smith

Modified R-hyper-CVAD is kind of dose-dense R-CHOP, and I find it interesting that the uptake for modified R-hyper-CVAD has been significant in the community. Based on the results of the survey, this is higher than what I would have thought, but it is a reasonable regimen (Figure 45).

One consideration with MCL is that the presentation is heterogeneous. Often we talk about aggressive treatments, but the median age of these patients is in the sixties. In addition to the classical biopsy or immunophenotype, I also consider comorbidities and the overall symptomatology. For a patient who is approximately age 75 or older, I have generally administered R-CHOP. However, these days I am much more likely to use BR as the initial treatment for such patients.

**Initial treatment for mantle-cell lymphoma (MCL)**

**DR SMITH:** For a 60-year-old patient who is healthy and has newly diagnosed MCL, I will try to administer the R-hyper-CVAD regimen. If the patient is slightly older, then the consideration of R-hyper-CVAD is dependent on the overall health of the patient. I generally go with R-CHOP for an older patient, expecting to follow with autologous stem cell transplant.

**Modified R-hyper-CVAD is kind of dose-dense R-CHOP, and I find it interesting that the uptake for modified R-hyper-CVAD has been significant in the community. Based on the results of the survey, this is higher than what I would have thought, but it is a reasonable regimen (Figure 45).**

One consideration with MCL is that the presentation is heterogeneous. Often we talk about aggressive treatments, but the median age of these patients is in the sixties. In addition to the classical biopsy or immunophenotype, I also consider comorbidities and the overall symptomatology. For a patient who is approximately age 75 or older, I have generally administered R-CHOP. However, these days I am much more likely to use BR as the initial treatment for such patients.

**DR FRIEDBERG:** In the Patterns of Care data, I see differences in the choice of R-hyper-CVAD versus R-CHOP followed by transplant in the community versus among clinical investigators (Figure 45). The use of stem cell transplant in the community is low. It might mean that they may be seeing much older patients who may not be eligible for transplant or they might be underusing that modality.

**Efficacy and tolerability of R-CHOP versus R-hyper-CVAD**

**DR SMITH:** According to the survey results, most of the participating clinical investigators thought that R-hyper-CVAD and R-CHOP followed by transplant have similar efficacy. However, a fair proportion of community practitioners thought that R-hyper-CVAD might be a bit more efficacious (Figure 46).

I believe that R-hyper-CVAD data from MD Anderson look good with prolonged follow-up. But they are only with 97 patients, and the question of selection bias always comes in a single-
They end up in the hospital frequently with R-hyper-CVAD and need transfusions and antibiotics. I believe that R-CHOP followed by stem cell transplant is unquestionably an easier regimen to go through.

**DR FRIEDBERG:** It surprises me that some physicians believe that R-hyper-CVAD is better tolerated than R-CHOP followed by transplant (Figure 46). Seeing these data makes me wonder how often they have administered R-hyper-CVAD.

**DR ANAS YOUNES:** The primary challenge in the treatment of MCL is that all available data are either from small single-arm Phase II trials or retrospective studies. The NCCN outcomes study showed equivalent benefit with R-hyper-CVAD and R-CHOP followed by transplant, although the Phase II studies suggested that R-hyper-CVAD is better. In the absence of randomized trials, I believe that both of these approaches are fine.

An agent that is moving up front in the treatment of MCL is bortezomib. It is currently approved for relapsed MCL and is now being combined with R-CHOP, R-EPOCH or R-hyper-CVAD in the initial treatment of this lymphoma (Figure 47). Lenalidomide is another interesting agent, with a response rate of approximately 30 percent as a single agent in relapsed MCL. Ongoing trials in relapsed MCL are evaluating the lenalidomide/rituximab combination.

**DR MCLAUGHLIN:** Bortezomib has been shown to be an effective agent for the treatment of MCL, and I find it attractive to incorporate bortezomib into front-line regimens. However, adding another agent to the backbone of R-CHOP or R-CVP may be troublesome, as it may lead to unacceptable

---

**FIGURE 46**

**How would you compare the efficacy of R-hyper-CVAD to R-CHOP followed by transplant in the front-line treatment of MCL?**

- R-hyper-CVAD is more efficacious than R-CHOP followed by transplant: 28% (46%)
- R-hyper-CVAD is about as efficacious as R-CHOP followed by transplant: 38% (56%)
- R-hyper-CVAD is less efficacious than R-CHOP followed by transplant: 8% (3%)
- I don't know: 8% (13%)

---

**In your opinion, which regimen is more tolerable for a patient with MCL?**

- R-hyper-CVAD: 12% (18%)
- R-CHOP followed by transplant: 55% (80%)
- Both of the above are equally tolerable: 8% (18%)
- I don't know: 0% (9%)

---

arm, Phase II study. The best data on R-CHOP followed by stem cell transplant are from a European study.

The data are not quite as good, and if you simply compare the curves, you might conclude that R-hyper-CVAD is better. However, one needs to remember that the data on R-hyper-CVAD are from a single-center study and the R-CHOP followed by transplant is a multicenter study and thus both of these are probably in the same ballpark.

I believe without question that it is easier for a patient to go through R-CHOP and autologous stem cell transplant than eight cycles of R-hyper-CVAD alternating with methotrexate/cytarabine.

R-hyper-CVAD is a toxic regimen, and I almost never administer it to patients older than age 60. Selecting the patients is important, and patients who can get through it will fare well, but it is toxic.
neuropathy. However, we presented a Phase I study of bortezomib with R-hyper-CVAD, which also includes vincristine, and we did not observe increased neuropathy in that study.

Weekly versus twice-weekly bortezomib in MCL

DR SMITH: Most clinical data with single-agent bortezomib are with the twice-weekly regimen, but clearly the neuropathy is less prevalent with weekly bortezomib. So for patients with underlying neuropathy, I will start with the weekly regimen, but otherwise I start with twice-weekly bortezomib with a low threshold for changing to a weekly regimen, especially when bortezomib is combined with rituximab.

SELECT PUBLICATIONS


Geisler CH et al. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 2010;115(8):1530-3.

LaCasce A et al. R-CHOP followed by high dose therapy and autologous stem cell rescue and R-hyper-CVAD have equivalent PFS and are superior to R-CHOP alone in younger patients with MCL: A comparative effectiveness analysis from the NCCN NHL outcomes database project. Proc ASH 2009; Abstract 403.


Rummel MJ 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). Proc ASH 2009; Abstract 405.
T-Cell Lymphoma

**CASE 6**

A 45-year-old man diagnosed with celiac disease presents 12 months later with bowel obstruction and is diagnosed with enteropathy-associated T-cell lymphoma. He receives treatment on a SWOG protocol with cisplatin, etoposide, gemcitabine and methylprednisolone sodium succinate. Approximately 18 months later, liver and lung lesions are detected on surveillance imaging. Biopsy confirms recurrent T-cell lymphoma, and the patient receives an investigational Aurora kinase inhibitor. He achieves a CR and then receives consolidation autologous transplant. — Dr. Friedberg

**FIGURE 50**

What is your typical induction therapy for peripheral T-cell lymphoma (PTCL)?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>76%</td>
</tr>
<tr>
<td>EPOCH</td>
<td>68%</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>4%</td>
</tr>
<tr>
<td>Fludarabine-based regimen</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Treatment of peripheral T-cell lymphoma (PTCL)**

**DR FRIEDBERG:** PTCL is not a common disease. I am a lymphoma specialist, and I see approximately two or three patients per year with PTCL. Also, I believe that the terminology "PTCL" is kind of a catch-all diagnosis and a number of different diseases are often lumped under this terminology. So this is an area in which it is much more difficult to simply state a usual approach because of the dearth of data, varied heterogeneity in the disease and the individualization of treatment.

The prognosis of PTCL with the current standard treatments is incredibly poor. Based on the physicians’ survey responses, the treatment approach for PTCL (Figure 50) varies. CHOP might be considered a "standard," but that results from the fact that currently we have nothing better than CHOP rather than CHOP being effective for these patients. We know that virtually no patient with PTCL will experience a durable response to CHOP.

From my perspective, the standard treatment approach for PTCL should be a clinical trial. Until recently few trials had been conducted, but fortunately, now we do have some new agents that are being incorporated into the treatment of PTCL.

**Hematologic Oncology Update**

**Issue 4, 2010**

**DR HORWITZ:** The term PTCL refers to a mature T-cell lymphoma — that’s the strict definition. However, the clinical definition describes the aggressive T-cell lymphomas, the most common of which are PTCL unspecified, angioimmunoblastic lymphoma and the various types of anaplastic large cell lymphoma. PTCL is distinguished from the cutaneous T-cell lymphomas, which still originate from mature T-cells but tend to have a more indolent course. Our general approach to the treatment of PTCL is combination chemotherapy with or without stem cell transplant.

In terms of treatment of PTCL, I believe we have been drawing parallels from our experience with the B-cell approach and thus historically have only used CHOP, which is still the most common combination chemotherapy and results in 15 to 25 percent long-term remission in the most common PTCL subtypes. We have a lot of retrospective data with consolidating the response to CHOP with an autotransplant. The chal-
have been generated with these agents is much better than the historical data. Pralatrexate received FDA approval for relapsed or refractory PTCL on the basis of the Phase II PROPEL study, which had 109 patients who were evaluable for efficacy.

Aside from studies of these two new agents, no study has enrolled more than 25 or 30 patients. In view of this, I believe that confidence is higher in the recent data sets.

In a single-center study initially conducted at Memorial Sloan-Kettering Cancer Center, the response rate with pralatrexate in relapsed or refractory PTCL was approximately 40 percent. When pralatrexate was investigated in the Phase II PROPEL study at more than 20 centers worldwide, the response rate by formal central review was determined to be 27 percent, with some of the responses being complete responses. The median duration of response was approximately 10 months.

Romidepsin is a histone deacetylase inhibitor and is approved for cutaneous T-cell lymphoma (CTCL). The National Cancer Institute experience with romidepsin looks good, reporting response rates of more than 30 percent across a number of different subtypes. The standard dose approved for CTCL is 14 mg/m² administered intravenously weekly for three out of four weeks. The drug is administered as a four-hour infusion. In PTCL studies, the same dose and schedule are being used. The toxicities are not cumulative, so patients can continue receiving romidepsin as long as it provides a benefit.

**DR SMITH:** I believe that it only makes sense to use salvage regimens such as ICE, DHAP or ESHAP if transplant is an option. If transplant is not an option, then I tend not to use these regimens for relapsed or refractory PTCL. In the past, I have used a gemcitabine-based regimen, but now that pralatrexate has been approved in this setting, I believe that is a reasonable choice. A fair proportion of clinical investigators are still using gemcitabine-based therapies in this setting, and it is interesting that commu-

---

FIGURE 51

**What is your typical treatment for relapsed or refractory PTCL?**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CI (%)</th>
<th>PO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not have any experience treating relapsed PTCL</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Salvage regimen such as ICE, ESHAP or DHAP</td>
<td>32%</td>
<td>48%</td>
</tr>
<tr>
<td>Gemcitabine-based regimen</td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>37%</td>
<td>16%</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Other*</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>

* CHOP, fludarabine-based regimen, alemtuzumab, denileukin diftitox

FIGURE 52

**PROPEL study: Single-agent pralatrexate in relapsed or refractory PTCL**

**Efficacy (n = 109)**

<table>
<thead>
<tr>
<th>Response Type</th>
<th>CI (%)</th>
<th>PO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Partial response</td>
<td>32%</td>
<td>48%</td>
</tr>
<tr>
<td>Overall response</td>
<td>29%</td>
<td>29%</td>
</tr>
</tbody>
</table>

**Safety**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CI (%)</th>
<th>PO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 thrombocytopenia</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>Grade 3/4 mucositis</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Grade 3/4 neutropenia</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Grade 3/4 anemia</td>
<td>18%</td>
<td>18%</td>
</tr>
</tbody>
</table>


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Challenge in interpreting the transplant data is that we tend to select fitter patients for transplant and thus may not be changing the natural outcome of the disease. I have been involved with trials evaluating the novel agents pralatrexate and romidepsin in T-cell lymphomas, and I would say that at a minimum the quality of the data that
Community physicians have taken up pralatrexate more quickly than the academicians (Figure 51). Physicians need to be aware of mucositis as a side effect of pralatrexate, but it’s manageable. Romidepsin is another agent that is reasonable to use, and it is not terribly toxic. Response rate is not that high, but we have seen patients with significant clinical benefit.

**DR FRIEDBERG:** My approach to relapsed or refractory PTCL is often a gemcitabine-based regimen. It seems that some of my colleagues chose the same regimens (Figure 51). I don’t believe we have a right or wrong answer here. Pralatrexate is now approved in this situation, although I am surprised to see such a high use and penetration of pralatrexate in the community because pralatrexate has modest activity and the administration is complicated. It is not a wrong answer.

**Defining CTCL**

Hematologic Oncology Update
Think Tank 2011

**DR FRANCINE FOSS:** The term “CTCL” is falling out of favor because the new WHO and EORTC classifications for T-cell lymphomas of the skin subdivide the term — which includes a number of different entities — into the specific diseases. In the past, CTCL referred to mycosis fungoides and Sézary syndrome. However, other cutaneous T-cell lymphomas exist, including the CD30-positive lymphomas of the skin, panniculitic T-cell lymphoma, PTCL not otherwise specified that presents in the skin and NK lymphomas presenting in the skin.

Patients with mycosis fungoides or Sézary syndrome require some form of cutaneous-based therapy because the disease is presenting on the skin. In the context of Sézary syndrome, many patients will undergo photopheresis because it has been shown to be beneficial in approximately 40 percent of patients and is associated with little toxicity.

CTCL is a unique disease because treatment is split between the dermatologist and the medical oncologist. Traditionally dermatologists would care for the patients longer, but now that a
number of systemic options are available, dermatologists are referring them to medical oncology sooner. In fact, it’s our recommendation that patients be referred to a medical oncologist at diagnosis even if they have early-stage disease, although the dermatologist may continue to care for the patient for the first year or more.

I believe it’s helpful to at least get a medical oncologist involved, and to facilitate this, the Cutaneous Lymphoma Foundation has a website that lists centers of excellence for CTCL. These are designated centers of excellence because they have multimodality therapy — dermatologists and medical oncologists — available.

Treatment approach for CTCL

DR SMITH: CTCL is mostly seen by dermatologists, and by the time I see patients with CTCL, they have tumor-stage disease or adenopathy or their disease might even have transformed. When I see these patients, they are in need of some systemic treatment such as denileukin diftitox, chemortherapy, alemtuzumab or the HDAC inhibitors, such as romidepsin or vorinostat.

If you believe that limited areas of skin could be controlled with skin-directed therapy, then that remains an option. If the disease is more extensive, but not too thick, then total skin electron beam therapy is reasonable.

Regarding the individual agents, denileukin diftitox is not a bad agent to use if you have experience with it. One should be careful with dosing and not using it for elderly patients and/or those with low albumin levels. In a study of CHOP with denileukin diftitox, the patients on the study tolerated the combination reasonably well, though at this time I would not recommend the combination off study.

Safety and tolerability of novel agents for T-cell lymphoma

DR HORWITZ: The Phase II study of CHOP and denileukin diftitox showed a high response rate with 70-plus percent achieving a complete response. However, almost 40 percent of the patients in...
In general, how would you characterize the safety of each of the following agents?

**Denileukin diftitox**

- Somewhat to very safe: 56%
- Somewhat to very unsafe: 29%
- I don’t know: 8%

**Romidepsin**

- Somewhat to very safe: 84%
- Somewhat to very unsafe: 4%
- I don’t know: 8%

**Pralatrexate**

- Somewhat to very safe: 68%
- Somewhat to very unsafe: 17%
- I don’t know: 5%

The study could not complete the whole course of treatment, thus limiting the interpretation of the results.

No cumulative toxicities occur with romidepsin. Historically, QTc prolongation has been an issue with this class of drugs, the HDAC inhibitors. If patients with known cardiac arrhythmias and those receiving concomitant medications that can cause QTc prolongation are excluded, then we see almost no changes in QT interval.

In the clinical studies, EKG monitoring was done before and after treatment. In clinical practice, I check electrolytes at baseline before each cycle to ensure that potassium and magnesium levels are normal, and in cases when these are below normal, I supplement them. I also check an EKG after administering the antiemetic in addition to after romidepsin within the first cycle. If these do not show QTc prolongation in the first cycle, then I don’t monitor EKGs further unless the patient has a susceptibility otherwise. Occasionally, patients may develop thrombocytopenia, necessitating next-cycle delay.

The main issue with pralatrexate is mucositis, and if it is severe or if we are unable to manage the mucositis optimally, then it is difficult to administer the drug long term. Prophylactic vitamin supplementation with folic acid and B12 helps in minimizing this side effect.

**SELECT PUBLICATIONS**


Horwitz M et al. Pralatrexate efficacy and tolerability in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL). *Proc EHA* 2010; Abstract 0300.


O’Connor OA et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. *J Clin Oncol* 2011; [Epub ahead of print].


PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th>Topic</th>
<th>BEFORE</th>
<th>4</th>
<th>Excellent</th>
<th>3</th>
<th>Good</th>
<th>2</th>
<th>Adequate</th>
<th>1</th>
<th>Suboptimal</th>
<th>AFTER</th>
<th>4</th>
<th>Excellent</th>
<th>3</th>
<th>Good</th>
<th>2</th>
<th>Adequate</th>
<th>1</th>
<th>Suboptimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose and schedule of rituximab maintenance therapy employed in the PRIMA trial</td>
<td>4 3 2 1</td>
<td></td>
<td>4 3 2 1</td>
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<tr>
<td>Published consensus recommended dose and schedule of bendamustine when combined with rituximab for FL</td>
<td>4 3 2 1</td>
<td></td>
<td>4 3 2 1</td>
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<tr>
<td>Clinical relevance of cytogenetic testing and biomarker analysis in CLL</td>
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<td>4 3 2 1</td>
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<tr>
<td>Practical opportunities for the evidence-based use of RIT in the NHL treatment algorithm</td>
<td>4 3 2 1</td>
<td></td>
<td>4 3 2 1</td>
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<tr>
<td>Activity and safety data with lenalidomide in NHL and CLL</td>
<td>4 3 2 1</td>
<td></td>
<td>4 3 2 1</td>
<td></td>
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</tbody>
</table>

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes  ☐ No
If no, please explain: ____________________________________________________________

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): ________________________________________________________

If you intend to implement any changes in your practice, please provide one or more examples:

__________________________________________________________________________

The content of this activity matched my current (or potential) scope of practice.

☐ Yes  ☐ No
If no, please explain: _______________________________________________________

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

<table>
<thead>
<tr>
<th>LO</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS A RESULT OF THIS ACTIVITY, I WILL BE ABLE TO:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Compare treatment strategies employed by community oncologists and cancer clinical investigators, and apply this knowledge to the routine management of NHL, including chronic lymphocytic leukemia</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Evaluate clinical issues for which relative agreement and heterogeneity exist in patterns of NHL care, and make treatment decisions considering this information.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Counsel patients with diverse subtypes of NHL about the benefits and risks of multiple acceptable treatment options when they exist.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Summarize common toxicities associated with the systemic treatment of NHL, and identify current approaches to reduce or ameliorate these side effects.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

__________________________________________________________________________

Would you recommend this activity to a colleague?

☐ Yes  ☐ No
If no, please explain: ________________________________________________________
Additional comments about this activity:

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.  ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty for this educational activity

To what extent do you feel the faculty members’ comments were helpful or not helpful?

Please be as specific as possible about individual faculty.

Please recommend additional faculty for future activities:

Other comments about the faculty for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ................................................................. Specialty: .................................................................

Professional Designation:
☐ MD  ☐ PharmD  ☐ NP
☐ DO  ☐ RN  ☐ PA  ☐ Other .................................................................

Street Address: ................................................................. Box/Suite: .................................................................

City, State, Zip: ................................................................. Telephone: ................................................................. Fax: .................................................................

Email: .................................................................

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I certify my actual time spent to complete this educational activity to be ____________ hour(s).

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Survey of 100 Practicing Medical Oncologists and 25 Clinical Investigators on Issues Related to the Treatment of Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

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