Dear Colleague:

Non-Hodgkin’s lymphoma (NHL), the most common hematologic malignancy in the United States, is rapidly increasing in incidence. As the treatment paradigm for NHL continues to evolve, it is imperative that healthcare professionals have access to current and clinically relevant information regarding the diagnosis, classification, and management of the disease. This newsletter series, Considerations in Non-Hodgkin’s Lymphoma, will provide oncologists/hematologists, nurses, and pharmacists with an overview of the various subtypes of NHL, as well as evidence-based treatment options, updates on current clinical research, and multidisciplinary perspectives on effective management strategies.

This second issue will discuss the latest advances in the management of follicular lymphoma, an indolent NHL that accounts for approximately 25% of all newly diagnosed lymphomas in the United States. Subsequent issues will focus on other NHL subtypes, including Waldenström’s macroglobulinemia, diffuse large B-cell lymphoma, and T-cell lymphomas. It is my sincere hope that the information presented here will help facilitate the optimal multidisciplinary approach to treating your patients with NHL.

Sincerely,

André Goy, MD, MS
Chief, Lymphoma Division
The Cancer Center
Hackensack University Medical Center

Considerations in Non–Hodgkin’s Lymphoma: Follicular Lymphoma

LETTER TO OUR READERS

Non-Hodgkin’s lymphoma (NHL), the most common hematologic malignancy in the United States, is rapidly increasing in incidence. As the treatment paradigm for NHL continues to evolve, it is imperative that healthcare professionals have access to current and clinically relevant information regarding the diagnosis, classification, and management of the disease. This newsletter series, Considerations in Non-Hodgkin’s Lymphoma, will provide oncologists/hematologists, nurses, and pharmacists with an overview of the various subtypes of NHL, as well as evidence-based treatment options, updates on current clinical research, and multidisciplinary perspectives on effective management strategies.

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Sincerely,

André Goy, MD, MS
Chief, Lymphoma Division
The Cancer Center
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Supported by an educational grant from
Takeda
Millennium Pharmaceuticals, Inc.

This activity is jointly sponsored by Global Education Group and Medical Learning Institute, Inc.
Content development and logistics for this activity provided by Center of Excellence Media, LLC.
At the completion of this educational activity, participants should be able to:

• Describe the clinical course of follicular lymphoma (FL)
• Identify current standard treatment regimens for patients with FL.
• Review novel agents and their clinical potential to expand the therapeutic armamentarium for FL.
• Identify management strategies for the common toxicities associated with newer therapies for FL.

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</tr>
</thead>
<tbody>
<tr>
<td>André Goy, MD, MS</td>
<td>Allos</td>
<td>Speakers’ Bureau Consultant</td>
</tr>
<tr>
<td>Sonja Crandon, RN, BSN</td>
<td>Biogen Idec</td>
<td>Speakers’ Bureau Consultant</td>
</tr>
<tr>
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</tr>
<tr>
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**Agenda: 1.5 hours**
**Articles/Commentaries: 75 minutes**
**Evaluation/Posttest: 15 minutes**

**Date of original release: September 21, 2009**
**Valid for CME credit through: September 21, 2010**
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**Publisher**

Phil Pawelko  
phil@greenhillhc.com

**Copy Editor**

Bonnie Nickel

**Senior Production Manager**

Alaina Pede

**Circulation Department**

circulation@greenhillhc.com

**Business Manager**

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Andrea Boylston
FOLLICULAR LYMPHOMA

RECENT ADVANCES IN THE TREATMENT OF FOLLICULAR LYMPHOMA

Introduction

Follicular lymphoma (FL) is an indolent non-Hodgkin’s lymphoma (NHL) with a variable histologic classification and clinical course, including a 3% annual risk of transformation to the far more aggressive diffuse large B-cell lymphoma (DLBCL). The current standard of care for FL reflects the variability of the disease. Options for initial therapy for stage III to IV disease may include rituximab (with or without several choices of chemotherapy) or radioimmunotherapy; patients with relapsed or refractory FL may also benefit from radioimmunotherapy, bendamustine, or chemotherapy (with or without rituximab), and high-dose therapy with stem-cell rescue. Rituximab is also used as maintenance therapy after initial or second-line treatment. FL is considered incurable via established treatments. This fact motivates the continuing search for novel, targeted therapies. Patients with FL may receive many different therapies over the course of their disease; therefore, careful management of adverse events is of paramount importance.

Definition and Epidemiology

FL is marked by a follicular or nodular growth pattern. It typically involves a mixture of clonally related small B cells with cleaved nuclei (centrocytes) and large B cells resembling those of DLBCL. The characteristic immunophenotype of FL includes CD20+, CD10+, Bcl-2+, CD23+/−, CD43−, CD5−, and cyclin D1−, but other proteins having diagnostic significance may also be expressed. Translocation between chromosomes 14 and 18 juxtaposes the Bcl-2 gene with the immunoglobulin heavy-chain locus and deregulates the expression of Bcl-2 protein. The resulting overexpression of Bcl-2 protein limits apoptosis and thus permits rampant growth of the malignancy.

In the United States, FL accounts for approximately 1 in 4 of the 74,490 new cases of lymphoma that occur each year. The average age of the FL patient is 60 years. Median overall survival (OS) is estimated at 8 to 10 years, and the disease is considered incurable. However, survival for a decade or more has become possible, ostensibly as the result of the adoption of a more aggressive approach to treatment. Some experts believe that the use of more intensive, multimodal treatment and emerging therapies may change the assumption that FL can never be cured.

Clinical Course

FL has an extremely variable presentation and clinical course. Initial diagnostic work-up, as recommended by the National Comprehensive Cancer Network (NCCN) (Table 1), may identify disseminated or local disease at various stages (stages I-IV by modified Ann Arbor staging). The majority of patients, however, have disseminated FL at presentation. Although the diagnosis of FL can be established on the basis of the morphologic features of malignant cells, fine-needle aspiration or core biopsy alone is generally insufficient for diagnosis. Immunophenotyping is recommended to help distinguish FL from mantle-cell and small-cell lymphomas.

Classification of FL exemplifies the variability of the disease. The World Health Organization (WHO) currently grades FL according to Berard criteria for the frequency of centroblasts (large cells). Grade 1, defined as 0 to 5 centroblasts per high-power field (HPF), consists of predominantly small cells (centrocytes); grade 2, defined as 6 to 15 centroblasts per HPF, is a mixture of both small and large cells; and grade 3, defined as more than 15 centroblasts per HPF, is a mixture of clonally related small B cells with cleaved nuclei (centrocytes) and large B cells resembling those of DLBCL.

Table 1. Basic, Initial, NCCN-Recommended Diagnostic Work-up for Follicular Lymphoma

- Biopsy and hematopathology of malignant cells*
- Immunophenotyping options
  - Immunohistochemistry: CD20, CD3, CD5, CD10, CD21, CD23, Bcl-2, Bcl-6, Ki67, cyclin D1
  - Cell-surface marker analysis (flow cytometry): kappa/lambda, CD19, CD20, CD5, CD23, CD10
- History and physical examination with performance status, staging, and B symptoms (eg, lymph node enlargement, fever, weight loss)
- Laboratory: complete blood count, lactate dehydrogenase, metabolic panel
- Chest and pelvic computed tomography
- Hepatitis B testing
- Bone marrow biopsy and aspirate
- Pregnancy testing in appropriate female patients considered for chemotherapy

*Fine-needle aspiration/core biopsy alone is insufficient for diagnosis. If incisional or excisional biopsy is not possible, fine-needle aspiration + core biopsy with immunohistochemistry and other testing may allow diagnosis. Histologic grade 1-3 cannot be determined by fine-needle aspiration.
The molecular profiles in FL are also variable. Although patients with FL consistently display Bcl-2 overexpression due to 14;18 chromosomal translocation, it is uncertain whether eradication of the t(14;18)-bearing clone is clinically meaningful. Moreover, some patients diagnosed with FL either do not have t(14;18) or have the translocation but do not overexpress Bcl-2 protein. Gene expression in FL should thus perhaps not be viewed in isolation. Ideally, it should be interpreted within the context of the microenvironments that interact with tumor cells and determine their behavior.

FL can remain an indolent disease for many years. In about 3% of patients annually, however, FL undergoes transformation to an aggressive DLBCL, which decreases the odds of survival. Currently, there are no biomarkers that predict the risk of transformation or OS in FL. Investigators are studying numerous genetic and microenvironmental factors that may have adverse prognostic significance in FL. Among these are a microenvironment containing a high, combined content of FOXP3+ and PD1+ T cells and the presence of MUM1 tumor cells in patients treated with immunochemotherapy.

The Follicular Lymphoma International Prognostic Index (FLIPI) was developed to identify clinical predictors of poor outcomes in FL. These include: older age, higher disease stage, low hemoglobin level, high lactate dehydrogenase level, and a high number of nodal sites at presentation (Table 2). Based on the number of factors identified, patients are categorized into 1 of 3 risk groups (ie, low-risk [0-1 factors], intermediate-risk [2 factors], high-risk [≥3 factors]).

**Table 2. FLIPI Indicators of Poor Prognosis**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥60 years</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>III-IV</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>&lt;12 g/dL</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td>&gt;ULN</td>
</tr>
<tr>
<td>Number of nodal sites</td>
<td>4</td>
</tr>
</tbody>
</table>

FLIPI indicates Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal.


**Table 3. NCCN Evidence Categories**

<table>
<thead>
<tr>
<th>Category</th>
<th>Evidence</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>High-level evidence</td>
<td>Uniform NCCN consensus</td>
</tr>
<tr>
<td>Category 2A</td>
<td>Lower-level evidence</td>
<td>Uniform NCCN consensus</td>
</tr>
<tr>
<td>Category 2B</td>
<td>Lower-level evidence</td>
<td>Nonuniform NCCN consensus</td>
</tr>
<tr>
<td>Category 3</td>
<td>Any evidence level</td>
<td>Major NCCN disagreement</td>
</tr>
</tbody>
</table>

NCCN indicates National Comprehensive Cancer Network.
FOLLICULAR LYMPHOMA

Table 4. Median Duration of Response and Time to Progression in Patients Treated With R-CHOP (9-Year Follow-up)

<table>
<thead>
<tr>
<th>Complete Responders</th>
<th>Partial Responders</th>
<th>All Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Confirmed and Unconfirmed)</td>
<td>(n=33)</td>
<td>(n=5)</td>
</tr>
<tr>
<td>Duration of response, months</td>
<td>Not reached (4.1-105.1+)</td>
<td>8.7</td>
</tr>
<tr>
<td>Time to progression, months</td>
<td>Not reached (8.6-105.60)</td>
<td>12</td>
</tr>
</tbody>
</table>

*29 of 38 patients had no prior chemotherapy. R-CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab.

Rituximab maintenance after first-line therapy

Currently, the NCCN assigns a category 2B recommendation for rituximab maintenance therapy after first-line therapy, and strongly encourages administering this maintenance regimen within a clinical trial. A study of patients with FL who achieved a response or stable disease to first-line therapy with rituximab and who then received maintenance therapy showed that 4 additional courses of rituximab nearly doubled the length of event-free survival compared with patients who did not receive rituximab maintenance (23 vs 12 months). In patients with advanced FL who achieved a response or stable disease with initial CVP chemotherapy, 2 years of rituximab maintenance therapy significantly improved PFS in comparison with observation over the same period.

Second-line therapy

The NCCN recommends various options for treating progressive, relapsed, or refractory FL and disease that has undergone histologic transformation to DLBCL. FL that progresses after an initial complete or partial response has been achieved or that is unresponsive to therapy may be treated with the following second-line regimens:

- Rituximab plus FCM (fludarabine, cyclophosphamide, mitoxantrone) (R-FCM) (category 1)
- Radioimmunotherapy (category 1)
- Bendamustine with or without rituximab (category 2A)
- Chemo/immunotherapy options that are also used for first-line therapy (category 2A)

Rituximab monotherapy has been shown to produce a 67% overall response rate (ORR) in treatment-naïve patients in various stages of FL. Rituximab is also the preferred monotherapy for first-line therapy in elderly or infirm patients.

The addition of rituximab to treatment regimens has been shown to improve clinical outcomes. In a randomized trial of patients with advanced FL, initial therapy with R-CHOP was superior to CHOP alone; R-CHOP reduced treatment failure by 60%, significantly prolonged time to treatment failure, and increased response rate (R-CHOP, 96% vs CHOP, 90%; P=.011). In another study of FL patients, most of whom were previously untreated, 9-year follow-up found that R-CHOP produced an 87% complete response (CR) rate and a median time to progression of 82.3 months (nearly 7 years) (Table 4). In this study, 24% of the patients had a poor FLIPI prognosis, and 90% had stage III or IV FL. Similarly, initial therapy with R-CVP has been shown to significantly improve time to progression, response, and OS in comparison with CVP alone in patients with advanced FL. Fludarabine-based regimens to which rituximab is added have also demonstrated relatively high response rates.

Radioimmunotherapy with either 131I-tositumomab (131I-T) or 90Y-ibritumomab tiuxetan (90Y-IT) can be used alone or following CHOP for the first-line treatment of advanced FL. A single course of 131I-T as initial therapy resulted in rates of 5-year progression-free survival (PFS) and OS of 59% and 89%, respectively. In addition, molecular response, defined as a switch from a positive to a negative assay for Bcl-gene rearrangement (translocation), occurred in 34 of 39 patients after treatment. Single-course 90Y-IT produced a 93% response rate and a 73% complete remission rate as initial therapy in advanced FL. Administering either of these therapies after CHOP has been shown to produce a CR or remission rate of about 70% over 3 to 5 years.
• High-dose therapy with autologous stem-cell rescue or, for highly selected patients, allogeneic stem-cell rescue (category 2A)

Some of these regimens, notably radioimmunotherapy, may be particularly applicable in cases of transformation to DLBCL.3

Radioimmunotherapy and R-FCM are the most strongly NCCN-recommended second-line therapies for FL, because of evidence from clinical trials.3

In a trial of 131I-T in patients with either refractory or transformed lymphoma, the majority of whom had FL, a single course of radioimmunotherapy was significantly more effective than a protocol-specified regimen of prior chemotherapy.19 The ORR to 131I-T was 65%, versus 28% for patients who had received prior chemotherapy (P<.001). Median duration of response was 6.5 months versus 3.4 months, respectively (P=.001). A randomized trial of 90Y-IT versus rituximab monotherapy in patients with refractory FL or transformed disease reported an ORR of 80% with radioimmunotherapy and a 30% rate of CR; for the patients treated with rituximab, the rates were 56% and 16%, respectively.20 90Y-IT has also been shown to be effective in patients with rituximab-refractory FL (74% ORR).23 R-FCM, in comparison with FCM alone, improved ORR (94% vs 70%) and resulted in a significantly longer PFS (median not reached for R-FCM vs 21 months for FCM; P=.0139) among patients with relapsed and refractory FL in a randomized trial.22

In recent years, there has been increasing interest in investigating the use of bendamustine for various types of lymphoma. Second-line therapy with bendamustine alone or in combination with rituximab has been shown to be effective in indolent lymphomas, including FL.23-25 In addition, high-dose therapy with autologous stem-cell rescue is effective for relapsed, refractory, and progressive FL; median PFS is 3 to 5 years.3 Allogeneic stem-cell rescue also appears to offer a survival benefit, although treatment-related mortality is relatively high, necessitating very careful patient selection.3

**Rituximab maintenance after second-line therapy**

Several trials have shown that maintenance therapy with rituximab can sustain response in patients with relapsed and refractory FL who have undergone second-line therapy; second-line rituximab maintenance therapy is now a category 1 NCCN recommendation.3 Among patients with relapsed or refractory FL treated in a randomized trial, rituximab maintenance after second-line therapy with R-CHOP or CHOP produced a median PFS of 51.5 months, versus 14.9 months for observation (P<.001).26 Maintenance therapy with rituximab has also significantly prolonged response in patients with relapsed or refractory FL who received second-line treatment with R-FCM, beyond the 16-months median for patients not receiving rituximab maintenance.27

**Second-line therapy with bendamustine alone or in combination with rituximab has been shown to be effective in indolent lymphomas, including FL.**

**Toxicity Issues**

Combination regimens carry the potential for significant, additive toxicities. Moreover, since patients with FL may be treated with many different regimens over the clinical course of their disease, they may be subjected to cumulative toxic effects over time. Careful monitoring for toxicities is of paramount importance in the management of patients with FL.

Rituximab is generally well tolerated, especially in comparison with chemotherapy, which is associated with significant and well-known hematologic, cardiac, dermatologic, and other adverse effects.8 In 2 studies of maintenance therapy with rituximab in FL (duration, 2 years28 and 8 weeks29), rituximab did not produce a time-related increase in expected hematologic or nonhematologic adverse events. Careful monitoring is required when rituximab is used in patients with hepatitis B or C, however, because of the drug’s potential to cause viral reactivation.3

Radioimmunotherapy is also fairly well tolerated. In clinical trials among patients with refractory or relapsed FL, the most common nonhematologic adverse events included asthenia and nausea, which were generally mild to moderate in severity (grades 1 or 2).19,20 Hematologic toxicities of grade 3 or 4 are not uncommon with radioimmunotherapy, but they usually consist of reversible depletions of platelets or other cells.19,20

**Emerging Therapies**

Numerous therapies are emerging for the treatment of advanced FL. These treatments have particular value for patients who experience a relapse or whose disease is refractory to current therapies.

**Proteasome inhibition**

The proteasome inhibitor bortezomib has been studied alone or in combination for patients with relapsed or refractory indolent lymphomas, including FL. Bortezomib degrades multiple pathways of the malignant cell cycle, including Bcl-2 expression and cyclin activity; it increases apoptosis and dysregulates cell growth, and it may also sensitize lymphoma cells to other drugs.30 In a recent phase 2 study in which bortezomib monotherapy was administered to patients with relapsed or refractory disease who had been previously treated with rituximab, median OS and PFS were 21.3 months and 5.2 months, respectively (Table 5).31 Two trials that included a sufficient sample of FL patients reported ORRs of 60%32 and 20% (2 of 10 patients)33 with bortezomib in relapsed or refractory disease.

Bortezomib has also been studied in combination with immunotherapy or che-
mootherapy. The dose-finding VERTI-
CAL trial reported antitumor activity
with a combination of bortezomib, ben-
damustine, and rituximab. Bortezomib
in combination with Y-IT RT has been
studied in patients with FL and other
lymphomas. The ORR to this combina-
tion therapy was 56%, and the rate of
PFS at 1 year was 60%. Bortezomib is
also being studied as first-line therapy
for advanced FL in combination with
R-CVP and R-CHOP. The combination
of bortezomib with R-CHOP pro-
duced a 100% ORR in previously
untreated patients with indolent NHL.
Combination therapy with borte-
zomib and other anticancer drugs does
not appear to change the known toxicity
profile of bortezomib, which is pre-
dictable and manageable.
Common nonhematologic adverse events observed
during combination therapy include
fatigue, peripheral neuropathy, and gas-
trointestinal effects. Thrombocyto-
penia is a very common hematologic ad-
verse effect associated with this therapy.
In many cases, the adverse effects of
bortezomib are short lived and resolve
during the nontreatment week in the
recommended dosing cycle for the
drug. Nevertheless, use of bortezomib
requires careful monitoring and manage-
ment of adverse events, with particular
attention to potential additive thrombo-
cytopenia or neuropathy that may result
during combination therapy.

Bcl-2 inhibition
Drugs that specifically inhibit Bcl-2
overexpression represent another prom-
ising avenue of therapy for FL. The
rationale for the use of Bcl-2 inhibitors is
to promote the death of lymphoma cells
by counteracting the antiapoptotic effects of
the Bcl-2 family of proteins. Bcl-2
inhibitors are also called BH3 mimetics,
for the antagonist they mimic in sup-
pressing Bcl-2. Preclinical data on the
Bcl-2 inhibitor ABT-737 indicate that the
drug enhances apoptosis of lym-
phoma cells and boosts the cytotoxicity
of chemotherapy. A phase 1 trial of
ABT-263 has shown minor nodal
responses in FL. In this trial, thrombo-
cytopenia was a common, predictable ad-
verse event that was generally transient
and manageable.

Monoclonal antibodies
Research continues to focus on mono-
clonal antibodies that are potentially
active against lymphoma cells. Inotuzu-
mab ozogamicin is an anti-CD22 che-
mothepapeutic agent that has shown
promising clinical activity in patients
with FL who were previously treated
with rituximab. Common adverse
events associated with this agent include
thrombocytopenia, neutropenia, and
leukopenia. Nausea, elevated aspartate
transaminase levels, and fatigue have also
been noted.
The combination of the anti-CD80
antibody galiximab with rituximab has
demonstrated long-term clinical benefit
in patients with relapsed and refractory
FL. The anti-CD20 antibody GA101
has also shown activity in an animal
model of FL.

Other novel therapies
Lenalidomide, which has immuno-
modulatory and antiangiogenic effects, is
under investigation for relapsed and
refractory FL. In a phase 2 trial of pa-
tients with relapsed or refractory indo-
lement lymphoma, lenalidomide monother-
apy produced an ORR of 23%; median
duration of response had not been
reached at the time of reporting but was
estimated to be at least 16.5 months.
Preliminary data have also shown
lenalidomide plus rituximab to be effec-
tive in both untreated and relapsed and
refractory indolent lymphoma.
Lenalidomide is generally well tolerat-
ed in patients with indolent lymphoma.
Toxicity reactions in recently reported
studies include grade 3 and 4 neutrope-
nia, lymphopenia, thrombocytopenia,
myalgia, rash, peripheral neuropathy,
and hyponatremia. A serious adverse
effect, tumor lysis syndrome, occurred in
2 of 6 patients in a preliminary investiga-
tion of the combination of lenalidomide
plus rituximab. Patients with hematolog-
ic malignancies are especially prone to

Table 5. Response and Survival Outcomes With Bortezomib
Monotherapy After Rituximab in Patients With Relapsed/Refractory
Indolent Lymphoma (n=59)³¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to response</td>
<td>2.2 months (1.2−4.0)</td>
</tr>
<tr>
<td>Duration of response</td>
<td>7.5 months (2.7−23.6)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>21.3 months (1.3−30.8)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>5.2 months (1.0−27.7)</td>
</tr>
<tr>
<td>Time to progression</td>
<td>5.2 months (0.2−27.7)</td>
</tr>
<tr>
<td>1-Year survival</td>
<td>71%</td>
</tr>
<tr>
<td>2-Year survival</td>
<td>46%</td>
</tr>
</tbody>
</table>

Monotherapy = up to eight 21-day cycles of bortezomib; patients with complete response could receive 4 additional cycles. A bortezomib maintenance phase followed for patients not achieving complete response, consisting of 42-day cycles given until the time of progression.
tumor lysis syndrome, which is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and acute renal failure. Prophylaxis for tumor lysis syndrome includes adequate hydration to sustain a high urine flow and control of hyperuricemia (eg, through dietary management).

Several other therapies are the subject of investigation for FL and indolent lymphomas. These include the multiple-kinase inhibitor sorafenib and the mammalian target of rapamycin inhibitor enzastaurin. Radioimmunotherapy with 177 lutetium-DOTA (a chelator)-rituximab is another potential approach. Idotype vaccination for FL has also effectively induced immunologic and clinical response, and it has improved survival when administered to chemotherapy-treated patients.

Conclusion
The approach to therapy for FL depends on the patient’s place in the course of the disease. Initial therapy for localized FL, however, is inevitably replaced by management of relapsed, refractory, or transformed disease. Despite the many established therapies for FL and the increasing potential for long-term survival, the disease is still considered incurable. Finding more effective treatments is thus a priority in clinical and basic science research. In the absence of cure, extending the duration of response in FL, as demonstrated with newer, molecularly targeted agents, holds promise in improving outcomes for these patients.

Dana Delibovi assisted in the development of this article.

References
A 58-year-old woman noted symptomatic right inguinal lymphadenopathy (LAD) in 1999. Her LAD persisted, and in 2002 she developed increasing cervical LAD and generalized fatigue. She underwent an excisional node biopsy, which showed follicular lymphoma (FL), grade 2. The patient received 4 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP). Restaging computed tomography (CT) scanning and bone marrow biopsy showed complete remission (CR). She received 2 subsequent R-CHOP cycles. The patient did well for 18 months, but in early 2004, she developed recurrence of cervical LAD and increased generalized fatigue, and her lactic dehydrogenase was 2 times the normal level. She received 4 doses of weekly 375 mg/m² rituximab without response; in fact, the patient experienced progressive disease with significant generalized fatigue, increasing size of painful LAD, and drenching night sweats. Lymph node biopsy was repeated, in part to rule out transformed lymphoma. It again showed FL, grade 2. On examination, she had bilateral cervical and axillary LAD with bulky (>5 cm), hard and fixed nodal disease noted on the left lower cervical/supraclavicular area. CT and positron emission tomography (PET) scans confirmed cervical, left axillary, iliac chain, mediastinal, and left inguinal LAD. She was enrolled in a phase 1/2 clinical trial where she received 90Yttrium-ibritumomab tiuxetan radioimmunotherapy in combination with the radiation enhancing agent, motexafin gadolinium (MGd). The treatment was well tolerated. Restaging CT scans taken 4 weeks after MGd/90Yttrium-ibritumomab tiuxetan treatment showed CR unconfirmed, and a 3-month PET scan confirmed CR. The CR was maintained for approximately 24 months, at which time the patient experienced relapse, with widespread LAD. The patient subsequently received 4 cycles of rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP), which resulted in CR. This was then followed by a consolidative autologous stem-cell transplant (SCT) using carmustine, etoposide, cytarabine, and methotrexate conditioning chemotherapy. The patient currently remains in CR, 36 months after SCT.

The CR was maintained for approximately 24 months, at which time the patient experienced relapse, with widespread LAD.

Implications for Physicians

FL comprises 70% of all indolent/low-grade non-Hodgkin’s lymphoma (NHLs) in the United States and accounts for approximately 30% of all adult NHL histologies, with only diffuse large B-cell lymphoma (DLBCL) being more common.1 FL is a heterogeneous group of lymphomas that have a diverse range of presentations and clinical behaviors; some patients have spontaneous remissions, whereas others have poor prognostic factors and a more aggressive clinical course. Transformation to a higher grade of NHL (most commonly DLBCL) occurs in 3% to 4% of patients each year and is typically heralded by a change in the patient’s clinical condition.2 Risk factors for transformation in 1 study included advanced-stage disease and the presence of a high number of adverse prognostic factors on the Follicular Lymphoma International Prognostic Index,3,4 a prognostic model for newly diagnosed5,6 and relapsed FL.7 Prior data showed a median survival for FL of 9 to 10 years,1,5 although recent data suggest this has improved.8

Immunotherapy

Past clinical trials comparing multiple- and single-agent chemotherapy in patients with advanced-stage FL did not show improvements in the natural history of the disease (ie, overall survival [OS]).8,9 Fludarabine, identified in the 1980s as having activity in FL, was incorporated into combination regimens that achieved high response rates—including molecular remissions—but meaningful differences in outcomes relative to other multiple-agent regimens have not been observed.10,11 Furthermore, there is concern that fludarabine-based treatment may make it difficult to collect stem cells from patients,12,13 and may increase the risk of transformation.2

More recently, several randomized phase 3 trials comparing varied chemotherapy regimens (ie, CVP, CHOP, and mitoxantrone, chlorambucil, and prednisone) in combination with rituximab versus chemotherapy alone in untreated patients with FL have been reported and updated.14-22 The overall response rate (ORR) and either median time to treatment failure or median event-free survival (EFS) were superior in the chemoimmunotherapy arms for both chemotherapy-naïve patients and those who had been previously treated. More-
Improvements in OS for the chemotherapy arms have become apparent. To improve the ORR and duration of response, and potentially prolong OS, additional doses of rituximab have been administered as postremission or maintenance therapy. Median EFS has been shown to be significantly prolonged with this approach, following chemotherapy induction14,18,22,23 or after rituximab therapy alone.24,25

Radioimmunotherapy
The anti-CD20 radioimmunoconjugates 111I-tositumomab and 90Y-ibritumomab tiuxetan deliver ionizing radiation to target cells and the surrounding tissue. They are safe, effective, and relatively easy to administer. In an integrated efficacy analysis of 5 clinical trials, heavily pretreated patients with refractory low-grade or transformed NHL treated with 111I-tositumomab had ORRs ranging from 47% to 68% (CR rates, 20%-38%), with a median duration of response of 12.9 months.26 In a compilation of relapsed/refractory FL and transformed DLBCL patients, 90Y-ibritumomab tiuxetan yielded an ORR of 73%, with a 51% CR rate.27 The associated median duration of response and time to treatment progression for all patients were 11.7 and 9.3 months, respectively. In a phase 2 trial of FL patients with disease refractory to rituximab, the response rates with 90Y-ibritumomab tiuxetan were high (ORR, 74%).28 Furthermore, consolidation therapy following induction chemotherapy with 90Y-ibritumomab tiuxetan or 111I-tositumomab has been studied with encouraging preliminary results.29,30

The dose-limiting feature of radioimmunotherapy is hematologic toxicity. At conventional doses, short-lived myelosuppression occurs from 4 to 6 weeks after 131I-tositumomab and from 7 to 9 weeks after 90Y-ibritumomab tiuxetan treatment. Recent updates show that the annualized incidence of myelodysplasia or leukemia in patients treated with radioimmunotherapy is consistent with that expected on the basis of the patient’s previous therapy.31,32 Additional ongoing studies of radioimmunoconjugate therapy in FL are evaluating radioimmunotherapy as a component of SCT33,34 as well as combinations of potentially synergistic/radiation-sensitizing agents (eg, MGd) with radioimmunotherapy.35

Over, improvements in OS for the chemoinmunotherapy arms have become apparent. To improve the ORR and duration of response, and potentially prolong OS, additional doses of rituximab have been administered as postremission or maintenance therapy. Median EFS has been shown to be significantly prolonged with this approach, following chemotherapy induction14,18,22,23 or after rituximab therapy alone.24,25

Stem-cell transplantation
Autologous and allogeneic SCT are additional treatment modalities for select patients with relapsed/refractory FL. Both are associated with durable remissions that may affect OS, especially allogeneic SCT. However, acute and long-term toxicities are apparent and must be considered when SCT is assessed for individual patients. For patients with relapsed FL, autologous SCT results in significantly prolonged remission, but it is not thought to be curative.36 Several groups have investigated the role of high-dose therapy and autologous SCT for patients in first remission, with vari-

<table>
<thead>
<tr>
<th>Target</th>
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<th>Agents</th>
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<tr>
<td>Proteasome</td>
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<td>Ofatumumab, IMMU-06, ocrelizumab, GA101</td>
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<td>CD22</td>
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<td>Epratuzumab, inotuzumab ozogamicin</td>
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<tr>
<td>Bcl-2 family</td>
<td>Small-molecule Bcl-2 inhibitors</td>
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<td>B-cell receptor</td>
<td>Fostamatinib disodium</td>
</tr>
<tr>
<td>Multiple</td>
<td>Immunomodulatory drugs</td>
<td>Lenalidomide, thalidomide</td>
</tr>
</tbody>
</table>

HDAC indicates histone deacetylase; mAb, monoclonal antibody; Syk, spleen tyrosine kinase.
able results. Progression-free survival (PFS) was improved in 2 of 3 phase 3 randomized trials in the prerituximab era; however, OS was not prolonged.\textsuperscript{4,7–9} A reported increase in secondary myelodysplastic syndrome after autologous SCT in patients in first remission has contributed to the lack of a survival benefit for high-dose therapy.\textsuperscript{17,18,40}

Allogeneic SCT has been investigated primarily in young patients with human lymphocyte antigen–identical sibling donors.\textsuperscript{41,42} Of note, allogeneic SCT still remains the only known curative treatment modality for patients with FL. However, treatment-related morbidity and mortality need to be considered. Reduced-intensity conditioning (RIC) is based on the assumption that a graft-versus-lymphoma effect is operative and has the potential to cure FL. Encouraging results with this strategy have recently been reported; with a median follow-up of 60 months, the estimated OS and PFS for patients with FL undergoing RIC were 85% and 83%.\textsuperscript{41}

**Novel agents**

Bendamustine, an alkylator with novel mechanisms of action, has been approved for use in patients with rituximab-refractory indolent NHL.\textsuperscript{44} Other new agents aimed at specific molecular targets have shown promise in the treatment of FL (Table). The proteasome inhibitor bortezomib has shown encouraging activity in relapsed or refractory lymphoma.\textsuperscript{45,46} Using bortezomib 1.5 mg/m² on days 1, 4, 8, and 11, O’Connor and colleagues recently reported an ORR of 50% (22% CR).\textsuperscript{47} The immunomodulatory drug lenalidomide has also shown clinical activity in FL; Witzig and colleagues reporting an objective response rate of 26% in relapsed/refractory indolent lymphoma with a 32% response rate in FL.\textsuperscript{48} Bortezomib and lenalidomide are being incorporated into frontline FL studies, such as the Bortezomib-based Induction Or New IMID-based Continuation (BIONIC) trial (Figure). In addition, next-generation anti-CD20 antibodies are also being developed. Hagenbeek and colleagues recently reported results of ofatumumab for the treatment of relapsed/refractory FL.\textsuperscript{49} Other novel agents being studied in FL include mammalian target of rapamycin inhibitors, histone deacetylase inhibitors, anti-apoptosis agents (eg, Bcl-2 family inhibitors), spleen tyrosine kinase inhibitors, and other monoclonal antibodies.

**References**


Introduction
Follicular lymphoma (FL) is a common form of slow-growing, or indolent, non-Hodgkin's lymphoma (NHL). Most patients are diagnosed in advanced stages of the disease, and the course of treatment varies according to factors such as prognosis, tumor burden, and performance status. Although FL is not considered curable, the introduction of novel agents into the treatment paradigm has led to improved clinical outcomes. However, these new therapies have also increased the number of agents to which patients may be exposed during successive courses of treatment, sometimes resulting in a higher incidence of additive and cumulative toxicities. In addition, most patients with FL are older, leaving them more susceptible to comorbid conditions that can be worsened by the effects of treatment.

The ability to anticipate and promptly manage treatment-related toxicities is an extremely important aspect of nursing care in the management of FL.

Some of the promising new agents now being incorporated into treatment regimens for FL include bortezomib, lenalidomide, and novel Bcl-2 inhibitors and monoclonal antibodies. The adverse events associated with these agents have been reported in numerous clinical studies, and for the most part, are considered predictable and manageable, although grade 3 and 4 toxicities do occur. This article will discuss some of the common adverse events associated with these novel therapies and appropriate management strategies.

Myelosuppression
Myelosuppression is a serious adverse event that can lead to potentially life-threatening complications and/or treatment interruptions. Manifestations of myelosuppression include neutropenia, anemia, and thrombocytopenia. Neutropenia, which is generally defined as an absolute neutrophil count of <1000 cells/mm³ or an anticipated decrease to <500 cells/mm³, places patients at an increased risk of infection. Therefore, precautions to prevent neutropenia and decrease this risk are essential. Patients should be advised to follow basic hygienic practices (eg, handwashing) and avoid crowds until cell counts have normalized. Fever (defined as a single temperature of 101.3°F or >100.4°F over a 1-hour sustained period) is a serious sign and may indicate a life-threatening infection, necessitating treatment with antibiotics, antifungals, or antiviral agents. Other signs and symptoms of infection include chills, flu-like symptoms, shortness of breath, sore throat, and loose stools. The use of hematopoietic growth factors, such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, may be necessary to mitigate the severity of neutropenia.

Neutropenia
Neutropenia is a common adverse event seen with the immunomodulatory agent lenalidomide and the anti-CD22 agent inotuzumab ozogamicin. In a phase 2 trial of single-agent lenalidomide for the treatment of indolent NHL (including FL), the most common grade 3 or 4 adverse event was neutropenia (30% and 16%, respectively). In a phase 1/2 study of inotuzumab ozogamicin plus rituximab for the treatment of indolent lymphoma, neutropenia occurred in 25% of patients receiving this therapy (grade 3/4, 15%).

Thrombocytopenia
Thrombocytopenia is typically considered a manageable and transient toxicity that usually resolves when patients discontinue therapy. Dose reductions are a common strategy used to limit this adverse event. However, platelet counts should be monitored carefully during treatment. In general, thrombocytopenia is not treated unless the patient's platelet count drops below 10,000 to 20,000 cells/mm³ or if there are signs of bleeding (eg, oral/nasal bleeding, oral mucosa, petechiae). Thrombocytopenia is one of the most common hematologic toxicities observed with the use of lenalidomide, the proteasome inhibitor bortezomib, inotuzumab ozogamicin, and the Bcl-2 inhibitor ABT-263. For example, it was the second most common grade 3 or 4 adverse event (14% and 5%, respectively) in the above-mentioned phase 2 trial of single-agent lenalidomide. In a phase 2 study of bortezomib in patients with relapsed/refractory indolent NHL (including FL), thrombocytopenia was one of the most common grade 3/4 toxicities, leading to a...
Peripheral Neuropathy

Peripheral neuropathy (PN) is a predictable, yet challenging and dose-limiting toxicity associated with some of the newer FL therapies, including lenalidomide, rituximab, and bortezomib. In a recently reported phase 2, single-arm study of lenalidomide and rituximab for indolent NHL, grade 3 PN occurred in 1 of 14 patients who were eligible for safety evaluation. In a multicenter single-arm study evaluating the efficacy and safety of the combination of bortezomib, bendamustine, and rituximab in patients with relapsed/refractory FL, PN was reported in 6 patients (38%), with 1 patient experiencing grade 3 PN.

PN is a highly subjective paresthesia that is difficult to quantify and manage. Therefore, assessment and monitoring for PN at each visit is necessary and should include patient and treatment-related risk factors, review of current medications and previous therapies, and identification of PN-associated symptoms, such as numbness and tingling, sensitivity to touch, burning pain, muscle weakness, and lack of coordination. Patient and family education is key to identifying early signs and symptoms of PN and reducing the risk of falls or other injuries. In addition, it is important to provide patients with information regarding the specific neurotoxic effects that can be expected with their particular treatment regimens. Symptoms of PN typically resolve or improve to baseline with the discontinuation of treatment. Since there are no known effective agents to manage neuropathic symptoms, dose and schedule modifications are the mainstay for management of this toxicity.

Conclusion

In the care of patients with FL, it is important to prevent or anticipate adverse events and to treat them promptly when they occur. Hematologic and neurologic toxicities are some of the most common adverse effects associated with novel agents that have been recently integrated into the treatment of FL. Awareness of these effects on the part of clinicians and nurses can help patients receive the full potential of these new treatments.

References

NEW TREATMENTS FOR FOLLICULAR LYMPHOMA: A PHARMACIST’S PERSPECTIVE

Cindy L. O’Bryant, PharmD, BCOP
Associate Professor, University of Colorado Denver, Department of Clinical Pharmacy, School of Pharmacy, Aurora, CO

Introduction

Follicular lymphoma (FL) is the second most common non-Hodgkin’s lymphoma (NHL), comprising 20% to 30% of all cases. This B-cell lymphoma is indolent in nature, but its clinical course is highly variable with recurrent remissions and relapses. It is associated with an approximate 3% per year risk of a histologic transformation into a more aggressive lymphoma. Typically, patients present with persistent, painless lymphadenopathy, which may be associated with periods of waxing and waning. FL is characterized molecularly by the expression of the CD20 surface antigen, and cytogenetically by translocation t(14:18), which results in the activation of the anti-apoptotic Bcl-2 gene and the inhibition of programmed cell death. At diagnosis, the majority of patients have advanced stage disease (stage III or IV as classified by the Ann Arbor staging system), with bone marrow involvement being the primary site of extranodal disease. Prognosis for patients with FL is most commonly determined by the Follicular Lymphoma International Prognostic Index (FLIPI). Although this index has been validated and shown to predict progression-free survival (PFS) and overall survival (OS), it was developed prior to the introduction of monoclonal antibodies for the treatment of FL, and as a result, there have been concerns with its continued use. However, recent data have shown that the FLIPI maintains its prognostic value even within this patient population. After decades with little to no change in survival, the median OS for patients with FL has improved to 8 to 10 years. The reasons for this improvement can be attributed to the addition of monoclonal antibodies to treatment and a move away from the traditional “watch and wait” approach.

Standard Treatment Strategies and New Directions

First-line treatment

Current treatment options for patients with FL include observation, radiation, single-agent or combination treatment, stem-cell transplant (SCT), and clinical trials. Single modality involved field radiation is curative in 30% to 40% of patients with early-stage (stage I and II) disease. For the majority of patients, the standard of care for first-line treatment is rituximab (a chimeric anti-CD20 monoclonal antibody) in combination with chemotherapy. The addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), MCP (mitoxantrone, chlorambucil, and prednisone), and CHVP-IFN (cyclophosphamide, doxorubicin, vindesine, and prednisone plus interferon) has resulted in a significant increase in overall response rate (ORR), complete response (CR) rate, median time to treatment failure, PFS, and OS (except for CHVP-IFN combinations), as shown in the Table.

The reasons for this improvement can be attributed to the addition of monoclonal antibodies to treatment and a move away from the traditional “watch and wait” approach.

Treatment of relapsed/refractory disease

Treatment options for relapsed or refractory FL are limited and should be individualized, taking into account patient/disease characteristics and treatment goals. SCT may still be curative in the salvage treatment setting, as evi-
therapy. Studies looking at either 131I-tositumomab or 90Y-ibritumomab in relapsed or rituximab–refractory patients have shown ORRs of 39% to 83%, CR rates of 13% to 38%, and duration of response (DR) from 8.5 months to 20 months.13 Bendamustine, an alkylating agent, was recently approved for the treatment of patients with indolent B-cell NHL that progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. In a single-arm trial, the ORR and median DR were 74% (95% CI, 64.3, 82.3) and 9.2 months (95% CI, 7.1, 10.8), respectively.14

Several novel anticancer agents are being evaluated for the treatment of FL in the second-line setting. Newer, more human anti-CD20 antibodies are being formulated to overcome issues associated with the chimeric antibody, rituximab. Other monoclonal antibodies targeted toward transmembrane proteins that are constitutively expressed on malignant B cells including CD80 and CD22 are in development.

Galiximab is an macaque-human chimeric anti-CD80 monoclonal antibody shown to inhibit cell proliferation, up-regulate proapoptotic molecules, and induce antibody-dependent cell-mediated cytotoxicity.15 As a single agent, galiximab showed moderate activity with an 11% ORR in relapsed or refractory FL patients.16 The combination of galiximab and rituximab in the same patient populations demonstrated an ORR of 66% with a favorable toxicity profile.15 Epratuzumab is a humanized anti-CD22 monoclonal antibody that has demonstrated ORRs of 18% to 77%.20,21 When given in combination with rituximab, response rates were 53% to 57% and median time to progression was approximately 9 months.22 Based on the results of these trials, new bortezomib-containing regimens are currently being investigated for FL. The immunomodulatory effects of lenalidomide resulted in a response in a small number of patients (3 of 12) in a phase 2 study that enrolled a variety of indolent lymphoma subtypes.22 Inhibition of Bcl-2 results in increased apoptosis and is a rational novel target for the treatment of relapsed or refractory FL. A number of Bcl-2 inhibitors have been explored in the preclinical setting with some promise22 and early-phase clinical studies have been conducted with guarded success. For example, data from a phase 2 trial with oblimersen sodium, a Bcl-2 antisense oligonucleotide in combination with rituximab, demonstrated an ORR of 60% in patients with FL.23

**Conclusion**

While there have been great strides made in the first-line treatment of FL over the last 10 years, little impact has been made in long-term OS and the treatment of relapsed and refractory disease. The result is a need for better understanding of the disease in this subset of patients and for newer more effective treatment options.

**References**


**Table. Results of Clinical Studies of Rituximab Plus Chemotherapy Versus Chemotherapy Alone for FL**

<table>
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<tr>
<th>Study</th>
<th>No. Patients</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>MTF (mo)</th>
<th>PFS (%)</th>
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<tr>
<td>CVP/R-CVP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>321</td>
<td>57/81</td>
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<td>15/34</td>
<td>17/54</td>
<td>↑ with R-CVP</td>
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<td>60/75</td>
<td>36/NR</td>
<td>37/53</td>
<td>↑ in patients with high FLIPI score</td>
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CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; CHVP-IFN, cyclophosphamide, doxorubicin, vindesine, and prednisone plus interferon; CR, complete response; CVP, cyclophosphamide, vincristine, and prednisone; EFS, event-free survival; FLIPI, Follicular Lymphoma International Prognostic Index; MCP, mitoxantrone, chlorambucil, and prednisone; MTF, median time to treatment failure; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab.


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