LETTER TO OUR READERS

Dear Colleague:

It is with great pleasure that I present the fourth issue of the second annual “Considerations in Non-Hodgkin Lymphoma” newsletter series. The goal of this case-based curriculum is to help clinicians integrate the latest advances in the treatment of non-Hodgkin lymphoma (NHL) into the clinical setting. Each issue will focus on a specific type of NHL and feature 2 case studies, with perspectives on treatment and supportive care by faculty members from a leading cancer institution.

In this fourth newsletter, faculty from Dana-Farber Cancer Institute discuss multidisciplinary approaches to treatment for 2 patients with Waldenstrom’s macroglobulinemia, a rare, low-grade B-cell lymphoma.

It is my sincere hope that the information presented here will help facilitate the optimal multidisciplinary approach to treating your patients with NHL.

Sincerely,

John P. Leonard, MD
Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Professor of Medicine
Clinical Director, Center for Lymphoma and Myeloma
NewYork-Presbyterian Hospital
Weill Cornell Medical Center
Sponsor
This activity is jointly sponsored by Global Education Group and Medical Learning Institute, Inc.

Coordination for this activity provided by Center of Excellence Media, LLC.

Statement of Need
This activity was developed for oncology physicians, nurses, and pharmacists who wish to enhance their competence concerning the treatment of patients with Waldenstrom's macroglobulinemia.

Target Audience
This activity was developed for physicians, nurses, and pharmacists.

Educational Objectives
At the completion of this educational activity, participants should be able to:
• Describe recommended agents for the first-line treatment of Waldenstrom’s macroglobulinemia (WM)
• Describe recent safety and efficacy data from clinical trials investigating novel therapies for patients with WM
• Review appropriate strategies for preventing and/or minimizing common toxicities associated with newer therapies for WM

Commercial Support Acknowledgment
This activity is supported by an educational grant from Millennium Pharmaceuticals, Inc.

Instructions for Credit
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• Irene Ghobrial, MD, is on the advisory board for Celgene, Millennium, Cell Therapeutics, Cephalon, EMD Serono, GlaxoSmithKline, Hospira, Johnson & Johnson, Millennium, Pfizer, and sanofi-aventis.

• John P. Leonard, MD, is on the advisory board for and receives consulting fees from Biogen Idec, Biostat, Calistoga Pharmaceuticals, Celgene, Cell Therapeutics, Cephalon, EMD Serono, GlaxoSmithKline, Hospira, Johnson & Johnson, Millennium, Pfizer, and sanofi-aventis.

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The information provided in this CME activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient’s medical condition.

Agenda: 1.25 hours
Articles/Commentaries: 60 minutes
Evaluation/Posttest: 15 minutes

Date of original release: December 23, 2010
Valid for CME credit through: December 23, 2011
Case Study: Management of a Patient Newly Diagnosed with Waldenström’s Macroglobulinemia

Introduction

Waldenström’s macroglobulinemia (WM) is a rare, low-grade B-cell lymphoma characterized by infiltration of the bone marrow with lymphoplasmacytic cells, as well as detection of an IgM monoclonal gammopathy in the serum. Features of WM include cytopenias, specifically anemia related to the replacement of the bone marrow with tumor cells. Another characteristic clinical presentation for WM is hyperviscosity related to elevated IgM levels, resulting in symptoms such as headache, blurred vision, and epistaxis. Rarer presentations include neuropathy, cryoglobulinemia, skin rash (Schnitzler’s syndrome), cold-agglutinin hemolytic anemia, Bing-Neel syndrome with central nervous system manifestations, and amyloidosis. The following case examines the frontline treatment of a patient with a family history of WM, who previously presented with monoclonal gammopathy of undetermined significance (MGUS), an indicator of risk for WM.

Case Presentation

KG, a 44-year-old woman, presented to her primary care physician with abdominal pain and loss of weight that had been ongoing for 1 month. She had a history of MGUS, which had been diagnosed 5 years earlier when she was screened through a clinical trial for familial diseases. Her father and brother were diagnosed with WM, but did not require therapy. For the past 5 years, the patient was followed closely for her MGUS; she had no symptoms or signs of disease progression until she started having abdominal pain. She had also been experiencing night sweats, but showed no signs of fever. She had not been exposed to pesticides or herbicides. The rest of her history was also noncontributory.

On examination, KG had some mild tenderness in the epigastric area, but no lymphadenopathy or hepatosplenomegaly. On examination, KG had some mild tenderness in the epigastric area, but no lymphadenopathy or hepatosplenomegaly.
chose to participate in a clinical trial and was treated with intravenous (IV) bortezomib dosed at 1.6 mg/m² once weekly on 28-day cycles and IV rituximab dosed once weekly in cycles 1 and 4. KG achieved a complete response (CR) within 3 cycles of this therapy and completed 6 cycles altogether. After more than 2 years of follow-up, she is still in complete remission. Her repeat positron emission tomography-computed tomography scans and her IgM M-spike are negative, with a negative bone marrow.

Oncologist Perspective
Irene Ghobrial, MD

The patient in this case presented with an IgM M-spike and bone marrow infiltration, 2 of the criteria used in the diagnosis of WM (Table 1).1-4 KG represents a case of familial WM, which occurs in about 20% of patients with the disease.5,6 A study by Royer and colleagues at the National Cancer Institute analyzed data on 103 WM patients and 272 unaffected relatives from 35 multiple-case WM, 46 mixed WM/B-cell disorder kindred, and 28 nonfamilial (sporadic) WM patients.7 Familial WM patients were more likely to report a history of autoimmune disease and infections, as well as exposure to farming, pesticides, wood dust, and organic solvents compared with unaffected family members. The results of this study suggest indications of possible genetic and environmental factors that may influence development of WM.

Patients at increased risk for WM include those with preexisting MGUS;8 as was the case with KG. A process of transformation may occur from asymptomatic IgM-MGUS to symptomatic WM as IgM levels rise over time.2 Some patients, however, remain asymptomatic or present with highly variable symptoms, which may include cytopenias, anemia, and organomegalias of the lymph nodes, liver, and spleen.7,4 The increase in circulating IgM may produce hyperviscosity of serum, leading to a host of manifestations, such as ocular bleeding and neurologic complications.3 Precipitating IgM may result in cryoglobulinemia.2

Table 1. Diagnostic Criteria and Differential Diagnosis in WM1-4

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Differential Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>• IgM-monoclonal gammopathy</td>
<td>- Splenic marginal zone lymphoma</td>
</tr>
<tr>
<td>• Infiltration of bone marrow, following intratrabecular pattern, by small lymphocytes with plasmacytoid/plasma cell differentiation</td>
<td>- IgM-monoclonal gammopathy of undetermined significance</td>
</tr>
<tr>
<td>• Immunophenotypea (cell surface markers): IgM+, CD5−, CD10−, CD19+, CD20+, CD22+, CD23−, CD25+, CD27+, FMC7+, CD103−, and CD138−</td>
<td>- Multiple myeloma with IgM elevation</td>
</tr>
<tr>
<td></td>
<td>- B-cell chronic lymphocytic leukemia</td>
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<td></td>
<td>- Mantle cell lymphoma</td>
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</table>

aImmunophenotype of individual patients may vary.

WM is a treatable but incurable disease, with a median survival time of 5 to 6 years.1,2,4 A recent study reported that the 10-year overall survival rate among patients with WM was 41%.8

KG represents a case of familial WM, which occurs in about 20% of patients with the disease.

Selection of therapy
Patients newly diagnosed with WM should receive therapy only if they have symptoms or signs related to WM or specific laboratory abnormalities.9 Treatment should not be based solely on serum M-protein levels.9 The most common reason for the initiation of therapy is the presence of anemia. To date, no standard of care has been established for the treatment of WM, and no specific agents have been approved by the US Food and Drug Administration.9 However, the Fourth International Workshop on WM recently published recommendations for the frontline and salvage treatment of WM.10 The panel emphasized that several factors should be considered in treatment decisions, including the age of the patient, the presence of cytopenias, and the rate of disease progression.10 Recommendations for frontline therapy of WM include alkylating agents, NAs, and the monoclonal antibody, rituximab.9,10 Combinations of these agents, such as fludarabine plus rituximab, fludarabine/cyclophosphamide/rituximab, cyclophosphamide/rituximab/dexamethasone, and R-CHOP are commonly used. These regimens produce high response rates but are associated with potential long-term side effects.10-12 Novel agents and combinations are currently being evaluated for the treatment of WM. Thalidomide plus rituximab has been studied in several clinical trials, with overall response rates (ORRs) of 72% to 78% and major response rates of 64% to 70%.11,13-15 Combinations of bortezomib plus rituximab and bendamustine plus rituximab have also shown promising activity in WM.11,16 The highest response rate
Peripheral neuropathy (PN) was the most common toxicity, although it resolved to grade ≤1 in the majority of patients at a median of 6 months. In the trial of bortezomib plus rituximab in which eligible patients had received at least 1 prior therapy, the ORR with bortezomib plus rituximab was 51%; when minimal response was included, this rate rose to 81%.27

Administering bortezomib once weekly as opposed to twice weekly results in lower rates of this toxicity with similar efficacy.24-26 This drug has also recently been investigated in combination with rituximab in newly diagnosed and relapsed/refractory WM. In these trials, patients received bortezomib 1.6 mg/m² on days 1, 8, and 15 every 28 days, and rituximab 375 mg/m² weekly in cycles 1 and 4.17,27 As described above, an ORR of 66% was observed in newly diagnosed patients with WM who were treated with this regimen.17 In the relapsed/refractory setting, in which eligible patients had received at least 1 prior therapy, the ORR with bortezomib plus rituximab was 51%; when minimal response was included, this rate rose to 81%.27

A PATIENT WITH NEWLY DIAGNOSED WM

To date was observed in a study by Treon and colleagues, in which bortezomib/dexamethasone/rituximab as frontline therapy provided a CR rate of 13% and an ORR of 96% (Figure).16 In this trial, bortezomib was given twice weekly at a dose of 1.3 mg/m².

Peripheral neuropathy (PN) was the most common toxicity, although it resolved to grade ≤1 in the majority of patients at a median of 6 months. In the trial of bortezomib plus rituximab in which our patient was enrolled, bortezomib was administered on a once-weekly basis to avoid increased PN.17 In this study, the ORR was 66% and the 1-year event-free survival rate was 79%.17

In a recent study, bendamustine plus rituximab was compared with R-CHOP as frontline therapy for WM.18 Interim results showed that the ORR was similar with the 2 regimens—96% and 94%, respectively. The median progression-free survival (PFS) for bendamustine plus rituximab had not been reached; the median PFS for R-CHOP was 40 months (no statistical difference between the 2 groups). The bendamustine regimen appeared to have a better toxicity profile than R-CHOP.

Pharmacist Perspective
Houry Leblebjian, PharmD

KG participated in a clinical trial that treated newly diagnosed patients with a combination of rituximab plus the proteasome inhibitor, bortezomib. The major activity of proteasome inhibitors occurs through the targeting of interleukin-6 (IL-6) and nuclear factor kappa B (NF-κB) signaling pathways, which are critical regulators of survival and proliferation in WM and other B-cell malignancies.19-21 Through reversible inhibition of the 26S proteasome, bortezomib blocks the ubiquitin-proteasome degradation, thereby affecting multiple signaling pathways, including NF-κB. This process induces apoptosis, resulting in antitumor, antiangiogenic, and antiproliferative activities.

In preclinical trials, bortezomib demonstrated activity in tumor cells of patients with WM.21 This agent’s mechanism of action is congruent with some of the many molecular pathways involved in the disease. One contributing factor in WM is upregulation of the gene that encodes for IL-6.22 In addition, a specific signature of microRNA (miRNA) has been identified for WM. This signature includes miRNA155, which may regulate the proliferation and growth of WM cells via several pathways, one of which is NF-κB.23 Bortezomib also had the ability to reduce IgM levels, an important consideration in WM patients.24

Bortezomib plus rituximab for the treatment of WM

Bortezomib has been studied in phase 2 trials as monotherapy for newly diagnosed and relapsed/refractory WM.24-26 Single-agent bortezomib provided ORRs of 26% to 85% in these trials.24-26 This drug has also recently been investigated in combination with rituximab in newly diagnosed and relapsed/refractory WM. In these trials, patients received bortezomib 1.6 mg/m² on days 1, 8, and 15 every 28 days, and rituximab 375 mg/m² weekly in cycles 1 and 4.17,27 As described above, an ORR of 66% was observed in newly diagnosed patients with WM who were treated with this regimen.17 In the relapsed/refractory setting, in which eligible patients had received at least 1 prior therapy, the ORR with bortezomib plus rituximab was 51%; when minimal response was included, this rate rose to 81%.27

An important consideration in the treatment of patients with WM is the potential for rituximab-mediated “IgM flare.”

Similar efficacy results were observed in the trial by Treon and colleagues of twice-weekly bortezomib given in combination with dexamethasone and rituximab.16 However, this schedule of bortezomib resulted in 30% of patients experiencing grade 3 PN.16 Administering bortezomib once weekly as opposed to twice weekly results in lower rates of this toxicity with similar efficacy.17,27

Herpes zoster reactivation may also occur in patients treated with bortezomib-based regimens. In the trial of bortezomib plus rituximab for relapsed/refractory WM, zoster reactivation occurred in 4 patients (11%).27 However, all patients who experienced this reactivation were either not on prophylactic viral medication or had stopped taking it. This prompted the study investigators to incorporate antiviral prophylaxis into the protocol, which decreased the rate of herpes zoster reactivation significantly. Other common grade 3/4 adverse effects observed in trials

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of bortezomib-based therapy for WM include neutropenia, thrombocytopenia, and anemia. These hematologic toxicities appear to be similar to those seen in studies of bortezomib for the treatment of multiple myeloma.

An important consideration in the treatment of patients with WM is the potential for rituximab-mediated “IgM flare,” particularly in patients with high IgM levels. In 2 trials, flare occurred in 54% and 91% of WM patients treated with rituximab. In one of these trials, IgM levels were higher in patients who did not have these flares (28% vs 80%). Interestingly, when rituximab was combined with bortezomib for the treatment of relapsed/refractory WM, IgM flare was seen in only 22% of patients.

The mechanism for this may be the therapeutic ability of bortezomib to suppress IgM production. Possible complications of IgM flare include hyperviscosity and cryoglobulinemia, as well as worsening of IgM-related neuropathy. These high IgM levels may persist for up to 4 months and may require plasmapheresis to reduce hyperviscosity.

**Based on our work-up, we considered the patient at intermediate risk, due to the presence of 2 risk factors at baseline.**

Table 2. International Prognostic Scoring System for WM

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Risk Strata</th>
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<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>Low</td>
</tr>
<tr>
<td>Hemoglobin ≤11.5 g/dL</td>
<td>0 or 1 risk factor (except age &gt;65 years)</td>
</tr>
<tr>
<td>Platelet count ≥100 x 10^9/L</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Beta-2-microglobulin &gt;3 mg/L</td>
<td>High</td>
</tr>
<tr>
<td>IgM concentration &gt;7.0 g/dL</td>
<td>Adapted from Morel, et al.</td>
</tr>
</tbody>
</table>

**Nurse Perspective**

**Stacey Chuma, RN**

**Patient education**

Patients newly diagnosed with WM require extensive education regarding their disease, therapies, and management of treatment-related toxicities. In the case of KG, it was also important to discuss her family history of WM and assist her in gaining perspective on her condition in relation to that of her father and brother, who were diagnosed but did not require treatment. This patient needed a different clinical approach because she was symptomatic. Fortunately, several treatment options were available, including novel targeted therapies. Once KG chose to participate in a clinical trial, she needed ongoing counseling to help her stay motivated and remain on protocol.

It was also important to discuss prognosis with this patient. An International Prognostic Scoring System for Waldenström’s Macroglobulinemia (ISSWM) has been developed, as shown in Table 2. This system stratifies WM patients as low, intermediate, or high risk, depending on the presence of 3 risk factors: age >65 years, low hemoglobin or platelet count, and elevated B2M and IgM concentrations. In the population evaluated to create the ISSWM, patients in the low-, intermediate-, and high-risk groups had 5-year survival rates of 87%, 68%, and 36%, respectively (P <.001). At the time when these data were gathered, however, newer therapies for WM were not available. The advent of molecularly targeted therapies is expected to have a favorable impact on survival.

Based on our work-up, we considered the patient at intermediate risk, due to the presence of 2 risk factors at baseline: elevated β2M (4.0 mg/L) and low hemoglobin (10.5 g/dL).

While participating in the 6-month clinical trial, KG was continually educated regarding her progress, response to therapy, particular medications to help with symptom management, and issues of prognosis. Oncology patients are usually aware of significant parameters regarding their response to therapy (eg, laboratory findings, bone marrow biopsy, and scan results). This close attention to specific numbers and outcomes can provoke anxiety; therefore, it is important to help patients try to see the “whole picture” as opposed to focusing on one particular result or laboratory value. This educational process is ongoing; we continue to work closely with the patient in this case at her follow-up appointments, even though she is currently not receiving treatment.
and low sodium.\textsuperscript{28} It was stressed to our patient that she should contact us immediately if she ran a fever of $\geq$100.5°F, which would indicate a need for antibiotics. KG reported fatigue, and we suggested frequent rest periods and the need for regular laboratory work to monitor all blood counts.

Long-term effects of bortezomib may include PN, characterized by weakness, tingling, burning, pain, and numbness in the hands and feet.\textsuperscript{29} The risk of neuropathy was addressed at the start of every cycle with both a formal evaluation tool and a verbal discussion regarding any changes to sensation in KG’s hands and feet. In addition, the patient, who was 44 years old, was instructed to use adequate birth control while on the clinical trial due to the potential for pregnancy.

For this patient, IV rituximab was administered following the bortezomib infusion; the administration of rituximab typically took anywhere from 4 to 8 hours, and in some cases, longer. Rituximab is an anti-CD20 monoclonal antibody, which has produced response rates of 50% to 70% in WM.\textsuperscript{30} A potential immediate side effect related to rituximab use is an infusion reaction, characterized by itching, severe skin reaction, lightheadedness, headache, nausea, shortness of breath, and flu-like symptoms such as fever and chills.\textsuperscript{31} This reaction can occur anywhere from 30 minutes to 2 hours after the start of the infusion and may be prevented or mitigated by premedicating the patient with steroids, acetaminophen, and histamine blockers. Slowing the rate of infusion of rituximab can also lessen potential reactions.

We let our patients know that, in the event of a reaction, the infusion will be stopped, medications will be given for the hypersensitivity, and the infusion restarted at a slower rate.

Effects of rituximab that can occur over days or weeks include nausea, vomiting, loss of appetite, bone marrow suppression, fevers, chills, cough, and fatigue.\textsuperscript{32} Possible long-term effects (months to years post-treatment) include fertility issues and visual changes, although these are very uncommon. Other late effects are arthralgias and infections. Rare, but potentially life-threatening effects include reactivation of hepatitis B and progressive multifocal encephalopathy.

**Conclusion**

The decision to treat patients with WM and the selection of appropriate therapies requires careful consideration of patient- and disease-related factors. In this case study, a young, newly diagnosed patient with familial WM was successfully treated with 6 cycles of bortezomib plus rituximab. Her clinical course was uneventful, and the regimen was generally well tolerated. This case illustrates the benefit of novel therapies in the treatment of patients with WM.

This reaction can occur anywhere from 30 minutes to 2 hours after the start of the infusion.

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**References**


Case Study: Management of a Patient with Multiple Relapses

Introduction

Waldenstrom’s macroglobulinemia (WM) is a unique lymphoproliferative disorder. Although indolent, it remains incurable and many patients eventually succumb to the disease. Alkylating agents and nucleoside analogs (NAs) are commonly used to treat patients with WM, but are limited by toxicities and their negative impact on future stem cell harvesting. In addition, patients receiving these agents are at increased risk of disease transformation or development of myelodysplasia or acute myelogenous leukemia (AML). As illustrated in the following case, there is a great need for the development and evaluation of novel therapeutic approaches that avoid these long-term side effects and offer patients a better chance at survival.

Case Presentation

TL is a 70-year-old man who was diagnosed with WM approximately 14 years earlier, presenting at that time with fatigue and epistaxis. During his initial work-up, he was found to have a markedly elevated IgM of 12,000 mg/dL and lymphoplasmacytic cells in the bone marrow occupying over 90% of his cellularity. He underwent plasmapheresis and was treated with fludarabine, which provided a good response for 2 years. The patient was then treated with chlorambucil and prednisone, with no response, and then with cladribine. The following year, he began receiving a regimen of rituximab and dexamethasone, and experienced a rituximab-mediated IgM flare, which required plasmapheresis. He continued to receive rituximab maintenance for approximately 10 years. At the time of the next relapse, he was enrolled in a clinical trial of enzastaurin, a novel protein kinase C-beta inhibitor, but his disease still progressed. This was followed by treatment with a combination of bortezomib plus rituximab. Despite this therapy, the patient showed progression, with his IgM increasing to 9000 mg/dL.

At the time TL was referred to us, a bone marrow biopsy showed 95% lymphoplasmacytic cells with normal cytogenetics.

Oncologist Perspective

Irene Ghobrial, MD

This case illustrates some of the long-term effects associated with alkylating agents (eg, chlorambucil) and NAs (eg, fludarabine and cladribine), which TL received over the course of his disease. A recent study has shown that alkylating agents are not the only drugs that can lead to myelodysplastic syndromes (MDS) and secondary leukemias; NAs are also associated with an increased risk of large-cell transformation.1 In the case of this patient, the use of these agents most likely contributed to the development of AML.

According to treatment guidelines for WM, the choice of appropriate first-line therapy should take into account a patient’s eligibility for high-dose chemotherapy, as prolonged use of both alkylating agents and NAs can deplete hematopoietic stem cells.2 Rituximab-based therapy is the preferred initial treatment for many patients with WM. The choice of salvage therapy depends on the specific frontline therapy that was used (Figure 1).2,3

Bortezomib-based therapy may also be an appropriate choice for second-line therapy, and alemtuzumab may represent a reasonable third-line treatment. High-dose therapy with autologous or allogeneic stem cell transplant requires further evaluation in the context of prospective trials, primarily for patients with aggressive high-risk disease.2-4

Newer agents, such as everolimus, may also be considered for the treatment of patients with relapsed WM.3,5 Other agents that have shown activity in WM include lenalidomide, perifosine, enzastaurin, panobinostat, and ofatumumab.6-10 Clinical trials are also evaluating the proteasome inhibitor, carfilzomib, and ONX912.11

Pharmacist Perspective

Houry Leblebjian, PharmD

mTOR inhibitors

Several novel agents for the treatment of WM inhibit the mammalian target of rapamycin (mTOR) pathway.12,13 One of these drugs is everolimus, which our patient received in the context of a clinical
A PATIENT WITH MULTIPLE RELAPSES

Figure 1. Treatment recommendations for newly diagnosed and relapsed/refractory Waldenstrom’s macroglobulinemia.2,3

Trial. Originally isolated from a fungus (Streptomyces hygroscopicus), the first member of this class of drugs is the selective mTOR inhibitor rapamycin (sirolimus). Oral sirolimus has been approved by the US Food and Drug Administration (FDA) for maintenance of immunosuppression in patients who have undergone kidney transplants. Temsirolimus, a dihydroster of rapamycin, and everolimus (RAD001), an oral derivative of rapamycin, have been FDA approved for the treatment of renal cell carcinoma.14,15

The mTOR is a high-molecular-weight serine-threonine kinase that belongs to the phosphatidylinositol 3-kinase (PI3K)-related kinase family. Activation of mTOR promotes a number of cellular functions that are integral to the development of malignancies, including cell growth, proliferation, survival, and angiogenesis.16-18 The PI3K-Akt-mTOR pathway is dysregulated in many cancers.16-18 Akt, a key member of the PI3K pathway upstream of mTOR, is often constitutively activated in malignant B cells from the bone marrow of patients with WM.19 In vitro studies have shown that incubation with rapamycin can lead to significant cytotoxicity and induction of apoptosis in WM cell lines and patient samples. Temsirolimus and everolimus are generally well tolerated.14,15 The most common grade 3/4 toxicities (incidence ≥3%) in clinical trials of patients with renal cell carcinoma included infections, dyspnea, fatigue, stomatitis, dehydration, pneumonia, and abdominal pain. The most common laboratory abnormalities (incidence ≥50%) associated with these agents were myelosuppression, hyper-

ASCT indicates autologous stem cell transplant; BDR, bortezomib, dexamethasone, rituximab; cp, centipoise; CPR, cyclophosphamide, prednisone, rituximab; FR, fludarabine, rituximab; RCD, rituximab, cyclophosphamide, dexamethasone; R, rituximab; VR, bortezomib, rituximab.

1 In patients being considered for an ASCT, stem cell collection should be undertaken before exposure to a nucleoside analog.
2 Consider an attenuated schedule for fludarabine administration in patients with more indolent disease presentation.
3 Avoid as monotherapy in patients with hyperviscosity and with FcRIIA-158 F/F polymorphism.

Adapted from Treon SP. How I treat Waldenstrom’s macroglobulinemia. Blood. 2009;114:2375-2385.
The median age of patients was 63 years and the median number of prior therapies was 3. Half of the patients were considered to have intermediate- or high-risk WM, based on the International Prognostic Scoring System for Waldenstrom’s Macroglobulinemia.22

<table>
<thead>
<tr>
<th>Disease progression</th>
<th>% No. Patients</th>
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<tbody>
<tr>
<td>Partial response</td>
<td>42 21</td>
</tr>
<tr>
<td>Minimal response</td>
<td>28 14</td>
</tr>
<tr>
<td>Stable disease</td>
<td>16 8</td>
</tr>
<tr>
<td>Disease progression*</td>
<td>8 4</td>
</tr>
</tbody>
</table>

*Patients who experienced disease progression on therapy without response (primary progression).

Glycemia, hyperlipidemia, and increase in creatinine.14,15

**Everolimus in WM**

Everolimus binds to an intracellular protein known as FK506-binding protein 12, forming a complex that inhibits mTOR kinase activity. Through this inhibition, the activity of the downstream effectors S6 ribosomal protein kinase and eukaryotic elongation factor 4E-binding protein are diminished. As a result, mTOR-mediated tumor cell proliferation and angiogenesis are reduced.20,21

On the basis of in vitro data, a phase 2 study was conducted to investigate the safety and antitumor activity of single-agent oral everolimus (10 mg/day) in 50 patients with relapsed and/or refractory WM.22 The median age of patients was 63 years and the median number of prior therapies was 3. Half of the patients were considered to have intermediate- or high-risk WM, based on the International Prognostic Scoring System for Waldenstrom’s Macroglobulinemia.23

The overall response rate (ORR) was 70%, with a partial response rate of 42%, and a minimal response rate of 28% (Table). The median duration of response, as well as median duration of progression-free survival (PFS), had not been reached. The estimated PFS rates at 6 and 12 months were 75% and 62%, respectively. Twenty-one patients remained on therapy after a median of 7.3 months (range, 4.1-25.0 months). The results of this trial are encouraging, because other treatment options for relapsed/refractory WM have shown a response rate of only 30% to 40%, with a median response duration of ≤1 year.1,24

Grade 3/4 toxicities were observed in 56% of patients;22 adverse events included myelosuppression, infections, metabolic/laboratory abnormalities, pulmonary toxicity, fatigue, diarrhea, and mucositis.22 Pulmonary toxicity (pneumonitis) that occurred during this trial was manageable. Dose reductions due to any toxicity occurred in 52% of patients.

Potential drug interactions are an important factor to consider in patients receiving everolimus.14 Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein. Co-administration should be avoided with P-glycoprotein and with strong or moderate inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, voriconazole, fluconazole, aprepitant, clarithromycin, erythromycin, ritonavir, verapamil, diltiazem, or grapefruit juice). An increase in the everolimus dose is recommended when coadministered with strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, and phenobarbital), although concomitant use of everolimus and strong CYP3A4 inducers should be avoided if possible. Any new medications prescribed to patients on everolimus should be screened for possible interactions, and potential risks versus benefits need to be evaluated.

**Secondary malignancies associated with NAs**

The NAs fludarabine and cladribine are widely used in the frontline and relapsed setting for the treatment of patients with WM. Nonetheless, there is concern for possible long-term adverse effects, including disease transformation to high-grade non-Hodgkin’s lymphoma, MDS, or AML, which was the case with our patient. A retrospective study examined the incidence of these events in 439 patients with WM.1 Of these patients, 193 had been previously treated with an NA and 136 had not. The remaining 110 patients had not received prior treatment of any kind. Among NA-treated patients, 12 (6.2%) developed transformation to an aggressive lymphoma or therapy-related MDS/AML (t-MDS/AML). Eight of the transformations were to diffuse large B-cell lymphoma (DLBCL) and 1 was to Hodgkin’s disease. In comparison, 1 patient (0.4%) developed DLBCL in the cohort whose treatment did not include an NA (P<.001). No events occurred among untreated patients. The median time from onset of NA therapy to occurrence of transformation to aggressive lymphoma was 5 years (range, 0-14 years). The median survival of NA-treated patients who developed transformation did not differ from that of other NA-treated patients as a result of effective salvage treatment. All patients treated with an NA who developed t-MDS/AML died at a median of 5 months. Previously studied risk factors (eg, sex, age, family history of hematologic malignancies in first-degree relatives, markers of tumor burden, prognostic markers, and characteristics of the NA treatment) did not predict for the occurrence of either transformation or t-MDS/AML events in NA-treated patients.1

Another retrospective study investigated the incidence of fludarabine-related t-MDS/AML in 176 patients with lymphoproliferative disorders. Nineteen cases of t-MDS/AML were identified (10.8%).25 Most patients had received other cytotoxic treatments (eg, alkylating agents, topoisomerase II inhibitors),...
but 3 had a fludarabine combination as their only treatment. These data reinforce an increased risk of secondary malignancy among patients with WM treated with NAs.

**Nurse Perspective**

**Janet Kunsman, MS, RN**

WM is a disease with a highly varied clinical course. Some patients never require treatment, while others, like the patient in this case, fluctuate between periods of treatment and observation. Throughout the course of illness, nurses must continually educate patients and caregivers regarding the disease process and treatment. Disease-related education in WM should include the manifestations of hyperviscosity, which, if left untreated, can lead to life-threatening events. Hyperviscosity symptoms may include peripheral neuropathy (particularly in the lower extremities), epistaxis, headaches, and vision changes. Patients with WM may experience anemia, fever, chills, and night sweats, and unintended weight loss may also occur. Those with relapsing disease require periodic reinforcement of disease information. In TL’s case, for example, symptoms such as night sweats and weight loss were recurrent, and heralded relapse; regular reminders on WM symptom patterns can help patients who are receiving long-term treatment more readily identify relapse. For patients who experience relapse and multiple courses and types of therapy, it is of paramount importance that nurses provide education and support for side-effect management.

Nurses must attend to the adverse effects of various agents used for the treatment of WM. As relapsing patients undergo successive courses of therapies and polypharmacy, drug–drug interactions and the effect of therapy on an increasingly debilitated patient are essential considerations. Other supportive therapies may also have effects requiring education and management. For example, our patient received plasmapheresis as an interim measure to lower his IgM and avoid the effects of hyperviscosity.

Plasmapheresis is typically carried out by blood bank personnel. The process includes plasma exchange that allows for the removal of proteins, as 80% of IgM is intravascular. Patients often require red blood cell and platelet transfusions; complications may include bleeding.

**Managing adverse effects related to everolimus**

TL was enrolled in a clinical trial evaluating everolimus plus rituximab. The common adverse events of everolimus in pivotal trials for an FDA-approved indication (renal cell carcinoma) are summarized in **Figure 2**. Side effects of everolimus may include declines in white and red blood cells and platelets. Blood counts are monitored regularly throughout treatment. To ensure adequate counts, our patient received supportive care with frequent red blood cell and platelet transfusions, as well as granulocyte colony-stimulating factors to support white blood cell count.

Another adverse effect of everolimus is mouth sores (stomatitis), for which patients must be instructed in the use of nonalcohol-containing regimens to alleviate pain and discomfort and reduce bacteria in the mouth. These regimens include warm saline rinses, topical anesthetics such as xylcaine, and steroid-based mouth rinses to reduce inflammation. Diarrhea or loose stools can usually be managed with loperamide or other antidiarrheal agents. Assessment for electrolyte imbalance is important if the patient is experiencing diarrhea.

Everolimus may also cause an elevation in lipids (cholesterol and triglycerides) as well as creatinine and blood sugar elevations and abnormal liver function tests. A lipid profile, glucose testing, and liver function tests should be performed before starting therapy and regularly throughout treatment. Reactivation of hepatitis B is a potentially serious complication of everolimus therapy, which can lead to fulminant hepatitis. Hepatitis B serologies should be checked before initiating therapy. Pneumonitis (pulmonary

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**Figure 2. Adverse events (all grades) occurring in ≥30% of patients treated with everolimus 10 mg/day in pivotal clinical trials**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>10%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10%</td>
</tr>
<tr>
<td>Anemia</td>
<td>10%</td>
</tr>
<tr>
<td>Infec	ive/Inflamatory</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>10%</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>10%</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>10%</td>
</tr>
<tr>
<td>Triglyceride increased</td>
<td>10%</td>
</tr>
<tr>
<td>Cholesterol increased</td>
<td>10%</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>10%</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>10%</td>
</tr>
</tbody>
</table>

Indication for these data: renal cell carcinoma; everolimus is also approved for subependymal giant cell astrocytoma. It is not approved for WM.
toxicity) may be seen with everolimus as well. In a recent trial of everolimus for relapsed/refractory WM, pulmonary toxicity occurred in 10% of patients. Patients may present with either dry nonproductive coughs or may be producing sputum. They usually do not have a fever. Radiographic evaluation with a chest x-ray or computed tomography scan is indicated, and treatment with steroids is often recommended.

AML and end-of-life issues

The patient in this case was very ill and severely compromised by the time he was diagnosed with AML. His white blood cell count was extremely low, placing him at high risk for developing a life-threatening infection. The focus of nursing care shifted toward assuring comfort and providing end-of-life support for TL and his family. He clearly expressed a desire to not receive any life-sustaining measures, such as intubation or resuscitation, and ultimately died of infection.

Conclusion

Although therapies for WM have evolved significantly over the past 20 years, the disease remains incurable. Therefore, it is imperative that new agents and combination regimens for both newly diagnosed and relapsed/refractory disease continue to be evaluated in clinical trials. Early therapy for WM has often included the use of NAs, such as cladribine and fludarabine. However, these drugs carry specific risks for patients as they continue through their clinical course, as shown in this case study. With the advent of newer targeted agents, greater consideration may be given to the use and timing of NAs, which may lessen the incidence of transformation to AML or MDS, and translate to better outcomes for patients with the disease.

References

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