Recognizing Hyperviscosity Syndrome in Patients With Waldenstrom Macroglobulinemia

Ellen C. Mullen, RN, ANP, GNP, and Michael Wang, MD

Hyperviscosity syndrome can develop in patients with plasma cell dyscrasias, particularly Waldenstrom macroglobulinemia (WM). Occurring in 10%–30% of patients with hyperviscosity syndrome, WM is an uncommon B-cell proliferative disorder characterized by bone marrow infiltration and production of monoclonal immunoglobulin M. The elevated blood viscosity in WM is the result of increased circulating serum immunoglobulin M. Because hyperviscosity syndrome can be lethal, it must be recognized and managed early. Hyperviscosity syndrome has a triad presentation: vision changes, neurologic abnormalities, and bleeding. Treatment includes hydration with diuresis, plasmapheresis, and control of the underlying disease. The current treatment for WM is chemotherapy (i.e., alkylating agents and nucleoside analogs) and the monoclonal antibody rituximab. Although hyperviscosity syndrome is not one of the most common conditions, when it does occur, oncology nurses play a critical role in patients’ assessment and care.

Ms. C is an 80-year-old woman who was diagnosed with Waldenstrom macroglobulinemia (WM) after being hospitalized twice for acute confusion. One of the episodes was severe enough to require admission to an intensive care unit. Ms. C has a history of coronary artery disease and status postendarterectomy two years ago, hypertension, and chronic renal insufficiency. Her confusion was believed to be related to cardiac problems or “mini strokes,” but her cardiac function showed normal ejection fraction. She underwent computed tomography and magnetic resonance imaging scans of the brain, which were negative for acute process.

On Ms. C’s second admission, her family reported that she complained of increasing fatigue and confusion. During the workup, she was anemic and received a blood transfusion. Because of the anemia and fatigue, malignancy was a concern; therefore, an additional workup was initiated. Ms. C’s chemistries showed elevated total protein and mild elevation of calcium. Immunoglobulin (Ig) M was elevated with depressed IgG and IgA. The workup included a serum protein electrophoresis that showed an IgM kappa paraprotein peak of 3.5 g/dl and urine immunofixation that had 14 mg of kappa Bence-Jones proteinuria.

Ms. C was referred to an oncologist who obtained a bone marrow biopsy that revealed B-cell lymphoplasmacytic population with monotypic kappa chains expressing IgM that was consistent with the diagnosis of WM. Ms. C sought a second opinion for confirmation of her diagnosis and treatment recommendations. At the time of her visit, she denied any fever, chills, or night sweats.

At a Glance
- The clinical presentation of hyperviscosity syndrome is not limited to vision and neurologic abnormalities and mucosal bleeding: cardiopulmonary symptoms, acute renal failure, and stroke also have been reported.
- Hyperviscosity symptoms appear when the viscosity level reaches 4–5 cp.
- Nursing implications for patients with hyperviscosity syndrome should include education, symptom management, and supportive care.

She reported weight loss of approximately 15 pounds in the previous six months and denied having any neurologic problems, bleeding, or visual disturbance. She had elevated blood pressure (190/110 mmHg), and a funduscopic examination revealed mild retinal vein tortuosity and retinal hemorrhages in the right eye.

Ellen C. Mullen, RN, ANP, GNP, is an advanced practice nurse and Michael Wang, MD, is an associate professor, both at the University of Texas M.D. Anderson Cancer Center in Houston. No significant financial relationship to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society. (Submitted November 2005. Accepted for publication April 7, 2006.)

Digital Object Identifier: 10.1188/07.CJON.87-95
Laboratory results showed the following: paraprotein level 4.8 g/dl, viscosity level 4.6, IgM more than 5,400 mg/L, hemoglobin 10.5 g/dl, hematocrit 30.5%, calcium 9.5 mg/dl, albumin 3.2 mg/dl, protein 10.5 mg/dl, and beta-2 microglobulin level 3.0 mg/L. Because Ms. C’s paraprotein, viscosity, IgM, and beta-2 microglobulin levels were elevated and because she had experienced an episode of syncope, her healthcare providers recommended that she begin treatment. The syncopal episode and confusion then were attributed to hyperviscosity. Combination therapy (rituximab, cladribine, and oral cyclophosphamide) was recommended after plasmapheresis. To complete the diagnostic work-up for WM, Ms. C was scheduled to have computed tomography scans (head, neck, chest, abdomen, and pelvis), a bone survey, and a bone marrow biopsy (three months had passed since her last biopsy). She also was referred to an ophthalmologist. Ms. C was instructed to return on completion of the tests and after undergoing single plasmapheresis.

Ms. C returned after two weeks for follow-up to review her test results. Her bone marrow aspiration and biopsy revealed 45% lymphocytes and 4% plasma cells; her biopsy was read as low-grade B-cell lymphoma with plasmacytid differentiation and immunophenotypes, which is consistent with WM. The bone survey revealed no lytic lesions, but spinal osteopenia out of proportion to age was noted. Computed tomography scans of the head, neck, chest, abdomen, and pelvis were negative. Ophthalmology findings suggested venous tortuosity and retinal hemorrhages but no vision loss. Ms. C reported feeling better and denied any further episodes of syncope, and her blood pressure was controlled. She presented in the clinic in a wheelchair, accompanied by her son. Her healthcare providers recommended that Ms. C begin systemic treatment with combination therapy (rituximab, cladribine, and oral cyclophosphamide).

Case Study Discussion

Patients with hyperviscosity syndrome can present with vague signs and symptoms. Ms. C’s presentation included fatigue, confusion, and syncope. She had several comorbidities that caused her to have confusion and syncope. Her chemistries (i.e., elevated calcium and total protein) suggested an underlying illness, and her complete blood count revealed anemia. The findings prompted her physician to rule out malignancy, mainly plasma cell dyscrasia. The flow cytometry immunophenotype studies demonstrated a population of abnormal B cells expressing CD5, CD19, CD20, and monotypic Ig kappa light chains. Ms. C’s diagnosis was consistent with WM. The diagnosis also was supported by her elevated IgM. She was considered symptomatic because of the syncopal episode (neurologic manifestation of hyperviscosity) and retinal vein tortuosity and hemorrhages, which suggest signs of hyperviscosity. Hyperviscosity is an indication for treatment in patients with WM. In addition, when she presented to the clinic, her paraprotein, IgM, and viscosity levels as well as beta-2 microglobulin were increased.

The treatment options were reviewed with Ms. C and her family. She was not a candidate for an autologous stem cell transplant because of her age and comorbidities; therefore, treating her with combination therapy consisting of rituximab, a nucleoside analog, and an alkylating agent was a reasonable alternative. Ms C needed a rapid response, which be obtained from the nucleoside analog and alkylating agent. Ms. C also needed plasmapheresis to decrease her IgM level and prevent worsening of hyperviscosity that could be induced by infusion of rituximab (i.e., studies have shown elevation of IgM after initiation of rituximab) (Gertz et al., 2004). Ms. C’s IgM level was greater than 5,000 mg/l and her serum viscosity level was greater than 3.5 cp, which were of concern. She underwent single plasmapheresis, and her IgM level decreased to 4,000 mg/l, her viscosity level decreased to 3.2 cp, and her paraprotein level decreased to 3.2 g/dl. Furthermore, Ms. C felt much better, her lethargy was resolved, and her blood pressure was better controlled. Ms. C subsequently received cladribine, oral cyclophosphamide, and rituximab.

Hyperviscosity Syndrome

The term hyperviscosity syndrome is used to describe the clinical symptoms related to increased blood viscosity, which usually is the result of increased circulating serum Igs (Kupas, 2005). Hyperviscosity syndrome commonly is seen in patients with WM, a plasma cell dyscrasia, and rarely in those with multiple myeloma. About 10%–30% of patients with WM develop hyperviscosity syndrome (Mehta & Singhal, 2005), but the syndrome also is seen in patients with conditions such as rheumatoid arthritis, polycthemia vera, IgA multiple myeloma, and IgG multiple myeloma. This article will discuss hyperviscosity syndrome in patients with WM.

Waldenstrom Macroglobulinemia

WM is a rare and chronic cancer that is classified as a low-grade or indolent lymphoma. It affects plasma cells that develop from white blood cells called lymphocytes or B cells. This uncommon B-cell proliferative disorder is characterized by bone marrow infiltration and production of monoclonal IgM (Owen, Hillmen, & Rawstron, 2005). The etiology of WM is unknown, but genetic factors may contribute to the pathogenesis of the disease. The main risk factor for the development of WM is preexisting IgM monoclonal gammopathy of uncertain significance (MGUS), a condition that is defined as the presence of serum or urine M protein in asymptomatic or healthy people. Accurate estimates of the prevalence of WM are complicated by the lack of standardized diagnostic criteria as well as by patients with asymptomatic disease. The accurate diagnosis of patients with IgM monoclonal gammapathy as IgM-MGUS or WM has not been straightforward because definitions of the conditions overlap (Ghobrial, Gertz, & Fonseca, 2003).

WM usually presents in the sixth and seventh decades of life, but it can occur in younger people. The disease affects about 1,500 Americans each year and is more common in Caucasian men (Munshi & Anderson, 2005). Because the median age of presentation is 63 years, the incidence of WM may increase as a result of a large number of the population entering their 60s (U.S. Census Bureau, 2005). At the University of Texas M.D. Anderson Cancer Center (2005), from 1981–1990, only 3 cases of WM were noted among patients aged 60–69 years compared to 72 cases in the same age group from 1991–2001. In comparison with adults aged 50–59 years, 7 cases were reported from 1981–1990 and 55 cases were reported from 1991–2001. The influence of age on the increased incidence of WM in the cancer center is unclear. Other
Clinical Manifestations of Hyperviscosity

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>Mucosal: gingival, epistaxis, gastrointestinal bleeding</td>
</tr>
<tr>
<td>Visual abnormalities</td>
<td>Diplopia, retinal vein thrombosis, papilledema, retinal hemorrhage</td>
</tr>
<tr>
<td>Neurological</td>
<td>Headache, syncope, seizure, cerebral hemorrhage, ataxia</td>
</tr>
</tbody>
</table>

**Figure 1. Diagnostic Workup for Hyperviscosity Syndrome**


Factors such as different coding systems, better diagnostic tests, and increased awareness of the disease may have contributed to the rise in the incidence of WM. Nevertheless, WM is expected to be seen more in the future.

Individuals can live with WM for years without showing any symptoms. Patients with asymptomatic WM should be observed and left untreated because they may remain stable for many years. In an analysis of 51 asymptomatic patients, the median time to disease progression was 6.9 years (Alexanian, Weber, Delasalle, Cabanillas, & Dimopoulos, 2005). However, symptomatic WM requires treatment. The symptoms of WM are attributable to tumor infiltration or monoclonal protein (Annibali et al., 2005). With tumor infiltration, the signs and symptoms usually are cytopenias (i.e., deficiencies of the cellular elements of the blood), fever, night sweats, weight loss, lymphadenopathy, organomegaly, and fatigue. If monoclonal IgM is overproduced, hyperviscosity, cryoglobulinemia (presence of cryoglobulins or abnormal forms of protein molecules in the blood), cold agglutinin (hemolytic anemia caused by autoantibodies that react at temperatures less than 37°C), neuropathy, and amyloidosis (accumulation of deposits of abnormal proteins known as amyloid in organ systems) are manifested. Patients often present to their primary care providers when they are already symptomatic or are in the late stage of the disease (Sym, Arcila, & Holtel, 2001). The most common symptoms are anemia and fatigue, but the one presentation that can be lethal is hyperviscosity syndrome.

Hyperviscosity syndrome in WM is a manifestation of excessive amounts of circulating IgM produced by abnormal plasma cells. Igs, most particularly IgM, are large and asymmetric molecules that have high carbohydrate content. Eighty percent of the proteins are intravascular (Dimopoulos, Kyle, Anagnostopoulos, & Treon, 2005). If the concentration of the proteins increases, they may form aggregates and bind to water through their carbohydrate components. Binding with water results in increased osmotic pressure and increased resistance to blood flow, which eventually lead to impaired transit through the microcirculation. Monoclonal IgM also may interact with red blood cells, increasing their internal viscosity and reducing their deformability (i.e., the ability of erythrocytes to change shape as they pass through the narrow spaces such as microvasculature) (Chiang, Begley, & Henderson, 2000). The increased viscosity causes microvascular congestion, which leads to decreased oxygen delivery to tissues and eventually results in tissue damage.

**Signs and Symptoms**

Hyperviscosity syndrome should be suspected in patients with a known malignancy who present with the triad of neurologic abnormalities, vision abnormalities, and bleeding (see Figure 1). However, patients may not present with the triad. In the case study, Ms. C presented with only two of the triad symptoms—neurologic abnormalities (i.e., syncope, confusion, and lethargy) and visual abnormalities. The manifestations of hyperviscosity can range from vague (i.e., headache) to severe (i.e., gastrointestinal bleeding), which can make the workup challenging.

Neurologic manifestations include headache, dizziness, vertigo, ataxia, encephalopathy, or altered mental status, especially delirium. They could be caused by electrolyte abnormalities such as hypercalcemia and hyponatremia, which are common in patients with hyperviscosity syndrome, or by intracerebral vascular occlusion as a result of increased IgM (Chiang et al., 2000). Coma and stroke also have been reported, but they are extreme presentations of hyperviscosity syndrome (Phatak, 2003). Although a few cases have been noted, sensorineural hearing loss is unusual. The loss is believed to occur from hyperviscosity of the blood, causing increased resistance to blood flow or thrombus formation in the middle ear (Sym et al., 2001). Mucosal bleeding is the most common clinical manifestation of hyperviscosity syndrome (Kupas, 2005) and is a result of increased serum proteins that directly affect the hematologic system by coating platelets and, thus, hinder their ability to form a clot (Chiang et al.). Bleeding can occur in the gastrointestinal tract, nose, gingivae (Ghobrial et al., 2003), and internal organs such as the uterus and intracranial sites (Rampling, 2003).

Visual abnormalities, including diplopia, retinal vein thrombosis, papilledema, and retinal hemorrhage, can occur in patients with hyperviscosity syndrome. The classic findings on funduscopic examination in patients with hyperviscosity syndrome are dilatation or engorgement and tortuosity of veins that give the appearance of “sausage links,” termed as fundus paraproteinaemicaus (Chiang et al., 2000). The engorgement of retinal veins is caused by stasis of blood flow and is considered an early funduscopic finding, but if untreated, it will progress to complete retinal vein occlusion, flame-shaped hemorrhages, microaneurysms, or proteinaceous exudates. Changes in the retinal veins may lead to blurring, decreased visual acuity, and blindness (Chiang et al.).

Acute renal failure resulting from ischemic acute tubular necrosis has been reported (Wong, Mak, Lo, Tong, & Wong, 2000). The circulating macroglobulin can be trapped in the glomerular loops, precipitate, and form subendothelial deposits that may cause glomerular damage, resulting in nonselective proteinuria, dehydration, and uremia. The complication can be aggravated by hyperviscosity and can be reversed by plasmapheresis (Dimopoulos et al., 2005). Several cases of pulmonary edema and congestive heart failure resulting from increased plasma volume also have been reported (Kundu, Dey, & Sengupta, 2005). Multorgan failure can occur if hyperviscosity syndrome is not treated promptly.
Diagnosis of Hyperviscosity Syndrome

Electrolyte imbalances are common in patients with hyperviscosity syndrome. Hypercalcemia and asymptomatic pseudohypoponatremia (an artifact caused by hyperproteinemia) are common and may contribute to neurologic symptoms (Chiang et al., 2000). Therefore, other possible causes of electrolyte imbalance such as diabetes, nephrotic syndrome, or hyperparathyroidism must be ruled out by obtaining chemistry levels and performing thyroid function tests. Anemia is a common presentation, so obtaining a baseline complete blood count is helpful. A peripheral blood smear also can be beneficial and usually reveals rouleau formation—a loose adherence of red cells giving the appearance of a “pile of coins” (Rampling, 2003). Large proteins in plasma such as the globulins cause the rouleau formation. The higher the rouleau intensity in the blood sample, the greater the resistance to flow, which leads to plugging of the small vessels.

Hypergammaglobulinemia increases serum viscosity. An IgM level greater than 3,000 mg/dl usually leads to the development of hyperviscosity syndrome, but it does not always correlate with increased serum viscosity and complications (Drew, 2002). The measurement of viscosity level is diagnostic. The normal viscosity level is 1.4–1.8 cp (Zarkovic & Kwaan, 2003). Signs and symptoms of hyperviscosity syndrome usually appear when the viscosity reaches 4–5 cp (Mehta & Singhal, 2003). The correlation between serum viscosity levels and symptoms may not be consistent among patients, and some can be asymptomatic even with high serum viscosity. However, most patients with a serum viscosity of less than 4 cp do not have symptoms of hyperviscosity.

WM should be included in the differential diagnosis of patients presenting with symptoms of hyperviscosity. If WM is suspected, serum protein electrophoresis and urine electrophoresis with immunofixation should be obtained. The serum protein electrophoresis will demonstrate IgM paraprotein, whereas urine electrophoresis will show a monoclonal light chain (usually kappa); however, gross Bence-Jones proteinuria is unusual. The minimum protein concentration needed for diagnosis is not universally accepted as a requirement for diagnosis and not recommended by a consensus panel (Ghobrial et al., 2003), but the presence of increasing protein concentrations of monoclonal IgM protein improves the diagnostic specificity. Bone marrow biopsy examination will reveal an intertrabecular monoclonal lymphoplasmacytic infiltrate ranging from predominantly lymphocytic to lymphoplasmacytic to overt plasma cells. Figure 2 lists the typical immunophenotype seen in WM. Standard cytogenetics is not recommended unless the diagnosis is doubtful or if myelodysplasia is suspected (Ghobrial et al.). Fluorescent in situ hybridization can be obtained to differentiate WM from IgM myeloma. Beta-2 microglobulin should be measured not for diagnostic purpose but for its prognostic relevance (Ghobrial et al.).

Depending on the patient’s presentation, imaging studies may be appropriate. A computed tomography scan of the head is indicated for patients who have experienced altered mental status, seizures, or coma. A computed tomography scan of the chest and a chest x-ray can be obtained to rule out infection, congestive heart failure, or pulmonary edema caused by hyperviscosity (Kundu et al., 2003). Fluorescein angiography is a test that is performed by an ophthalmologist and can confirm hyperviscosity syndrome by measuring the transit time of retinal microvasculature (Chiang et al., 2000). A bone survey may show osteoporosis, but lytic lesions, although rare, have been reported (Rothschild, Ruhl, & Rothschild, 2002). The diagnosis of hyperviscosity syndrome should not be based solely on laboratory values or imaging studies. A thorough history and physical examination, including fundoscopy, should be obtained when hyperviscosity syndrome is suspected. Table 1 summarizes the workup for hyperviscosity syndrome.

### Treatment and Management

Symptomatic hyperviscosity requires emergent treatment that includes hydration with diuresis, plasmapheresis, and, eventually, control of the malignancy. In the community setting where plasmapheresis is not easily accessible, phlebotomy with the removal of 100–200 cc of whole blood has been found to effectively reduce the acute symptoms (Zarkovic & Kwaan, 2003). Rehydrating patients with normal saline as loop diuretics (i.e., furosemide) are being infused has been recommended to correct hypercalcemia and reduce the effective protein concentration. Automated plasmapheresis, which separates plasma from the cellular blood elements by centrifugation, is used most commonly in the United States and remains the treatment of choice (Drew, 2002). Used solely to treat symptoms associated with hyperviscosity, automated plasmapheresis has no effect on the tumor burden and can be used for short- or long-term management. Plasma is removed from the patient’s circulation and replaced with a protein-based fluid (e.g., 5% human albumin solution, plasma protein fraction). In patients with WM, single plasmapheresis with one plasma volume replacement (about 3 L) usually results in a dramatic improvement (reduction of serum viscosity by 50% or more) because of the intravascular distribution of the monoclonal protein (Drew). Patients may require several plasmapheresis treatments before seeing an improvement. Patients who have acute hyperviscosity usually need treatment of at least 2–3 L daily for four to five days or as long as needed until viscosity is less than 4 cp. Long-term use of plasmapheresis is reserved for older adults, individuals with severely compromised performance status, or those who are resistant to systemic treatment (Mehta & Singhal, 2003). In those patients, plasmapheresis can be used for maintenance or prevention of hyperviscosity. Plasmapheresis should be performed prior to treatment with chemotherapy or radiation therapy.

---

**Figure 2. Diagnostic Criteria for Waldenstrom Macroglobulinemia**

*Note.* Based on information from Johnson et al., 2005.

- Immunoglobulin (Ig) M monoclonal protein of any concentration
- Bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation
- Intertrabecular pattern of bone marrow infiltration
- Surface IgM+; CD5+ or CD5−; CD10−; CD19+, CD20+, CD22+, CD23−, CD25+, CD27+, FMC7+, CD103−, and CD138 immunophenotype
  - Supportive but not necessary for the diagnosis of Waldenstrom macroglobulinemia

### Table 1. Diagnostic Workup for Hyperviscosity Syndrome

<table>
<thead>
<tr>
<th>TEST</th>
<th>FINDINGS</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone scan†</td>
<td>Presence or absence of lytic lesions</td>
<td>Patients with Waldenstrom macroglobulinemia can present with lytic lesions.</td>
</tr>
<tr>
<td>Bone marrow aspiration or biopsy†</td>
<td>Infiltration by small lymphocytes, plasmacytoid cells, and plasma cells</td>
<td>Confirms a diagnosis of Waldenstrom macroglobulinemia.</td>
</tr>
<tr>
<td>Chemistries</td>
<td>Hypercalcemia, hyponatremia, and hyperproteinemia</td>
<td>Used to rule out other metabolic abnormalities.</td>
</tr>
<tr>
<td>Chest x-ray or computed tomography of the chest</td>
<td>Congestive heart failure or pulmonary edema (interstitial disease)</td>
<td>Can be seen in hyperviscosity because of the increase in plasma volume.</td>
</tr>
<tr>
<td>Coagulation test</td>
<td>Elevation in prothrombin time (PT) or partial thromboplastin time (PTT)</td>
<td>PT or PTT may be prolonged because of interactions of immunoglobulin (Ig) M with coagulating factors V, VII, and VIII.</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Anemia and thrombocytopenia</td>
<td>Commonly seen in Waldenstrom macroglobulinemia.</td>
</tr>
<tr>
<td>Computed tomography scan (abdomen or pelvis)†</td>
<td>Presence or absence of hepatosplenomegaly and bulky lymphadenopathy</td>
<td>Organomegaly and lymphadenopathy can be seen in Waldenstrom macroglobulinemia.</td>
</tr>
<tr>
<td>Computed tomography scan (head)</td>
<td>Cerebral hemorrhages</td>
<td>Cerebral hemorrhages can occur in patients with hyperviscosity syndrome and are helpful in ruling out other possible causes of neurologic abnormalities.</td>
</tr>
<tr>
<td>Funduscopic examination</td>
<td>Retinal hemorrhages and dilated tortuous vessels</td>
<td>Common presentations of hyperviscosity syndrome.</td>
</tr>
<tr>
<td>Igs (quantitative)</td>
<td>Elevated IgM level (for Waldenstrom macroglobulinemia)</td>
<td>An IgM level greater than 3 g/dl usually leads to the development of hyperviscosity syndrome.</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Rouleaux formation</td>
<td>Seen in hyperviscosity syndrome.</td>
</tr>
<tr>
<td>Serum protein electrophoresis†</td>
<td>Presence of monoclonal protein spike</td>
<td>Used to determine the cause of hyperviscosity syndrome.</td>
</tr>
<tr>
<td>Serum viscosity</td>
<td>More than 1.8 units or centipoises</td>
<td>Hyperviscosity syndrome usually is seen when viscosity levels are more than 4 cp.</td>
</tr>
<tr>
<td>Thyroid function test</td>
<td>Normal</td>
<td>Used to rule out hyperparathyroidism as a cause of altered mental status.</td>
</tr>
<tr>
<td>Urine protein electrophoresis†</td>
<td>Presence of Bence-Jones protein</td>
<td>Used to determine the cause of hyperviscosity syndrome.</td>
</tr>
</tbody>
</table>

*† This test is performed when Waldenstrom macroglobulinemia is suspected.

### Alkylating Agent-Based Therapy

Oral alkylating agents have been used for the management of WM since the 1960s (Gertz, 2005). Chlorambucil is an alkylating agent used in the treatment of WM. The drug initially is given at a dose of 6–12 mg daily by mouth until leukopenia develops. Maintenance therapy with doses of 2–8 mg daily may be given indefinitely (Gertz). Chlorambucil acts on lymphocytes and to a lesser degree on neutrophils and platelets. Once it was established as an effective treatment for WM, chlorambucil was...
Nucleoside Analogs

Purine nucleoside analogs (fludarabine and cladribine) have been effective in the management of WM. They have been used in patients with WM because of their effectiveness in other lymphoproliferative disorders or indolent lymphomas (Ghobrial et al., 2003). Fludarabine and cladribine work well in indolent lymphomas because of their ability to induce programmed cell death ( apoptosis ) by inhibiting DNA synthesis (Zinzani, 2002). The increase in IgM is related to the release of intracellular IgM (Gertz). The flare phenomenon is associated with apoptosis of tumor cells induced by rituximab. The increase in IgM is related to the release of intracellular IgM (Gertz), which does not translate as treatment failure; most patients return to their baseline IgM level by 12 weeks (Treon, Emmanouilides, et al., 2005). One rationale for the delayed response is that rituximab may differentially target members of the malignant clone in WM. An increase of serum IgM following initiation of rituximab has been documented (Gertz). The flare phenomenon is associated with apoptosis of tumor cells induced by rituximab. The increase in IgM is related to the release of intracellular IgM (Gertz), which does not translate as treatment failure; most patients return to their baseline IgM level by 12 weeks (Treon, Emmanouilides, et al.).

Rituximab should be used cautiously in patients experiencing hyperviscosity symptoms because serum IgM and viscosity level may rise abruptly. Hence, plasmapheresis should be considered first for patients with IgM levels greater than 5,000 mg/l or serum viscosity greater than 3.5 cp (Treon et al., 2006). Plasmapheresis first was applied with Ms. C.

Rituximab has been shown to be effective as a standard dose or an extended dose. The standard dose (i.e., four weekly infusions at 375 mg/m²) demonstrated a partial response in approximately 27% of patients (Gertz et al., 2004). Its suppressive effect on T lymphocytes, which results in impaired cell-mediated immunity (Zinzani, 2002). Cell-mediated immunity, in turn, leads to the development of infections such as Pneumocystis carinii pneumonia. Side effects are rare but include hair loss and neurologic abnormalities.

Patients taking cladribine can achieve complete remission when the drug is used as an initial and salvage therapy. It can be used as a single agent or can be combined with other agents. In addition, cladribine combined with cytoxan and rituximab provided excellent response rates with minimal toxicity (Weber et al., 2003). The toxicity of cladribine is similar to that of fludarabine (i.e., mainly myelosuppression and infection). Patients who are resistant to fludarabine may not benefit from cladribine, and information is insufficient to recommend one purine nucleoside analog over another (Dimopoulos et al., 2005).

Monoclonal Antibody Therapy

Rituximab is a monoclonal antibody that has been proven for the effective management of WM. Most WM malignant cells express the B-cell surface membrane CD20, which is the target antigen of rituximab. Rituximab is an ideal treatment because of its selective action and tolerable side effects. The drug is the treatment of choice for patients who do not need rapid tumor control and have severe or moderate cytopenias (leukopenia and thrombocytopenia) (Gertz, 2005). It can be used as a single agent in a standard or extended dose or in combination with other alkylating agents and nucleoside analogs. Rituximab is preferred in cases of relapse, especially if stem cells have not been harvested previously (Gertz). Rituximab does not cause myelosuppression, and its primary toxicity is infusion related during the first treatment (Bjorkholm, 2004). Its toxicities (rigors, fever, hypotension, and throat swelling) usually are controlled with low-dose corticosteroids and antihistamines. However, the time to response after rituximab is slow and usually takes three months or longer (Treon, Emmanouilides, et al., 2005). One rationale for the delayed response is that rituximab may differentially target members of the malignant clone in WM. An increase of serum IgM following initiation of rituximab has been documented (Gertz).

Figure 3. Updated Consensus Panel Recommendations for Frontline and Salvage Therapy From the Third International Workshop on Waldenstrom Macroglobulinemia

The response rate in the studies was higher (44%–48%) than those previously reported with standard doses of rituximab (Dimopoulos et al., 2002). Treon, Emmanouilides, et al. found that extended doses of rituximab yielded a partial response in 48.3% of patients; however, additional study is needed to determine the effect on the duration of response for rituximab extended over standard dose therapy.

Alemtuzumab is a monoclonal antibody against the CD52 antigen and is effective in patients with chronic lymphocytic leukemia. Owen et al. (2005) were able to demonstrate that WM also expresses the CD52 antigen. As a result, alemtuzumab was tested and data have shown that it has activity on WM. The panel of the Third International Workshop on WM in 2004 recommended alemtuzumab as salvage treatment for WM (Treon et al., 2006). The toxicity related to alemtuzumab includes infections such as cytomegalovirus reactivation, herpes simplex reactivation, aspergillosis, and tuberculosis (Owen et al.).

**Thalidomide**

Thalidomide is recommended as a salvage treatment for WM and can be used as a single agent or in combination therapy. Thalidomide has been shown to be effective in multiple myeloma, so it has been tested for use in WM. Its exact mechanism of action is unknown, but because of its antiangiogenic and immunomodulatory properties, thalidomide has been effective in patients with multiple myeloma. Several studies have demonstrated the effectiveness of thalidomide in patients with WM (Coleman, Leonard, Lyons, Szelenyi, & Niesvizky, 2003; Dimopoulos et al., 2005; Singhal et al., 1999). Dimopoulos et al. (2001) tested thalidomide at a dose of 200 mg daily with the dose escalating in 200 mg increments every 14 days as tolerated to a maximum of 600 mg daily and found that constipation, somnolence, fatigue, neuropathy, skin rash, and depression were associated with thalidomide. Dimopoulos et al. (2001) were able to conclude that thalidomide had activity in WM, but patients are able to tolerate only low doses because of its neurologic toxicity. In another study, thalidomide was tested at a lower dose in combination with clarithromycin and dexamethasone. Again, neurologic toxicity was the main side effect (Coleman et al.). Therefore, thalidomide is only recommended as salvage therapy as a single agent or in combination with steroids. Studies evaluating the use of thalidomide analog (lenalidomide) as a potential treatment for WM are being planned because this agent is less neurotoxic than thalidomide (Hideshima, Richardson, & Anderson, 2006).

**Autologous Stem Cell Transplant**

High-dose chemotherapy followed by stem cell transplantation is used to treat several types of cancer, such as multiple myeloma, lymphoma, and leukemia. In autologous stem cell transplants, patients’ own stem cells are used. After the success and proven survival benefit of stem cell transplantation in multiple myeloma, the technique was applied to patients with WM, although it is reserved for selected patients younger than age 65 with a poor prognosis (Anagnostopoulos et al., 2001). Autologous stem cell transplantation is a recommended salvage therapy for WM, with patients usually receiving the transplant years after their initial diagnosis. Most patients receive multiple treatments before transplantation. When considering high-dose therapy and autologous stem cell transplantation as treatment options for patients with WM, the use of alkylating agents or nucleoside analogs should be avoided because of their myelosuppressive effects. Some studies have shown that previous exposure to the agents have caused delay or failure in mobilizing blood stem cells (Gertz, 2005). Rituximab should be considered as treatment for WM if autologous stem cell transplantation is indicated because it is nonmyelosuppressive.

**Referrals and Consultations**

When a diagnosis of hyperviscosity syndrome is confirmed, immediate referrals are necessary. Patients should be referred to an ophthalmologist as soon as possible to confirm hyperviscosity via fluorescein angiography. If the funduscopy examination and fluorescein angiography reveal or confirm hyperviscosity, an emergent plasmapheresis is warranted (Chiang et al., 2000). A large-bore catheter (Quinton) should be used for the plasmapheresis, and a surgeon should be consulted for line placement. A consultation with a hematologist who will perform the plasmapheresis should be expedited (Chiang et al.). In the community setting where plasmapheresis is not readily available, a phlebotomy and hydration can be performed. Patients eventually will be transferred to a center where plasmapheresis is offered. Because other disorders can cause hyperviscosity, its cause must be determined upfront to dictate treatment. If the cause is WM, patients must be referred to a hematologist who will formulate and discuss the treatment plan.

**Current and Future Directions**

WM currently is incurable, and patients have a median survival of five to seven years; therefore, more research is needed to evaluate new agents such as bortezomib, ibritumomab tiuxetan, oblimerson sodium, sildenafil, imatinib mesylate, vaccines, and lenalidomide (Dimopoulos et al., 2005; Gertz, Geyer, Badros, Kahl, & Erlichman, 2005) and different combination therapies such as thalidomide and rituximab. Furthermore, even though frontline treatment has been established for WM, optimal frontline treatment must be confirmed. In addition, researchers must determine whether the efficacy and toxicity of combination therapy are better than single-agent alkylator, nucleoside analog, or rituximab therapy. An active phase III study currently is examining chlorambucil versus fludarabine as initial therapy for WM and related disorders (Johnson et al., 2005). The prospective, randomized, open-label study includes patients with previously untreated WM, splenic lymphoma with villous lymphocytes, and non-IgM lymphoplasmacytic lymphoma. Johnson et al. are examining the efficacy of alkylator versus nucleoside analogs in patients with WM.

Splenectomy has been mentioned in the literature as a possible treatment for WM in patients who are resistant to chemotherapy (Bjorkholm, 2004). Few studies have reported that, after splenectomy, patients have demonstrated major reduction in monoclonal protein concentration, with remissions lasting for many years. However, whether the patients who
had splenomegaly had WM or another type of lymphoma was unclear (Dimopoulos et al., 2005). Because current available data still are limited, a more prospective evaluation of this option is required.

**Nursing Implications**

Nurses may encounter patients with symptomatic WM in the clinic, emergency department, on the medical/surgical floor, and in an intensive care unit. Nurses are in a key position to help in the management of this patient population. For example, in the emergency setting, nurses can help to stabilize patients and ensure that patients receive adequate oxygenation and hydration. If plasmapheresis is indicated, nurses should facilitate placement of a Quinton catheter. When patients have been stabilized and the diagnoses of WM and hyperviscosity syndrome have been established, nurses' role becomes more supportive and educational.

Patients with cancer require physiologic, psychosocial, and economic supportive care; therefore, nurses must assess patients' support systems prior to treatment and ensure that they are referred to proper disciplines such as social work or case management and dietary services. Patients with WM who are undergoing treatment require frequent monitoring (Salmon & Cassady, 2005). Patients who are undergoing chemotherapy treatments need their blood counts monitored between chemotherapy cycles. The frequency of visits varies from one to three times per week, depending on blood counts. Patients' support systems should be reassessed at each visit because caretakers may become overwhelmed. Nurses can explore respite care or home healthcare options.

WM is a chemosensitive malignancy, but it remains an incurable disease. Patients may reach a point when they do not respond to therapy and may choose to forgo additional treatment. Again, nurses play a critical role in facilitating discussion with the physician about further therapy versus quality of life. Patients should be informed about treatment alternatives such as palliative and hospice care. Depression and anxiety can occur, so patients should consider obtaining psychiatric counseling.

Patients with cancer are faced with an overwhelming array of treatment options. Patients and their significant others may have difficulty understanding and navigating the variety of options available. Oncology nurses play an important role in educating patients who need to understand their illness and treatments. Patients should be aware of what to expect regarding treatment, both in terms of outcomes and side effects. Patients should be educated about managing side effects such as nausea and vomiting and about precautions for neutropenia and thrombocytopenia. Nurses can assist in clarifying misconceptions by facilitating discussions with treating physicians and in providing and guiding patients toward reliable sources of information. Figure 4 lists some resources for patient information and support. Nurses should emphasize that adherence to a proposed treatment is very important and close monitoring is required. Patients with WM need regular monitoring of their paraprotein levels (Roberts-Thomsom, Nikloutstopoulos, & Smith, 2002). According to guidelines from the National Comprehensive Cancer Network (2006), complete blood counts, serum protein electrophoresis, and quantitative Igs should be monitored every two cycles of treatment.

**Conclusion**

As the population ages, the number of patients with WM may increase. The epidemiology of WM and its common clinical presentations must be understood so that healthcare providers can consider WM in their differential diagnosis. By recognizing that hyperviscosity syndrome can occur in patients with WM, healthcare providers can prevent serious complications and chronic sequelae from the disease process. Prompt management and appropriate referral to other disciplines will increase the chance for survival and improve quality of life. Healthcare providers should be aware of and educated about the management and treatment of hyperviscosity syndrome. Plasmapheresis is the treatment for symptomatic patients, but the ultimate aim of treatment for the syndrome is to control the underlying disease. Alkylating agents, nucleoside analogs, rituximab, and combination therapies are the current frontline therapies for WM. Several salvage therapies are available, but they do not yield cure; therefore, new agents must be developed. Because primary care providers and oncology nurses play a pivotal role in the care of patients with WM, they must recognize hyperviscosity syndrome and mediate immediate intervention. Oncology nurses also need to stay current on new and emerging therapies for WM.

**Author Contact:** Ellen C. Mullen, RN, ANP, GNP, can be reached at ecatuiza@mdanderson.org, with copy to editor at CJONEditor@ons.org.

**References**


