Multiple Myeloma and Waldenstrom’s Macroglobulinemia

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Cover Illustration by Christine Schaar

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INTRODUCTION

Multiple myeloma, which accounts for approximately 10% of hematologic malignancies, is a disease of plasma cells involving bone and bone marrow. It is characterized by the increased production of monoclonal immunoglobulin. The disease can produce skeletal problems (including pathologic fractures), bone marrow failure (often limited to anemia), renal failure, and an increased risk of infection. The median age at diagnosis is in the seventh decade. With the exception of younger patients treated with allogeneic transplantation, therapy is palliative rather than curative. Median survival is approximately 3 years when patients are treated with chemotherapy. Autologous stem cell transplantation apparently increases median survival by 18 to 24 months, but there is no evidence that autologous transplantation can produce cures.

CASE REPORT: INITIAL PRESENTATION

A 58-year-old man seeks medical attention because of low back pain and pain in the left hip. Past medical history is positive only for hypertension, for which he takes an angiotensin-converting enzyme inhibitor. Physical examination is unrevealing. Radiographs reveal osteopenia of the lumbar spine and a possible lytic lesion of the left pubic ramus. A number of blood tests are obtained. The hematocrit is 36%. The leukocyte count is $8.4 \times 10^3/\text{mm}^3$ with a normal differential. The platelet count is $185 \times 10^3/\text{mm}^3$. The erythrocyte morphology on the peripheral smear is normal. The serum sodium, potassium, chloride, and bicarbonate levels are within normal limits. The blood urea nitrogen level is 42 mg/dL, and the serum creatinine level is 2.9 mg/dL.

Because of the patient’s anemia, skeletal findings, and renal dysfunction, myeloma is suspected. A bone
marrow biopsy is performed, which shows 50% plasma cells. The cells are positive for kappa light chain but do not stain for IgG, IgM, or IgA. A serum protein electrophoresis is performed and shows hypogammaglobulinemia and no evidence of an M-spike. IgG, IgA, and IgM levels are all decreased. However, a 24-hour urine collection shows a marked increase in monoclonal kappa light chains, with a total light chain excretion of 1.5 g in 24 hours.

- Is the patient’s clinical picture diagnostic for multiple myeloma?
- Why is there no serum M-spike in this patient?

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF MYELOMA**

**CRITERIA FOR DIAGNOSIS**

Diagnosis of multiple myeloma requires bone marrow plasmacytosis with greater than 30% plasma cells and a serum monoclonal globulin spike: 3500 mg/dL for IgG, 2000 mg/dL for IgA, or urine light chain excretion of more than 1.0 g/24 hr in the absence of amyloidosis. In approximately 60% of myeloma cases the monoclonal protein is IgG\(\lambda\) or IgG\(\kappa\); in approximately 20% of cases the monoclonal protein is IgA\(\lambda\) or IgA\(\kappa\); in approximately 20% of cases, the myeloma is associated with the production of lambda or kappa light chains only. Fewer than 1% of cases of myeloma are associated with IgD or IgE, or are nonsecretory. Monoclonal gammopathies of IgM are generally classified as Waldenstrom’s macroglobulinemia rather than myeloma; the clinical picture is generally dominated by problems caused by serum hyperviscosity rather than those usually seen in myeloma.

Because light chains have a low molecular weight and are filtered at the glomerulus, patients with light chain—only myeloma do not have a serum monoclonal spike and may actually have decreased serum globulin levels. Monoclonal light chains will, however, be present in the urine in these cases.

Patients with increased numbers of marrow plasma cells in whom the monoclonal IgG or IgA spike does not meet the quantitative criteria for myeloma (or in whom the plasma cells bear IgD or IgE, for which established quantitative criteria do not exist) may be diagnosed as having multiple myeloma if lytic bone lesions are present. However, although lytic bone lesions, anemia, and renal dysfunction may suggest the diagnosis of myeloma, one must remember that metastatic malignancies such as lung cancer, breast cancer, and prostate cancer can also produce skeletal lesions. In the absence of lytic bone lesions, patients with monoclonal serum or urine proteins that do not meet quantitative criteria for myeloma are regarded as having monoclonal gammopathy of unknown significance (MGUS). This condition was previously called benign monoclonal gammopathy, but the term MGUS is more appropriate because approximately 10% of such patients will prove to have myeloma within 10 years of follow-up, and 15% to 20% of patients may have myeloma in 20 years of follow-up.

In patients who may have either myeloma or MGUS, the level of the “uninvolved” globulins may provide a hint as to the eventual diagnosis. In patients with a borderline elevated monoclonal IgG or IgA, an IgM level of less than 50 mg/dL suggests a diagnosis of myeloma. Similarly, in a patient with IgA monoclonal gammopathy, an IgG level of less than 600 mg/dL suggests a diagnosis of myeloma.

**STAGING OF MYELOMA**

Complicated formulae have been devised to calculate the total body tumor burden in patients with myeloma. However, a simplified staging model that considers the hemoglobin level, the serum calcium level, the extent of skeletal disease, and the quantity of serum or urine monoclonal protein is generally used (Table 1). Advanced stage, diminished renal function, increased \(\beta_2\) microglobulin, and dysplastic cell morphology are each associated with diminished survival.

**CLINICAL FEATURES OF MYELOMA**

- Are the patient’s radiographic findings consistent with a diagnosis of myeloma?
- What is the likely basis of renal failure in this patient?

**BONE DISEASE**

Myelomatous involvement of the skeleton most commonly affects the spine, ribs, sternum, clavicles, skull, pelvis, femurs, and humeri. Disease distal to the knees or elbows is uncommon. Back pain is common with myeloma, and progressive compression fractures may cause a loss of several inches in height during the course of the disease. Bone pain may be insidious in nature or may manifest acutely from a pathologic fracture.

Bone resorption in myeloma appears to be mediated by activation of osteoclasts, but the exact cellular mediators of this phenomenon have not been completely elucidated. Lytic lesions are seen radiographically in
nearly all cases of myeloma. These lesions classically appear as round, “punched-out” areas. Sclerotic reactions to these lytic lesions and new bone formation are generally not seen. Approximately 2% of myeloma cases are associated with osteosclerotic lesions. These osteosclerotic lesions in myeloma are commonly associated with the POEMS syndrome—Polyneuropathy, Organomegaly (hepatosplenomegaly, lymphadenopathy), Endocrinopathy (gonadal dysfunction, diabetes, hyperprolactinemia, hypothyroidism), Monoclonal gammopathy, and Skin changes (hyperpigmentation, scleroderma-like thickening, hypertrichosis, clubbing, and Raynaud’s phenomenon).

Lesions nearly always occur multiply, hence the name multiple myeloma; however, approximately 5% of cases of plasma cell myeloma present as solitary plasmacytoma of bone (SPB). SPB is diagnosed when a solitary bone lesion shows plasma cells, the skeletal survey is otherwise negative, a random bone marrow biopsy shows no evidence of myeloma, and there are no complications of myeloma such as renal failure, hypercalcemia, or anemia.

Treatment for lytic lesions consists of local radiotherapy; clinical studies have not established a role for adjuvant chemotherapy. Even when a skeletal survey and bone marrow examination fail to reveal evidence of a disseminated disorder, approximately 70% of cases of apparent SPB evolve to multiple myeloma during 5 to 10 years of follow-up. Recently, magnetic resonance imaging (MRI) has been advocated as a means of staging SPB. Data using this approach is limited. However, in 1 study, MRI revealed evidence of disseminated disease in one third of patients who would otherwise have been classified as SPB. Furthermore, in contrast to the 70% incidence of evolution to myeloma reported in older series, only 1 of 7 cases of SBP and negative results on MRI evolved to multiple myeloma.

RENAL DISEASE
Renal dysfunction is a common clinical feature of multiple myeloma. Nearly half of patients are found to have some degree of renal dysfunction at diagnosis. Renal dysfunction is most frequent in patients with IgD myeloma and occurs in more than half of cases of light chain myeloma. Renal dysfunction is slightly more frequent in patients with IgA myeloma than in those with IgG myeloma.

A number of factors contribute to renal failure in myeloma. The filtration of light chains at the glomerulus, leading to tubular damage, is the major cause of renal dysfunction in myeloma. Hypercalcemia, hyperuricemia, recurrent pyelonephritis, and the use of nonsteroidal anti-inflammatory drugs may also contribute to renal failure in myeloma. The Fanconi syndrome may occur in patients with myeloma and includes a type 2 renal tubular acidosis with increased loss of glucose and amino acids in the urine along with a defect in the ability of the kidney to excrete acid or concentrate the urine. The diagnosis of Fanconi’s syndrome may precede the diagnosis of myeloma.

INFECTION
Infection is the major cause of death in myeloma, and the clinical course of many myeloma patients is characterized by recurrent episodes of infection. Although myeloma is associated with an increase in total serum globulin, the increase is in monoclonal globulins, and levels of functional immune globulins are decreased. For this reason, patients with myeloma are similar to patients with hypogammaglobulinemia and are at increased risk for both gram-positive and gram-negative infections. T-cell defects have been identified in myeloma, but their role in increased infections in myeloma is not well established.

The catabolism of immune globulins is proportional to the square of the concentration of the specific

### Table 1. Staging of Multiple Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All of the following:</td>
</tr>
<tr>
<td></td>
<td>- Hemoglobin level &gt; 10 g/dL</td>
</tr>
<tr>
<td></td>
<td>- Serum calcium level normal (≤ 12 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>- Normal bone structure or solitary plasmacytoma on radiograph</td>
</tr>
<tr>
<td></td>
<td>Low M component:</td>
</tr>
<tr>
<td></td>
<td>- IgG &lt; 5000 mg/dL</td>
</tr>
<tr>
<td></td>
<td>- IgA &lt; 3000 mg/dL</td>
</tr>
<tr>
<td></td>
<td>- Urine light chains &lt; 4 g/24 hr</td>
</tr>
<tr>
<td>II</td>
<td>Not meeting criteria for either stage I or stage III</td>
</tr>
<tr>
<td>III</td>
<td>One or more of the following:</td>
</tr>
<tr>
<td></td>
<td>- Hemoglobin level &lt; 8.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>- Serum calcium level &gt; 12 mg/dL</td>
</tr>
<tr>
<td></td>
<td>- Extensive skeletal destruction on radiograph</td>
</tr>
<tr>
<td></td>
<td>High M component:</td>
</tr>
<tr>
<td></td>
<td>- IgG &gt; 7000 mg/dL</td>
</tr>
<tr>
<td></td>
<td>- IgA &gt; 5000 mg/dL</td>
</tr>
<tr>
<td></td>
<td>- Urine light chains &gt; 12 g/24 hr</td>
</tr>
</tbody>
</table>

Sources:
1. Renal dysfunction is a common clinical feature of multiple myeloma. Nearly half of patients are found to have some degree of renal dysfunction at diagnosis. Renal dysfunction is most frequent in patients with IgD myeloma and occurs in more than half of cases of light chain myeloma. Renal dysfunction is slightly more frequent in patients with IgA myeloma than in those with IgG myeloma.
2. A number of factors contribute to renal failure in myeloma. The filtration of light chains at the glomerulus, leading to tubular damage, is the major cause of renal dysfunction in myeloma. Hypercalcemia, hyperuricemia, recurrent pyelonephritis, and the use of nonsteroidal anti-inflammatory drugs may also contribute to renal failure in myeloma. The Fanconi syndrome may occur in patients with myeloma and includes a type 2 renal tubular acidosis with increased loss of glucose and amino acids in the urine along with a defect in the ability of the kidney to excrete acid or concentrate the urine. The diagnosis of Fanconi’s syndrome may precede the diagnosis of myeloma.
immune globulin type. Therefore, in IgG myeloma replacement of immune globulin is not clinically feasible. Replacement of immune globulin has not been extensively studied in IgA myeloma or in light chain–only myeloma.

NEUROLOGIC COMPLICATIONS

Extradural compression of the spinal cord is the most critical neurologic complication of myeloma. Patients may present with radicular pain. Sensory or motor deficits—which may progress to paraplegia—are late signs that can rapidly become irreversible. After 24 hours, the chance of reversing paraplegia is small; therefore, early evaluation of neurologic dysfunction by computed tomographic scanning or MRI is essential in patients with myeloma.

Treatment of cord compression by radiotherapy or surgical decompression is essential if neurologic function is to be restored. However, it is not clear which approach is superior. When cord compression results from massive vertebral collapse and the spinal cord is compressed by bony fragments, neurosurgical intervention is likely to produce superior results. Direct compression of the spinal cord by tumor may respond to either modality.

Amyloidosis may occur in myeloma and is associated with carpal tunnel syndrome as well as with a progressive sensorimotor polyneuropathy. This polyneuropathy may also occur independent of amyloidosis. This neuropathy is usually sensory and autonomic and tends to be progressive.

UNUSUAL CLINICAL EFFECTS OF MONOCLONAL PROTEINS

Some myeloma proteins have the characteristics of cryoglobulins—that is, they undergo reversible precipitation at low temperatures. Cryoglobulins may produce acrocyanosis, tingling, numbness, or Raynaud’s phenomenon. Cryoglobulins are usually complexes of IgG and IgM (ie, mixed cryoglobulins); whenever a monoclonal cryoglobulin is found, the diagnosis of multiple myeloma should be considered.

Although hyperviscosity is generally associated with Waldenstrom’s macroglobulinemia, markedly elevated levels of IgG or IgA may also produce symptoms of hyperviscosity. In rare cases, myeloma proteins may act as anticoagulants by means of binding to coagulation factors, or, more commonly, by binding to platelets and decreasing platelet function. Myeloma proteins that interact with factors V, VII, VIII, II (prothrombin), and I (fibrinogen) have been described. These myeloma proteins have the characteristic pattern of inhibitors; that is, abnormal coagulation states do not correct when plasma from a patient with an inhibitor is mixed with normal plasma.

Amyloidosis, which can be a complication of myeloma, has been associated with acquired factor X deficiency, presumably as a result of increased binding of factor X to tissue deposits of amyloid. Unlike the coagulation dysfunction associated with myeloma, however, that associated with factor X deficiency corrects in vitro when mixed with normal plasma. (Unfortunately, in vivo, the factor X deficiency does not correct as easily, as added factor X is rapidly eliminated, presumably as a result of binding to tissue amyloid.)

LABORATORY FINDINGS

- Are the normal leukocyte and platelet counts in the presence of marrow involvement seen in the patient presented unusual in myeloma?

BLOOD CELL FINDINGS

Patients with myeloma often have an anemia that is normochromic and normocytic, although rouleaux formation may be present. The anemia is generally moderate (ie, a hematocrit between 25% and 30%) and the reticulocyte count is generally low. An artificially elevated mean corpuscular volume of greater than 130 µm³ may be present in some patients with myeloma as in other patients with elevated globulins. This occurs because erythrocytes may agglutinate in the particle counter in the presence of a monoclonal protein. As a result, the erythrocyte count is underestimated, and the mean volume per cell is thereby overestimated. Other causes of macrocytosis (ie, folate deficiency or B₁₂ deficiency) need to be ruled out in this setting.

The anemia of myeloma is multifactorial. Contributors include renal failure and the replacement of marrow cells with plasma cells. In addition, the anemia of chronic disease may be present. It is therefore not surprising that anemia in myeloma patients may respond to recombinant human erythropoietin.

The total leukocyte count and platelet count are almost always normal at presentation in myeloma, although neutropenia and thrombocytopenia may occur as a consequence of chemotherapy. Marked elevation of circulating plasma cells (ie, plasma cell leukemia) is a rare manifestation of myeloma. Immature plasma cells may be noted in the blood of patients with myeloma if a buffy coat preparation is examined or if flow cytometry is performed. Plasma cells in myeloma stain for CD38 and CD45. However,
unlike in other B-cell neoplasms (eg, chronic lymphocytic leukemia, follicular lymphoma), CD20 is not present in myeloma, rendering rituximab and other antibodies to CD20 irrelevant in the therapy of myeloma.

BONE MARROW FINDINGS

Bone marrow involvement is essential for the diagnosis of myeloma. The diagnosis generally requires that sheets of plasma cells or focal collections of plasma cells be identified in the marrow. When plasma cells comprise 30% of bone marrow cells, it is usually easy to identify such focal collections of plasma cells. When only 10% to 20% of the marrow is composed of plasma cells, however, even if the cells are monoclonal, clumps of plasma cells are rarely seen. In that situation, confirmatory evidence such as lytic bone lesions or a very elevated monoclonal protein level must be present to make the diagnosis of myeloma.

SERUM AND URINE FINDINGS

Nearly all cases of myeloma are associated with the presence of monoclonal proteins in either the serum, the urine, or both. In the 20% of myeloma cases characterized by the production of only light chains, the light chains are observed in the urine only. However, in cases of IgG and IgA myeloma, in which complete immunoglobulin molecules are found in the serum, free light chains may also be found in the urine. One must remember, however, that the standard urine dipstick test for protein is actually a specific test for albumin and does not reflect the absence or presence of light chains. For this reason urine protein electrophoresis, rather than a test for urine protein, is a necessary part of the baseline evaluation in myeloma.

Biclonal gammopathies may occur in up to 2% of cases of myeloma. In some cases, 2 separate populations of cells are involved, whereas in other cases, double staining of single cells is observed.

CLINICAL CORRELATES OF MYELOMA PROTEINS

A number of specific clinical correlates with specific myeloma proteins have been described. IgA myeloma has a higher incidence of hypercalcemia than other types of myeloma. Also, because IgA may form multimers, IgA myeloma may also be associated with the hyperviscosity syndrome that is generally associated with IgM myeloma. IgD myeloma is often associated with hepatosplenomegaly, lymphadenopathy, extraosseous lesions, renal failure, and hypercalcemia. Patients with light chain myeloma have the highest incidence of renal failure, as well as a high incidence of severe bone disease, hypercalcemia, and amyloidosis.

TREATMENT OF MYELOMA

- Is therapy necessary in the patient presented? If so, should the lytic lesion be treated with radiation therapy prior to beginning chemotherapy?
- What supportive measures are appropriate in addition to chemotherapy?

CHEMOTHERAPY

Initial Chemotherapy

Systemic chemotherapy is the treatment of choice in myeloma. However, because therapy is generally palliative, therapy may be delayed in asymptomatic stage I patients. This fact makes the distinction between MGUS and early myeloma academic rather than an issue of critical clinical importance, because observation with follow-up quantitation of the monoclonal protein is a reasonable option for both disorders.

Therapy is indicated for patients with symptomatic disease or with a marked progression of the monoclonal protein. Although radiotherapy may palliate local problems, unless cord compression or fracture of a long bone is imminent, it is reasonable to administer chemotherapy for 1 or 2 cycles before making a decision to initiate radiation therapy.

Several chemotherapy regimens have been employed in multiple myeloma (Table 2). No regimen has consistently been shown to be superior in terms of overall survival, and the choice of a specific regimen may depend on the general medical condition of the patient and the overall plan (eg, the desire to proceed to stem cell transplantation).

Despite the investigation of numerous chemotherapy regimens, oral melphalan and prednisone (MP), a regimen that has been employed for 30 years, remains a rational option for initial therapy in myeloma. Melphalan is generally administered orally at a dose of 0.25 mg/kg body weight per day or 9 mg/m² body surface area per day for 4 days. Prednisone is administered orally at a dose of 1 mg/kg per day for 7 days or 100 mg per day for 4 days. Treatment is repeated every 4 weeks as tolerated; many older patients require an interval of every 6 weeks or longer. The melphalan dose should be reduced by 50% in the presence of renal failure.

Criteria for response in myeloma are not rigidly established, leading to great difficulty in evaluating response rates. If response is defined as a 50% decrease in the monoclonal protein level, response rates to MP may be greater than 60%. The major toxicity of the regimen
is myelotoxicity, which may require chemotherapy cycles to be delayed.

High-dose dexamethasone is another regimen that is effective in myeloma and is easily administered on an outpatient basis. The drug is usually given at a dose of 40 mg per day or 20 mg/m² per day, and is given on days 1 to 4, 9 to 12, and 17 to 20 of a 4-week cycle. The major complications of dexamethasone therapy are decreased glucose tolerance and increased risk of infection. Patients who have type 2 diabetes may require insulin when placed on this regimen.

Although dexamethasone may be given as a single agent, it is often given in conjunction with vincristine and doxorubicin (Adriamycin) as part of the VAD regimen. The usual regimen includes vincristine 0.4 mg per day and doxorubicin 9 mg/m² per day, with both drugs given as an intravenous continuous infusion for 4 days. This regimen generally requires hospitalization for convenience of administration. Although the VAD regimen has not been proven to produce higher response rates or superior survival as compared to the MP regimen, it can produce more rapid responses than MP. This may be important in myeloma patients with renal failure or hypercalcemia. Additionally, if the overall plan is to proceed to autologous stem cell transplantation, VAD may lead to a quick diminution of the tumor burden without producing marrow damage and without compromising the ability to harvest adequate numbers of stem cells.

The usual policy in myeloma is to administer a fixed number of cycles of therapy, such as 12 cycles of MP or 6 cycles of VAD, in hopes of achieving a response. Further maintenance cycles do not increase survival over what can be obtained with reinstitution of therapy at the time of disease progression. Additionally, chronic administration of chemotherapy can increase the risk of producing a secondary myelodysplastic syndrome or acute leukemia. Thirty years ago, when the most common clinical plan was the daily administration of melphalan, the 5-year survival was approximately 25%, with approximately 20% of these patients (5% overall) developing acute nonlymphoblastic leukemia. The VMCP (vincristine, melphalan, cyclophosphamide, prednisone) and VBAP (vincristine, carmustine, doxorubicin, prednisone) regimens for initial chemotherapy are also shown in Table 2.

Salvage Chemotherapy

Any of the regimens in Table 2 that are not used for induction therapy are reasonable choices for salvage chemotherapy. As is generally true in the management of malignancy, drugs that have previously been used are less likely to produce a salvage response, although drugs that have produced a long first response may be considered for re-induction. Additionally, the AB regimen, consisting of carmustine (BCNU) 30 mg/m² and doxorubicin 30 mg/m², both given as intravenous bolus doses every 3 weeks, and the EDAP regimen (etoposide, dexamethasone, cytarabine, and cisplatin) are effective salvage regimens. The AB and EDAP regimens are shown in Table 3. The AB regimen has not been used frequently as primary therapy.

In addition to the chemotherapy regimens presented in Tables 2 and 3, interferon-α has been shown to produce responses in approximately 15% of patients with myeloma. However, a role for the drug in the chemotherapy of myeloma is not firmly established because interferon-α has not been proven to produce increased survival.

### Table 2. Chemotherapy Regimens Commonly Used for Multiple Myeloma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cycle Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MP</strong></td>
<td>Melphalan 9 mg/m² body surface area per day PO days 1–4&lt;br&gt;Prednisone 100 mg/day PO days 1–4&lt;br&gt;Repeat every 4–6 weeks</td>
</tr>
<tr>
<td><strong>High-dose dexamethasone</strong></td>
<td>Dexamethasone 40 mg/day PO or IV days 1–4, 9–12, 17–20</td>
</tr>
<tr>
<td><strong>VAD</strong></td>
<td>Vincristine 0.4 mg/day IV continuously days 1–4&lt;br&gt;Doxorubicin 9 mg/m² per day IV continuously days 1–4&lt;br&gt;Dexamethasone 40 mg/day PO or IV days 1–4, 9–12, 17–20&lt;br&gt;Repeat every 4 weeks</td>
</tr>
<tr>
<td><strong>VBAP</strong></td>
<td>Vincristine 1 mg/m² IV day 1&lt;br&gt;Carmustine (BCNU) 30 mg/m² IV day 1&lt;br&gt;Doxorubicin 30 mg/m² IV day 1&lt;br&gt;Prednisone 60 mg/m² per day PO days 1–4&lt;br&gt;Repeat every 3 weeks</td>
</tr>
<tr>
<td><strong>VMCP</strong></td>
<td>Vincristine 1 mg/m² IV day 1&lt;br&gt;Melphalan 6 mg/m² per day PO days 1–4&lt;br&gt;Cyclophosphamide 125 mg/m² per day PO days 1–4&lt;br&gt;Prednisone 60 mg/m² per day PO days 1–4&lt;br&gt;Repeat every 3 weeks</td>
</tr>
</tbody>
</table>

IV = intravenously; PO = by mouth.
Thalidomide has been shown to produce responses (defined as a 25% or greater reduction in monoclonal protein levels) in 32% of patients with myeloma. Because of thalidomide’s association with birth defects, use of the drug requires special precautions. However, because it is not cross-resistant with any of the other drugs used in myeloma, and because the major toxicity of the drug is fatigue, thalidomide is of interest with respect to salvage therapy.

**SUPPORTIVE CARE**

In addition to chemotherapy, patients with myeloma require several types of supportive care. Bone disease may require narcotic analgesics or radiation therapy. In randomized studies, bisphosphonates have been shown to be effective in decreasing the development of new osteolytic lesions and decreasing the occurrence of pathologic fractures. Intravenous pamidronate, 90 mg monthly, has been studied most extensively and has become part of the routine supportive care of patients with myeloma. Renal failure in myeloma may require dialysis. Although myeloma is a terminal illness, hemodialysis may improve quality of life and facilitate the delivery of chemotherapy. Anemia in myeloma, with or without renal failure, may respond to recombinant human erythropoietin 40,000 units weekly, administered subcutaneously.

Although infection is a major cause of morbidity and mortality in myeloma, prophylactic antibiotics have not been shown to be of value in myeloma. Additionally, the value of prophylactic administration of intravenous immunoglobulin has not been established.

**CASE REPORT: DIAGNOSIS AND MANAGEMENT**

The case patient is diagnosed as having multiple myeloma, light chain–only type, complicated by renal failure. He is started on the VAD chemotherapy regimen, along with pamidronate to limit bone complications, and Percocet (oxycodone and acetaminophen) for pain. Radiation therapy is not considered necessary. Four weeks after therapy is initiated, the patient returns for his second cycle of VAD and reports that his pain is markedly decreased. During the second cycle of VAD, he is slowly tapered off the Percocet.

The patient completes 4 cycles of chemotherapy. At that time, radiographs reveal that the bone disease is much improved, and the lesion in the pubic ramus has healed. A repeated 24-hour urine test reveals a marked decrease in light chains to a level of 0.3 g/24 hours. The serum creatinine has fallen to 1.2 mg/dL.

- Is this patient a candidate for autologous transplantation?

**HIGH-DOSE THERAPY WITH AUTOLOGOUS TRANSPLANTATION**

High-dose therapy in conjunction with autologous stem cell transplantation (ASCT) is based on 2 assumptions, both of which are counterintuitive in the treatment of multiple myeloma. First, ASCT is based on the assumption that high-dose therapy will produce substantial tumor reduction and increased survival; however, in the treatment of myeloma, newer combination chemotherapy regimens have not proved any more advantageous to survival than the older MP regimen. Secondly, even though myeloma is bone marrow–based, ASCT rescues patients from the effects of high-dose chemotherapy by infusing unpurged bone marrow cells or peripheral blood stem cells. Even though these cells are likely to be involved by tumor cells, the assumption is made that tumor cell contamination will not prevent ASCT from producing a clinical benefit. In this regard it is important to note that, as in most tumor models, no method of purging autologous stem cells in myeloma has been proven to produce superior results to those achieved with unpurged stem cells. Additionally, no source of stem cells (marrow or peripheral blood) has been proven to produce superior results.

Nevertheless, despite these apparent limitations, the empirical results using ASCT have been impressive. In a randomized clinical trial, patients were assigned to receive either standard therapy or high-dose therapy with ASCT. Standard therapy was 18 alternating cycles of VMCP or VBAP every 3 weeks for 12 months. High-dose

### Table 3. Salvage Chemotherapy Regimens for Multiple Myeloma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB</td>
<td>Doxorubicin 30 mg/m² body surface area IV day 1</td>
</tr>
<tr>
<td>EDAP</td>
<td>Etoposide 100–200 mg/m² per day IV continuously days 1–4</td>
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</table>

IV = intravenously; PO = by mouth.
therapy prior to stem cell transplantation was 4 to 6 cycles of VMCP or VBAP followed by administration of melphalan 140 mg/m² plus total body irradiation, 800 cGy in 4 fractions over 4 days. High-dose therapy with ASCT was associated with significantly longer event-free survival as well as overall survival. Median overall survival in patients who received standard therapy was 37 months, compared with 5 years (60 months) in patients who received high-dose therapy and ASCT. Additionally, 5 year survival was 52% in patients who underwent stem cell transplantation, as compared with 12% in patients treated with standard therapy. Because of this study, high-dose therapy with ASCT has become a routine part of initial therapy in patients with multiple myeloma.

This aggressive palliative therapy is not appropriate for all patients with myeloma, however. Although exceptions may be made, patients with myeloma are generally candidates for ASCT only in the presence of normal cardiac, pulmonary, hepatic, and renal function. Although older patients may be more likely to have characteristics that preclude transplantation, advanced age alone is not a contraindication to transplantation. In an analysis that controlled for known prognostic features, age was not a negative prognostic variable for stem cell transplantation in myeloma.

If only patients with adequate organ function are selected for ASCT, the mortality of the procedure should be less than 5%. Additionally, it is reasonable to limit transplantation to patients who have had a good response to initial chemotherapy (eg, a 50% reduction in monoclonal protein level). As in most malignancies, the best predictor of a favorable response to ASCT is a favorable response to standard chemotherapy; transplantation is of limited value in patients with refractory disease.

Ongoing studies of myeloma are investigating whether early use of ASCT produces results superior to those obtained using ASCT after disease progression. In a randomized trial, early transplantation has been associated with superior disease-free survival. Although this has been the justification for early use of stem-cell transplantation, a survival advantage of this approach has not yet been proven. Another issue under investigation is whether performing multiple transplants can produce results superior to those achieved with a single transplant.

It should be recognized that for patients with myeloma, as for most patients treated with ASCT, trials designed to determine the optimal preparative regimen have not been conducted. No specific regimen has been established as the optimal preparative regimen for stem cell transplantation, and the usual approach is to use melphalan at a dose of 140 to 200 mg/m² body surface area. Alternatively, lower doses of melphalan within this range may be used in conjunction with total body irradiation.

**ALLOGENEIC TRANSPLANTATION**

In contrast to autologous transplantation, which is considered palliative therapy because it carries the risk of reinfecting myeloma cells, allogeneic transplantation represents potentially curative therapy for younger myeloma patients with a matched related donor. Unfortunately, toxicity of allogeneic transplantation in patients with myeloma has been higher than expected, with mortality rates of 40% to 50% in some series. Nevertheless, allogeneic transplantation can produce complete remissions in patients with multiple myeloma, and up to 40% of patients who receive transplants may survive more than 5 years. Although some long-term survivors of allogeneic transplantation have evidence of persistent myeloma, recent studies using polymerase chain reaction techniques have documented long-term disease-free status in some myeloma patients undergoing allogeneic transplantation. Thus, cure may indeed be possible with this approach. Nevertheless, in view of the average age of patients with myeloma and the high morbidity and mortality associated with allogeneic transplantation, the ultimate role of allogeneic transplantation in the treatment of patients with myeloma has not yet been established.

**CASE REPORT: FURTHER TREATMENT AND CLINICAL COURSE**

The patient was considered a good candidate for ASCT based on the good response to chemotherapy and the improvement in renal function as compared to baseline. An evaluation of organ function was undertaken. Pulmonary function, including diffusion capacity of the lung for carbon monoxide, was normal. The cardiac ejec tion fraction was 55%. Serum levels of bilirubin, aspartate aminotransferase, and alkaline phosphatase were normal. The patient underwent stem cell collection after receiving cyclophosphamide and filgrastim, and underwent stem cell transplantation following administration of melphalan 100 mg/m² per day for 2 days. The post transplant course was complicated by fever during the period of neutropenia, but with standard supportive care, the patient had engrafted by day 14 and was discharged from the hospital on day 17. Interferon was administered for 1 year following the transplant. The patient continued to do well 2 years after ASCT. However, at his 2-year evaluation, the bone marrow examination showed 15% plasma cells, and the 24-hour urine collection showed an increase in kappa light chains suggesting early relapse.
WALDENSTROM’S MACROGLOBULINEMIA

Waldenstrom’s macroglobulinemia (WM) is a neoplasm characterized by proliferation of plasmacytoid lymphocytes. It is associated with elevated levels of monoclonal IgM. The disease is about one-tenth as common as myeloma. The distinction between WM and MGUS associated with IgM is difficult to make, and absolute criteria have not been established. In general, however, patients with an IgM level greater than 3000 mg/dL are almost always symptomatic, and that level can be taken as the general level at which WM can be considered to be present. The median age of patients is 65 years, and the median survival is 5 years.

CLINICAL FEATURES

In contrast to multiple myeloma, bone lesions are rare in WM, occurring in fewer than 2% of patients. One third of patients present with lymphadenopathy and/or hepatosplenomegaly. Peripheral neuropathy occurs in approximately 5% of patients with WM and is generally caused by infiltration of myelin sheaths by monoclonal IgM. In contrast to myeloma, renal disease is quite uncommon in WM, even when light chains are present in the urine, as occurs in approximately one fourth of cases.

A major clinical problem in WM is the hyperviscosity syndrome, which is related to circulatory disturbances caused by resistance to blood flow. The monoclonal IgM is a large pentameric molecule and, as a result, diminishes the velocity of blood flow. A variety of symptoms of hyperviscosity may be present, including headaches, dizziness, vertigo, deafness, cardiac failure, Raynaud’s phenomenon, livedo reticularis, and peripheral gangrene. Nonspecific symptoms (eg, weakness, fatigue, anorexia) may also be present. In terminal stages of WM, markedly elevated viscosity may cause neurologic symptoms to progress to stupor, coma, and seizures. In a small minority of cases, the monoclonal IgM has the characteristics of a type I cryoglobulin.

Symptoms in WM are related to serum viscosity. The relative viscosity of normal serum, compared to water, is between 1.4:1 and 1.8:1. Patients with a relative viscosity of 2 to 4 are rarely symptomatic. Most patients with a relative viscosity between 4 and 8 are symptomatic, and nearly all patients with a relative viscosity greater than 8 are symptomatic.

Relative viscosity is a measure of plasma viscosity only; however, in vivo, the whole blood viscosity—which is also affected by the hematocrit and cell-protein interactions—is the parameter that is of clinical importance. In this regard, it should be noted that anemia lowers the whole blood viscosity, and therefore, unless a life-threatening anemia is present, patients with WM should not be transfused with packed erythrocytes until the IgM level has been reduced by plasmapheresis or by chemotherapy.

LABORATORY FINDINGS

Anemia is usually present in WM, but neutropenia and thrombocytopenia are rare until the later stages of the disease. Rare plasmacytoid lymphocytes may be seen in the peripheral blood early in the course of the disease. In terminal stages of the disease, marked increases in such cells may be seen. The blood smear is usually normochromic and normocytic, although rouleaux formation is often present, especially if the viscosity is markedly elevated.

The bone marrow in WM shows an increase in the numbers of plasmacytoid lymphocytes in nearly all cases. The morphology is variable: in some cases, the cells resemble those characteristic of chronic lymphocytic leukemia, whereas in other cases, the morphology is more plasmacytic.

TREATMENT

Because the vast majority of IgM is confined to the intravascular space, most patients with WM respond to plasmapheresis. Generally, about one half of the plasma volume must be removed to significantly decrease the serum viscosity. Plasmapheresis is usually performed every 2 weeks, although more frequent treatment may be used to lower an extremely high viscosity.

Plasmapheresis is often used to control symptoms of hyperviscosity, whereas chemotherapy is generally used to lower the tumor burden in WM. Drugs used to treat low-grade non-Hodgkin’s lymphoma (ie, chlorambucil, alkylating agents with prednisone, and fludarabine) are most commonly employed. The nucleoside analogue cladribine has also been shown to be effective in the treatment of WM. Response rates in the range of 50% to 75% are to be expected, with higher response rates in previously untreated patients. In contrast to myeloma, cells in WM may express surface CD20, making rituximab a rational therapy for this disease. When rituximab is used, responses may be delayed and may not occur until 4 to 8 weeks after completing therapy.

Randomized studies have not been conducted to define the optimal therapy in this disease, which is generally treated with palliative intent. Regardless of therapy, complete remissions are rarely achieved; when remission is achieved, however, it may be associated with a survival in excess of 10 years.
ASCT has been employed in patients with WM. However, because the disease occurs much less frequently than myeloma, large-scale trials to demonstrate the value of ASCT in WM have not been conducted, and therefore the role of ASCT in the management of WM has not been defined. The data regarding allogeneic transplantation are extremely limited, and in view of the average age of patients with WM, it is not a frequent clinical consideration.

REFERENCES