MULTIPLE MYELOMA IDENTIFICATION IN PRIMARY CARE

By

DEBBIE COURTNEY ANDERSON

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To the Faculty of Washington State University:

The members of the Committee appointed to examine the manuscript of DEBBIE COURTNEY ANDERSON find it satisfactory and recommend that it be accepted.

Chair: Lorna Schumann, PhD, RNCS, NP-C, ARNP, CCRN

Billie Severtsen, PhD, RN

Merry Armstrong, DNSc, ARNP, CNS

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IN PRIMARY CARE

Abstract

by Debbie Courtney Anderson, B.S.N.
Washington State University
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Chair: Lorna L. Schumann

Multiple myeloma is a complex disease process that has a variety of presenting symptoms. It is the most common bone cancer found in the adult, therefore it is important that primary care practitioners be able to notice the subtle physiologic changes that occur in multiple myeloma. Recent discoveries are providing hope for those who are inflicted with this incurable disease. Investigators continue to search for causes, factors that may promote tumor growth, and ways to decrease the suffering of multiple myeloma patients. This manuscript reviews research on multiple myeloma, in addition to identifying current diagnostic and treatment protocols.

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Dedication

This paper is dedicated to my mother-in-law,

Margaret Ruth Stakes Anderson.

She passed away in 1975 from the effects of multiple myeloma.

I wish I could have known her better.

Identification of Multiple Myeloma in the Primary Care Setting

Introduction

Multiple myeloma belongs to a cluster of disease entities classified under the term monoclonal gammopathies or M-protein proliferation. It is the most common neoplastic bone disorder in adults, and comprises almost 1% of all non-skin malignancies in the United States (Kyle, 2000). Discovered in the mid 1800's, multiple myeloma has proved to be a complex and involved cancer that continues to challenge many of our greatest scientists. In 1873, Rustizky introduced the term "multiple myeloma" to explain the presence of multiple tumors found in the bone (Durie, 1996). Since then, scientists have made it their passion to find a cure for this unique disease. Table 1 lists many of the historical milestones of multiple myeloma. The primary care nurse practitioner should be aware of the many symptoms of multiple myeloma and hold a high index of suspicion in select populations. Nurse practitioners need to identify the possibility of multiple myeloma and make timely referrals to an oncologist for definitive diagnosis. The purpose of this article is to provide an overview of information that may assist the nurse practitioner in the recognition, diagnosis, and treatment for multiple myeloma.

Epidemiology

Multiple myeloma is a complex and incurable disease that presents with a spectrum of localized and diffuse symptoms, scattered throughout various organ systems (Leeson, 2001). Approximately 30% of patients are diagnosed incidentally while being evaluated for other problems, while another 10% are found to have the disease after a pathologic fracture (George & Sadovsky, 1999). There are few confirmed cases of multiple myeloma in people under 25, as the majority of cases are discovered in patients between 70 and 80 years old (Hernandez, Land, & McKenna, 1994). Each year there are 13,500 new cases of multiple myeloma in the United

States, or around 4 per 100,000. Blacks have twice the occurrence as whites (Durie, 1996).

Etiology

There is no known etiology for multiple myeloma, but scientists speculate that environmental factors, radiation, heredity, and viral disease may be potential malignancy producing agents. Table 2 highlights a list of possible risk factors. Studies continue to negate the effect of environmental exposure, however, length of exposure to carcinogenic agents has been linked to an increased risk (Bourguet & Logue, 1993). If the etiology of multiple myeloma can be isolated, a cure may not be far away.

Hereditary Factors

A familial link to multiple myeloma was discovered by Deshpande, Hu, Marino, Jan, & Wiernik (1998). Their study of 6 parent-child pairs and 20 previously reported cases, strengthened assumptions that offspring had an earlier occurrence and a more serious case of multiple myeloma. The phenomenon of *anticipation*, or the similarity in the amplification of genetic sequences, can be passed from generation to generation (Deshpande et al., 1998). *Anticipation* may be responsible for a 17 to 19 year earlier presentation of myeloma in the children patients diagnosed with multiple myeloma. For example, a mother may have myeloma at age 72, while her son may be found to have the disease at 55. Deshpande et al., (1998) stated that improved diagnostic and treatment protocols, occurring over the past 20 years, may have made their study biased.

Radiation Exposure

An epidemiological study by Wing et al., (2000) investigated and measured the relationship between whole body radiation exposure and multiple myeloma. Information concerning the age at time of exposure, and amount of total body exposure, was collected from

four Department of Energy facilities for this retrospective study. Unlike prior research, Wing et al. (2000) made adjustments for such factors as, previous work-related exposure, and employee fitness. Those employees exposed during World War II had the highest rate of myeloma. Wing et al. speculated that those employed during WWII were less physically fit than those employed during other years. Age at time of exposure was found to be the single most common variable leading to a diagnosis of multiple myeloma. A decline in the immune response of older workers was believed to be the reason for higher rates of myeloma.

Environmental Factors

Links between occupational exposure and multiple myeloma continue to be controversial. Benzene, a natural particle found in petroleum products, has been most widely studied (Bergsagel et al., 1999). Cigarette smoke is another source of benzene exposure. Wong, Trent, & Harris (1999), performed a nested case-controlled study of data gathered from various cohort investigations. Approximately 18,000 petroleum distributors and truck drivers who had been exposed to products that contained 2% - 3% benzene, where studied. Despite the high degree of benzene exposure, there was no measurable increase risk of multiple myeloma.

Farm workers and food processors may have an increase risk of developing multiple myeloma. In a case controlled study, Cuzick & De Stavola (1988), interviewed 399 patients who had myeloma, plus a comparative number of matched controls. Farm chemicals used in the production of food was thought to contribute to the higher levels of multiple myeloma found in these two groups of workers.

Prolonged use of dark hair dye has long been associated with various forms of cancer, including multiple myeloma. Altekruse, Henley, & Thun (1999), performed a prospective self-report study of thousands of women. Death rates from cancers, including multiple myeloma,

were not reliably increased in those women who used hair dye of any color. In a recent literature review by Correa, Jackson, Mohan, Perry, & Helzlsouer (2000), such factors as duration of use, frequency, or age at first exposure to hair dye showed no appreciable increase in risk. Since millions of people use hair dye, hypothetical connections between multiple myeloma and hair dye should continue to be queried.

Autigenic Stimulation

In 1993, Bourguet and Logue performed a prospective study of 14,407 people. Four risk factors: (a) allergies, (b) autoimmune conditions, (c) chronic bacterial conditions, and (d) inflammatory conditions were used to investigate the possible connection between autigenic stimulation and an increased risk of multiple myeloma. As inflammatory conditions increased, so did the cases of multiple myeloma. There appears to be an increase in relative risk, if patients had an autoimmune disease for 5 or more years.

Biologic Aspects of Multiple Myeloma Cells

The human body requires a vast array of host defense immunoglobulins (Ig) to protect against a multitude of infectious organisms. The primary function of B-cells is to secrete a heterogeneous sampling of immunoglobulin (Ig). Multiple myeloma is a disease process where one type of Ig predominates over other types.

B-Cells

Multiple myeloma plasma cells are born from a single clone of immunoglobulin-secreting plasma cells of the B-cell lymphocyte series. Ordinarily, there is ". . . great diversity of normal immunoglobulins, however in monoclonal gammopathies, a single abnormal cell line predominates . . ." (Attaelmannan & Levinson, 2000, p. 1231). Approximately 50% of multiple myeloma patients have an abnormal karyotype on their gene sequence, with single or

combination defects on certain chromosomes (George & Sadovsky, 1999). The myeloma plasma cell travels to the bone marrow and establishes itself within the marrow. The malignancy adheres to stromal cells, while interfering with bone's structural physiology. Nawawi, Samason, Apperley, & Girgis (1996), documented the probability that osteoclast activity is tightly regulated by a balance of cytokines, especially interleukin-6 (IL-6). An increase in IL-6, directly caused by an increase in multiple myeloma plasma cells, leads to an increase in osteoclast resorption on the bone surface. Greater resorption creates the classic bony lesions found in multiple myeloma. Van Riet and associates (2000), at the Free University in Brussels, Belgium, are attempting to explain why myeloma cells travel to, and remain primarily in the marrow. Van Riet's hypothesis questions the influence of adhesion molecules as magnets for myeloma cell binding to bone marrow endothelial cells. He also wants to know whether chemotactic factors influence this migration (Van Riet as cited in Durie, p. 2).

Mutant forms of B-cells found in multiple myeloma undergo immunologic changes within the marrow. This change leads to an altered cell clone that proliferates, producing the classic multiple myeloma marker, or myeloma protein (M-protein). Occasionally, some of the altered B-cell clones are found circulating in the peripheral blood stream. Identification of these cells could be an early marker for multiple myeloma (Pilarski & Belch, 1997). Table 3 identifies several growth factors that support the proliferation and retention of myeloma cancer. Treatment protocols focus on altering these factors in order to obtain optimum myeloma cell destruction.

Monoclonal Protein

Monoclonal proteins (M-Proteins) are secreted by a single clone of immunoglobulin secreting homogeneous B-cells (Kyle, 2000, p. 977). Each M-protein consists of two heavy (H) polypeptide chains and two light (L) polypeptide chains (see Figure 1). Changes in gene

expression within the constant regions of the heavy and light chain determine the immunoglobulin, or Ig classification of B-cell lymphocytes. These changes also determine the protein's biological properties (see Table 4). The majority of multiple myeloma patients have a proliferation of IgG class M-proteins within the bone marrow. A variety of physical symptoms can appear once the percentage of IgG monoclonal proteins increases.

Clinical Presentation

Bone destruction, renal disease, and infection, are the three major symptom areas affected by multiple myeloma. Increased levels of M-proteins can have varying degrees of harmful effects on several body systems. Nurse practitioners need to be aware of the variety of symptoms, as well as their target organs (see Figure 2).

Bone Involvement

Severe, sudden back pain may be the first sign of a vertebral fracture caused as a result of myeloma bone damage. Vertebral fractures occur in two-thirds of patients with multiple myeloma (Burton, Fairham, Millet, DasGupta, & Sivakumaran, 1998). If a patient presents with acute or chronic bone pain, the practitioner should have a high index of suspicion of multiple myeloma. Decreased bone density and hypercalcemia are usually found with initial presentation of bone symptoms (McConnaghey, Thornton, & Wu, 1999). Radiographs of the skull, spine, pelvis, and long bones, remain the gold standard for identification of bone lesions according to Woolfenden, Pitt, Durie, & Moon, (1980).

Infection

Infections occur frequently with myeloma patients. Increases in IgG immunoglobulins, coupled with a decrease in the initial infection responders, IgA and IgM, allow bacteria to gain a stronghold (Vescio & Berensen, 2000). As multiple myeloma progresses, and/or chemotherapy

is initiated, white blood cell counts decrease, adding to a decline in the immune response. Most infections are caused by encapsulated bacteria such as *Streptococcus pneumoniae* that often attack the lungs and sinuses. Indwelling catheters, placed for chemotherapy, are common sites for staphylococci infection (Vescio & Berenson, 2000). Prednisone administration, one of the treatment options for multiple myeloma, has immunosuppressive effects that blunt the immune response.

Renal Disease

Bence Jones proteins (BJP), present in the urine with multiple myeloma, may lead to renal damage or complete renal failure in a variety of ways (see Figure 2). Approximately 48% - 77% of multiple myeloma patients have kidney damage (Rodriguez, 2000). Anemia and fatigue caused by a decline in erythropoieten production is common in myeloma patients. Pallor from anemia may be the initial physical presentations (Kyle, 2000). Castes, fibrils, or crystals can form to damage or destroy the kidney's basement membrane, leading to electrolyte imbalances. Multiple myeloma patients may have either acute or chronic renal failure. Creatinine levels should be monitored often.

Miscellaneous Problems

Myeloma proteins may deposit in tissue compartments causing a hyperviscosity syndrome that may induce nosebleeds, headache, or even heart failure (Kyle, 2000). Although weight loss is rare, hypercalcemia presenting as tiredness, thirst, and nausea, is present in approximately 30% of patients (Durie, 1996, p.9).

Differential Diagnosis

Differential diagnosis should rule out the following: (a) metastatic disease from the breast, prostate, lungs, kidney, and thyroid, (b) primary bone malignancies, including sarcomas and lymphomas, and (c) metabolic bone disease from renal or gastrointestinal disorders that alter levels of bone supporting electrolytes or hormones.

Fifteen percent of patients who test positive for the presence of M-proteins have multiple myeloma. Others who test positive for M-proteins may have one of a variety of diseases under the term monoclonal gammopathy (MG) (see Table 5). Monoclonal gammopathies of undetermined significance (MGUS) is a benign condition that may transform into multiple myeloma in 1%-3% of those affected. Approximately 64% of all monoclonal gammopathies are MGUS. Waldenström's macroglobulinemia accounts for 3% of all monoclonal gammopathies and displays IgM protein proliferation, as compared to the IgG of multiple myeloma. Primary amyloidosis (AL) has an increase in fibrous protein deposits within tissue and organ systems, and makes up 10% of all monoclonal gammopathies. Approximately 3% of MG patients will have smoldering multiple myeloma (SMM). These patients have all the classic laboratory markers of multiple myeloma, without the presence of lytic bone lesions, renal involvement, or anemia (Kyle, 2000).

Diagnostic Testing for Multiple Myeloma

Table 6 reviews the current recommendations for clinical and laboratory evaluations as initiated by a review board of oncologists and scientists (Keren et al., 1999). The guidelines include: (a) clinical criteria for testing M-proteins, (b) optimal sequence of testing, (c) timing of diagnosis and monitoring, and (d) most effective laboratory tests.

M-Protein Identification

High-resolution serum protein electrophoresis with agarose gel (SPEP) remains the most reliable and affordable test for M-protein detection. Some laboratories have a monoclonal gammopathy panel that includes SPEP, total protein, immunofixation, and quantitation. Other laboratories continue to screen for the presence of Bence Jones Protein with a urinary protein electrophoresis. Immunofixation remains the more sensitive test. Improvements in laboratory technology over the past six years have led to newer, more sensitive tests. Immunofixation of isoelectric focusing is five times more sensitive than high-resolution immunofixation electrophoresis (SPEP). Capillary electrophoresis (CE), with 99% sensitivity for M-proteins, has become the "researcher's" method of diagnosing multiple myeloma (Jenkins & Ratnaike, 1999). Unfortunately, the newer, more sensitive tests are beyond the price range of most clinical laboratories.

A monoclonal spike, the pattern traced from the original gel electrophoresis, is the hallmark for the presence of M-proteins. Each section of the gel tracing corresponds to areas of protein concentration. Normal tracings have a large spike at the beginning of the sequence. In a positive electrophoresis (monoclonal pattern), there will be two distinct spikes. The first spike will occur in the protein section, while the second spike occurs in the IgG section. Immunofixation is required to designate its light-chain class. In greater than 50% of multiple myeloma patients, IgG will be the predominant monoclonal protein. Excess of a single monoclonal immunoglobulin can suppress the levels of vital immunoglobulins that are required for immunological protection (Fruchtman, 1999).

Radiology

Evidence of lytic bony lesions, osteoporosis, or pathological fractures on simple axial x-rays is seen in approximately 70% of patients at the time of diagnosis (Durie, 2000). Lytic lesions, often found on the skull, will have a punched out appearance. Lesions may also be seen within the thoracic cage, pelvis, and vertebrae. Radionuclide bone scans are useful to detect metastatic tumors from prostatic cancer and breast cancer. Bone scans are not helpful with the diagnosis of multiple myeloma. In order to provide a more accurate diagnosis of multiple myeloma, Watanabe, Shimizu, Kageyama, and Tanimura (1999) combined bone scintography with Thallium-201. A small improvement in diagnosis was found, despite observing some mixed results. Magnetic resonance imagining (MRI) may be helpful by differentiating between myeloma lesion and compression fracture, but is not diagnostic.

Bone Marrow Examination

Bone marrow aspiration, usually performed by a surgeon or oncologist, is necessary to quantify the amount of plasma or myeloma cells within the marrow and is crucial for diagnosis and/or staging. It may be necessary to aspirate multiple sites because myeloma cells tend to localize in a variety of regions. Approximately 4 to 5 milliliters of aspirate is required for routine studies. Multiple myeloma bone marrow will have greater than 10% malignant plasma cells, however 20% and 50% is common (Durie, 1996).

Routine Laboratory Tests

Numerous laboratory findings may be abnormal at the time of diagnosis. One abnormal laboratory finding, plus clinical signs of multiple myeloma, should suggest the need for further investigation. Table 7 shows typical laboratory findings that may or may not be present with multiple myeloma.

Staging

Therapeutic outcomes are closely linked to the "stage" the patient is in at time of diagnosis. There have been few changes in the staging system that Durie and Salmon developed in 1975 (see Table 8). Serum beta-2-microglobulin and total albumin concentrations may also be used to assess prognosis (Bataille, Grenier, & Sany, 1984). Symptoms of multiple myeloma are usually present when patients are in Stage III.

Treatment

Multiple myeloma is a progressive disease with low cure rates. Treatment goals target pain and symptom relief (Vescio & Berenson, 2001). There appears to be no increase in survival time when treatment is initiated prior to onset of symptoms (Bergsagel, 1994). Many physicians believe that it is best to watch and wait, and to delay treatment until the tumor load is sufficient enough to cause problems. Safe, well-tolerated, and reliable treatment options should be used to prolong life, reduce pain, and protect normal bodily function (Oken, 2000). Laboratory markers, age, co-morbidities, and symptoms, dictate the choice of a treatment regime. What may work for a strong 40 year-old would not be in the best interest of a frail 75 year-old. Reduction of the tumor load with chemotherapy and management of the destructive pathophysiology of multiple myeloma remains the focus of *all* treatment modalities. Therapies recently thought of as experimental are now considered standard treatment, especially for those under 50 years old (Quade, 2000).

Melphalan (Alkeran™) and Prednisone (Meticorten™, Orasone™, Panasol™, Prednicen-M™)

Melphalan and Prednisone have long been, and are still considered, standard chemotherapy for multiple myeloma. Melphalan and Prednisone (MP) are well tolerated with

consistent and effective results (Gregory, Richards, & Malpas, 1992). Approximately 60% of patients with normal body weight, have successful response to MP while adhering to the following protocol: (a) prednisone 1mg/kg/day for 4 days every 4 to 6 weeks, and (b) melphalan 0.25 mg/kg/day for 4 days every 4 to 6 weeks. Platelet and white blood counts (WBC) should be closely monitored for neutropenia and pancytopenia. Melphalan and prednisone treatment can lead to significant blood dyscrasias (Fruchtman, 1999). Dermatitis and pneumonitis are potential problems because of an increased risk of skin hypersensitivity and pulmonary fibrosis (George & Sadovsky, 1999). Other adverse effects include mild nausea and vomiting, diarrhea, and stomatitis. As with all chemotherapy, women of childbearing age should avoid pregnancy.

Vincristin (Oncovin™), Doxorubicin (Adriamycin PFS™, Adriamycin RDF™), & Dexamethasone (Decadron™, Hexadrol™)

Intravenous infusion of Vincristine and Doxorubicin with high-dose Dexamethasone, commonly known as the VAD protocol, has long been considered optional therapy for newly diagnosed or recurring multiple myeloma. VAD therapy has a 15% higher remission rate than Melphalan and Prednisone, however there was no change in survival rates (Alexanian, Barlogie, & Tucker, 1990).

Protocol usually includes: (a) Vincristin 0.4 mg in 100 ml NaCl 0.9% by intravenous (IV) infusion for 4 consecutive days, (b) Doxorubicin 9 mg/m^2 in 100 ml NaCl 0.9% by I.V. infusion for 4 days, and (c) Dexamethasone 40 mg orally on days 1-4, 9-12, and 17- 20. This cycle is to be repeated at 4-week intervals (Segeren, et al., 1999). Since Vincristin, Doxorubicin, and Dexamethasone are not excreted by the kidneys, it has a safer profile in patients with renal failure (Alexanian, Barlogie, & Tucker, 1990). Studies by Giles et al., (2000), members of the International Oncology Study Group (IOSG), investigate the benefits of adding two more

chemotherapy agents to the VAD protocol, Cyclophosphamide and Etoposide. Initial results have been discouraging, with no appreciable increase in the length of survival. Adverse reactions to VAD chemotherapy treatment may include any number of problems ranging from peripheral neuropathy, foot-drop, and muscle weakness, to agitation, depression constipation, and urinary retention. As with other forms of chemotherapy, VAD may induce mild reversible anemia and leukopenia (Chemotherapy Handbook, 1994).

Interferon-Alfa (INTRON A™)

Interferon-Alfa inhibits the growth of plasma cells and can prolong remission rates when added to standard chemotherapy protocols (Osterborg et al., 1993). Interferon-Alfa is especially helpful in treating elderly patients with refractory or resistant multiple myeloma. Positive results were noted when patients were given Intron™ three time a week for 12 months. High cost and Interferon-Alfa's toxicity, make it a poor choice for initial therapy, but it is still being used in the research community (Vescio & Berenson, 2001). Common adverse reactions to Interferon-Alfa include: gastrointestinal symptoms, dry mouth, and various central nervous system (CNS) problems, such as depression, emotional lability, and headache (ePocrates, 2001).

Thalidomide (Thalomid™)

Banned for more than 35 years, thalidomide is now being used as a treatment option for refractory multiple myeloma. Thalidomide was introduced in 1956 and was used extensively as a sedative. When used in the first trimester of pregnancy, Thalidomide caused malformed limbs and congenital defects in the affected offspring. Although the exact mechanism of action is unknown, Thalidomide appears to block the blood flow of growing tumor cells. Reduced blood flow leads to decreased production of cancer promoting cytokines (Alexanian, 2000). Comparisons studies have been made between Thalidomide, VAD, high-dose Dexamethasone,

and autologous stem cell transplants, with encouraging results (Alexanian, 2000). Initial doses of Thalidomide are 200 mg per day, with biweekly increases of 200 mg per day up a maximum of 800 mg per day. This regimen has a 25% positive response rate (Rajkumar et al., 2000). Thalidomide rarely causes toxic adverse effects, if carefully titrated. Older patients may experience some constipation, fatigue, or neuropathy. These symptoms quickly respond to appropriate treatment.

Bisphosphonates

Bone pain in multiple myeloma remains one of the most serious and difficult symptoms to control. Spinal cord compressions and fractures caused by bone lesions, lead to immobility that further accelerates bone destruction. Until recently, only radiation therapy was helpful in alleviating 90% of moderate bone pain (Mill & Griffith, 1980).

Originally used for the treatment of hypercalcemia, bisphosphonates are now being administered to reverse or slow down the destructive skeletal effects of multiple myeloma. Bisphosphonates disrupt the bone resorption process by binding to the mineralized bone matrix (Rogers, Watts, & Russell, 1997). Pathological fractures and bone pain are the direct result of excess resorption. Bisphosphonates may also cause tumor apoptosis or cell death, by inhibiting enzyme pathways (Pluijm, Lowik, & Papapoulos, 2000). Research is underway measuring the effectiveness of the bisphosphonates: Pamidronate (Aredia™), Etidronate (Didronel ™), Clodronate, Ibandronate, and Zolendronate. Both advanced breast cancer and multiple myeloma may benefit from the many clinical trials that are currently in process (Coleman, 2000). Pamidronate is the most widely used bisphosphonate for myeloma therapy. Berenson et al., (1996), performed a prospective study of 392 patients with advanced multiple myeloma. After administering Pamidronate 90 mg over a 4-hour period every 4 weeks, skeletal events,

pathologic fracture, and spinal cord compressions were dramatically reduced. There were 2.05 fractures for the placebo group, while the Pamidronate group had 1.1 fractures. Due to its great success, this study was extended for almost 2 years. While skeletal benefits remained strong, there was no change in survival rates.

Intravenous administration of bisphosphonates is the most effective route because the adverse gastrointestinal side effects common with all medications in this class. Newer bisphosphonates, such as Zoledronate and Ibandronate, can be administered intravenously over a matter of minutes rather than the 2 to 4 hours required for Pamidronate (Kyle, 2000, p. 736). Common adverse reactions include: (a) gastrointestinal upsets, (b) confusion, (c) fever, (d) electrolyte imbalances, and (e) generalized pain (ePocrates, 2001).

Bone Marrow Transplantation

Allogeneic, syngeneic, autologous bone marrow transplantation, and peripheral stem cell transplant, is offered to a select group of multiple myeloma patients. Those younger than 65 years old appear to have better response rates with bone marrow transplants and experience lower mortality rates than older patients. According to Vescio and Berenson (2001), transplantations from syngeneic or identical twin donors, achieve the longest survival time, around 72 months. Allogeneic (related or unrelated) transplantation has a 40% - 50% transplant related mortality rate (Gahrton, 1999). Autologous (patient's own) marrow transplantations respond with a 36 - 65 month survival time (Jagannath, Tricot, & Barlogie, 1997).

Peripheral stem cell transplantations (PSCT) are increasing in frequency due to several positive research findings. Bensinger, Martin, & Clift (1999), observed a 2 year survival rate for PSCT of 70% as compared to a bone marrow transplant rate of 45%.

While there appears to be promising success with bone marrow or peripheral stem cell

transplantations, two major problems exist. Despite aggressive chemotherapy and total-body irradiation, multiple myeloma cells are not totally eradicated. Relapse occurs when the patient is re-infused with these renegade cells (Kyle in Goldman & Bennett Eds., 2000, p. 982).

Pain Control and Supportive Care

Problems associated with advanced multiple myeloma include weakness, bone pain, hypercalcemia, and anemia. Risks for immobility and infection should be monitored. The knowledge to address these concerns, and the compassion to embrace this task, make nurses well suited to support the cancer patient.

Weakness

Unfortunately there is no drug that can increase strength. There are however, treatments that can induce a feeling of well-being. The nurse can explore complaints of weakness as it relates to feelings of helplessness and dependency. A trial of steroids, or an antidepressant, may lift spirits enough to give patients a reason to exercise. Fatigue caused by myeloma induced anemia, responds well to blood transfusions. The help of a physical therapist can be elicited to organize exercise routines for bedridden patient (Kaye, 1997).

Bone Pain

Adequate assessment of bone pain is critical prior to prescribing therapy. The nurse practitioner clarifies the onset, location, duration, character, alleviating, and aggravating factors of bone pain. Radiation and bisphosphonates are helpful agents for bone pain, but noninvasive forms of pain control such as touch therapy, biofeedback, or imagery may be helpful. It is also important to assess the spiritual aspects of pain. What does pain mean to this patient? Possibly the patient's primary complaint is their lack of sleep caused by pain (McGuirre, Yarbro, & Ferrell, 1995).

Prostaglandin inhibitors are the preferred analgesic for bone pain. Approximately 80% of patients will have some relief with non-steroidal anti-inflammatory drugs (NSAIDs). Opioids are helpful for a more severe, constant pain, while NSAIDs help with the sharp pain that occurs with movement.

Hypercalcemia

Common symptoms of hypercalcemia include lethargy, anorexia, dry mouth, muscular weakness, confusion, and anxiety. Calcium levels above 16 mg/dL can be fatal, however, hydration with normal saline, potassium, and etidronate (bisphosphonate) often bring calcium levels down within three days. Maintenance therapy with oral phosphate is then required to keep levels within normal limits.

The Future: Gene and Vaccine Therapy

Gene therapy holds the promise of killing only myeloma cells, while sparing other cells from the destructive forces of radiation and chemotherapy. This therapy is a long way off, yet initial exploratory trials are underway. Genes act as off and on switches that control the proliferation of mutant cells. Gene therapy requires the placement of a specific gene sequence into the mutant cell of multiple myeloma, thereby altering its growth. Crippled viruses are used to transport the gene into a myeloma cell and turn on genes that promote apoptosis or cell death. Gene therapy may also help accelerate cellular growth within the bone marrow, creating stronger cells that are more able to resist the damaging effects of chemotherapy (Stewart, 1998).

Although still in the early stages of development, vaccines may have a future in the battle against multiple myeloma. Myeloma proteins contain immunological properties that make them vulnerable to the properties of a vaccine. Vaccines could bolster the immune system of myeloma patients by using " . . . the protein alone, dendritic cells plus the protein, or the DNA that is

found in the myeloma cells that is responsible for the protein . . . " (Stockerl-Goldstein, 2000, paragraph 5). Vaccine therapy research is underway at the University of Arkansas, the Fred Hutchinson Cancer Research Center, Mayo Clinic, and Stanford University.

Non-Traditional Therapy for Multiple Myeloma

Many patients with multiple myeloma have become proactive and are becoming full participants in their own therapeutic program. Searching the Internet for support groups and help partners, as well as seeking out non-traditional methods of healthcare, can be liberating for the patient who has an incurable disease (cancernet.nci.nih.gov). Chinese herbs may boost the body's immune system, as well as help offset the adverse effects of chemotherapy. Psychotherapy and/or psychotropic medication helps to ease mood swings, sleeping problems, and eating disorders. Spiritual counseling can supply support for the soul and help deal with the many losses that cancer inflicts upon people. Blending traditional and non-traditional multiple myeloma therapy gives the patient more control over the events that have taken control of their lives (Porrath, 1998).

Conclusion

Treatment and ongoing management of patients with multiple myeloma is beyond the scope of most nurse practitioners. It is however, important to have a basic knowledge of the variety of presenting symptoms. Abnormal laboratory results or symptoms suspicious of multiple myeloma as outlined in Figure 2 need to be promptly evaluated. Multiple myeloma continues to be an incurable and challenging disease. Early detection, supportive care, and pain control will help patients maintain quality in their lives.

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TABLE 1

HISTORICAL MILESTONES IN MULTIPLE MYELOMA

Year	Event
1844-1850	Description of cases of soft and fragile bone. Dr. Henry Bence Jones discussed findings of and "unusual urine problem". Mr. John Dalrymple noted that the diseased bones held increased amount of plasma cells. Dr. Macintyre and Dr. Solly publish report of "myeloma".
1873	Rustizky coined term "multiple myeloma" for the varied tumors found in bones.
1900	Wright noted that multiple myeloma cells were actually plasma cells.
1930's	Bone marrow now aspirated more routinely.
1953	Immunoelectrophoresis identifies monoclonal proteins.
1962	First treatment of multiple myeloma with melphalan.
1975	Durie/Salmon staging system for MM.
1984-1986	Allogeneic transplants for MM patients.
1986-1996	Various studies with autologous bone marrow or stem cell rescue for MM.

Note. MM = multiple myeloma. Revised from Durie, 1996.

TABLE 2

RISK FACTORS

Factor	**Increased (⇑) Decreased (⇓) No Risk (⇒)**
♦ Age	⇑ Greater than 60 years
♦ Sex	⇑ Males
♦ Racial	⇑ Blacks ⇓ Asians (Durie, 1996)
♦ Heredity	⇑ Siblings (Deshpande, Hu, Marino, Jan, & Wiernik, 1998)
♦ Radiation	⇑ Atomic bomb survivors, ⇑ radiologist
♦ Environmental	⇑ Black hair dye (Brown, Everett, Burmeister, & Blair, 1992) ⇒ Black hair dye (Correa, Jackson, Mohan, Perry, & Helzlsouer, 2000; Herrinton et al., 1994; Altekruse, Henley, & Thun, 1999) ⇑ Pesticide exposure (Khuder & Mutgi, 1997; Mahaswaran, Arnold, & Jessop, 1999; Cuzick & De Stavola, 1988) ⇑ Petroleum exposure (Linet, Harlow, & McLaughlin, 1987) ⇒ Petroleum exposure (Wong, Trent, & Harris, 1999)
♦ Autigenic Stimulation	⇑ Infection, allergic, autoimmune, or inflammatory (Bourguet & Logue, 1993)

Source unless otherwise noted from Vescio, R.A., & Berenson, J.R. (2001). Myeloma, macroglobulinemia and amyloidosis. In Charles M. Haskell, (Ed.), Cancer treatment (pp.1503-1539). Philadelphia: W.B. Saunders Company.

TABLE 3

MYELOMA GROWTH FACTORS

Factor	Function
Interleukin-6 (Cytokine)	♦ Primary growth factor for multiple myeloma ♦ Large amounts secreted by bone marrow stromal cells (Uchiyama, Barut, Mohrbacher, Chauhan, & Anderson, 1993) ♦ Elevated levels indicate poor prognosis (Ludwig, Nachbaur, Fritz, Drainer, & Huber, 1991) ♦ Protects from chemotherapy-induced apoptosis (Xu et al., 1998)
Interleukin-1β (Cytokine)	♦ Can be made by the myeloma cells & is a potent bone resorption factor (Cozzolino et al., 1989) ♦ Increases IL-6 stromal cell production (Carter, Merchav, Silvian-Draxler, & Tatarsky, 1990)
Tumor Necrosis Factor Alpha (TNF-α)	♦ Protects MM cells from apoptosis if lacking in IL-6 (Georgii-Hemming, Wiklund, Ljunggren, & Nilsson, 1996) ♦ Increased levels found in MM (Filella et al., 1996). ♦ Thalidomide inhibits
Insulin-like growth factor (HGF)	♦ Stimulates MM cell growth (Georgii-Hemming, et al., 1996) ♦ Increase sensitivity to IL-6 and decrease sensitivity to beneficial therapy of steroids (Xu et al., 1997)
Human herpesvirus 8 (HHV-8)	♦ Contains viral form of IL-6 (v-IL-6) (Neipel et al., 1997) ♦ Found in MM patient's bone marrow (Rettig et al., 1997)

Note: MM: multiple myeloma

TABLE 4

POLYPEPTIDE CHAINS	
Heavy Chain or Immunoglobulins	**Characteristics**
♦ IgG or γ	Largest class, account for 80% of immunoglobulins, resistant against some viruses, bacteria, and bacterial toxins
♦ IgA or α	Found in glandular secretions, attack pathogens before they enter internal tissues
♦ IgM or μ	First antibody at the scene of bacterial invasion, decline in number after IgG increases
♦ IgD or δ	Found on surfaces of B-cells, help to bind antigen
♦ IgE or ϵ	Attaches to basophils and mast cells, stimulates release of histamine
Light Chains	
♦ Kappa or κ ♦ Lambda or λ	When found in the urine are classified as Bence Jones Protein (BJP)

TABLE 5

DIAGNOSTIC CRITERIA FOR MONOCLONAL GAMMOPATHIES

Diagnostic	**MM**	**MGUS**	**Amyloidosis**	**SMM**
Serum Protein Concentration	> 3 g/dL	< 3 g/dL		> 3 g/dL
Plasma Cells in Bone Marrow	>10%	< 10%	~ 7 %	>10%
M-Protein in Urine	Present	Small amount	Present in 70–90 % of pts.	Small amount
Lytic Lesions	Present in 80% of patients.	Absent		None
Anemia	Present	None	Possibly	None
Hypercalcemia	Present	None		
Renal Insufficiency		None	Present in 50 % of pts.	None

Note. MGUS= monoclonal gammopathy of unknown significance; MM= multiple myeloma; SMM= smoldering multiple myeloma. Information source: Kyle, 2000.

TABLE 6

GUIDELINES FOR LABORATORY EVALUATION – MULTIPLE MYELOMA

- Who to test? All patients over 35 years of who exhibit the symptoms suspicious of multiple myeloma as presented in Figure 2.
- Detect presence of Monoclonal Protein: Serum protein electrophoresis with high resolution agarose gel (SPEP)

  Sensitivity: >95% Specificity: Cost: $55 Time Frame: 24-48 hours
- Define abnormal protein type: Immunofixation

  Sensitivity: >95% Specificity: Cost: $80 Time Frame: 72 hours
- Follow M-protein via quantitation: nephelometry or densitometric quantification
- Perform urine protein electrophoresis (UPEP)

  Sensitivity: >95% Specificity: Cost: $55 Time Frame: 24-48 hours
- Monitor levels of M-protein every 1-2 months throughout treatment.
- Monitor for hyperviscosity syndrome causes by high amount of circulating M-proteins. Signs include blurring or loss of vision, nosebleeds, headaches, vertigo, diplopia, CHF, somnolence, and paresthesias (Kyle, 2000).
- Monitor for cryoglobulins or protein precipitates in the blood.

Sources: Pathologist Regional Laboratory, Lewiston, ID; Alexanian, Weber, & Liu (1999); Kyle (2000); & Keren, et al., (1999).

TABLE 7

LABORATORY FINDINGS AT TIME OF DIAGNOSIS

Test	Laboratory Outcome	Clinical Manifestation
RBC	• Normochromic, normocytic in 80% of patients • Rouleaux formation on peripheral smear due to protein changes • Decreased erythropoisis may be caused by renal involvement	• Weakness, fatigue • Difficulty cross-matching for blood transfusions • Weakness, fatigue
WBC	• Usually normal but decreased in around 20% of patients.	• Increased risk of infection especially with *S. pneumonia* and *H. influenzae* • Herpes zoster infections
Platelets	• Usually normal but decreased in around 20% of patients.	• Clotting difficulties
ESR	• Elevated	• Inflammation
Calcium	• Elevated in 30% of patients • Calcium salts may precipitate	• Fatigue, thirst, nausea • Kidney damage
Protein	• High myeloma protein levels leads to hyperviscosity syndrome	• Purpura ecchymoses, epistaxis, hazy vision, headache, GI bleeds, sleepiness, and numbness & tingling
Kidney function	• Proteinuria • BUN increase • Creatinine increased • Uric acid increased	• Bence Jones protein increases damage kidney leading to "Myeloma Kidney" a decrease in renal tubular function with associated reabsorption and excretion problems • Gout and uric stones are rare

Sources: Durie, 1996; Leeson in Dambro & Griffith, 2001; Linker In Tierney, McPhee, & Papadakis, 2001.

TABLE 8

DURIE & SALMON STAGING SYSTEM

CRITERIA	Stage I	Stage II	Stage III
Hemoglobin value	> 10 g/dL	Not fitting stage I or III criteria	< 8.5 g/dL
Serum calcium	Normal	Not fitting stage I or III criteria	> 12.0 mg/dL
Bone X-ray	Normal structure	Not fitting stage I or III criteria	> 3 lytic lesions
Kappa & lambda light chains	< 4 g/24hrs.	Not fitting stage I or III criteria	> 12.0 g/24hrs
IgG	< 5.0 g/dL	Not fitting stage I or III criteria	> 7.0 g/dL
IgA	< 3.0 g/dL	Not fitting stage I or III criteria	> 5.0 g/dL
Estimated cell mass	Low burden	Intermediate burden	High burden
Creatinine with subclasses	A: < 2.0 mg/dL B: ≥ 2.0 mg/dL	A: < 2.0 mg/dL B: ≥ 2.0 mg/dL	A: < 2.0 mg/dL B: ≥ 2.0 mg/Dl

Impaired renal function worsens prognosis.

Revised from Durie, 1996 and Patient's PDQ, 2000.