Norwood Hospital
A STEWARD FAMILY HOSPITAL

Cancer Center at Foxboro

Steward

2015 Cancer Care Report to the Community. Multiple Myeloma Site Specific Study.

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INTRODUCTION:

Multiple myeloma is a tumor arising in bone marrow, created by clonal proliferation of plasma cells. The hallmarks of myeloma are osteolytic bone lesions, hypercalcemia, anemia, and renal failure.

Fulfillment of certain criteria establishes a diagnosis of multiple myeloma. Bone marrow biopsy showing clonal plasma cells constituting at least 60% of the cellular population indicates myeloma even in the absence of other signs/symptoms. With at least 10% but fewer than 60% plasma cells present in the marrow and/or a biopsy-proven plasmacytoma, end-organ damage accompanied by a serum or urinary monoclonal protein suffices for diagnosis.

Evidence of end-organ damage comprises hypercalcemia with total serum calcium greater than 11.5 mg/dl, renal insufficiency with creatinine clearance less than 40 mls/min, normochromic normocytic anemia with hemoglobin less than 10.0 g/dl, and/or osteolytic lesions, severe osteopenia, or pathologic fracture. None of these

findings can be attributable to a different etiology. The majority of patients present with fatigue and bone pain, leading to laboratory studies and x-rays that demonstrate organ involvement.

The absence of end-organ damage, a serum monoclonal protein of less than 3 g/dl and marrow plasmacytosis less than 10% defines MGUS, a monoclonal gammopathy of undetermined significance. Lastly, serum monoclonal protein greater than 3 g/dl with a marrow plasma cell proliferation greater than 10% but less than 60% lacking any evidence of end-organ damage catergorizes so-called “smoldering” myeloma.

EPIDEMIOLOGY:

In the United States there are approximately 20,000 new cases and 10,000 deaths from myeloma each year. The age-adjusted incidence is 4.3 per 100,000. For unknown reasons, the disease is twice as common in the black population as it is among whites. Median age at diagnosis is 65.

The etiology of the disease is unknown, though exposure to several toxic agents including ionizing radiation, pesticides, and organic solvents are among the suspected but unproven contributory factors.

Three percent of individuals over the age of 50 have monoclonal gammopathies of undetermined significance. Among these patients, there is a 1% per year risk of progression to multiple myeloma. Patients with smoldering myeloma are at an even higher risk of progression, approximately ten times greater than that seen with MGUS.

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Norwood Hospital Cancer Care Services

Norwood Hospital offers community-based care for most cancers. Services are conveniently located at the hospital and its Cancer Center at 70 Walnut Street in Foxboro. Our goal is to provide local access to current treatment to achieve the best possible outcomes. We offer:

- Leading-edge radiology:
  Digital mammography • PET CT • Ultrasound
- Medical oncology
- Surgical services
- Outpatient chemotherapy clinic
- Intensity-Modulated Radiation Therapy (IMRT)
- Seed implants
- National cancer research trials
- Community health screenings and education, including American Cancer Society programs
- Pain management
- Rehabilitation

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STAGING:

Two staging systems are in common use: the Durie-Salmon and the International systems. The Durie-Salmon system recognizes patients with up to one bone lesion, a hemoglobin higher than 10.0, a normal calcium, and a low level monoclonal protein as Stage I disease. Alternatively, the International system defines Stage I as albumin greater than 3.5 and β2-microglobulin less than 3.5 mg/L. Stage III in the Durie-Salmon system represents advanced bone disease, hemoglobin less than 8.5, increased calcium, and high monoclonal protein levels. The International system uses a single criterion for Stage III disease, a β2-microglobulin greater than 5.5. In both systems, Stage II disease contains all patients whose laboratory results do not place them into either Stage I or Stage III. Because of the subjectivity involved in the Durie-Salmon system and the relative paucity of criteria in the International System, neither staging system is as clinically relevant as is staging of other neoplasms.

TREATMENT:

Myeloma is an incurable disease, but major strides in treatment have occurred over the past two decades. Twenty-five years ago the standard treatment of myeloma was an oral regimen of melphalan and prednisone. Although most patients developed significant myelosuppression, 78% response rates led to progression-free survival of up to 19 months. With these drugs patients could expect an average life expectancy of just three years. Nonetheless, the relative success with melphalan led to interest in using high dose melphalan with autologous stem cell support, an approach that would ultimately prove more successful with the development of newer, more effective chemotherapy agents.

In 1995 a new proteasome inhibitor, bortezomib, began clinical testing and soon proved superior to either melphalan or to high dose dexamethasone. This drug was soon followed by the introduction of lenalidomide, an oral derivative of thalidomide with multiple mechanisms of action: inhibition of tumor angiogenesis, inhibition of secreted cytokines, and facilitation of apoptosis. With such anti-proteosome and immunomodulatory medications, induction therapy followed by autologous transplant was able to achieve remissions lasting years rather than months.

Current management of myeloma begins with evaluation of suitability for autologous transplant. Generally this is a function of age, performance status, and the presence or absence of significant co-morbidities. For patients otherwise in good health, transplant is currently possible in the United States up to the age of 75.

For transplant candidates, treatment begins with two to four cycles of a non-melphalan regimen followed by stem cell harvest, with subsequent high dose consolidation therapy with melphalan and stem cell transplant. Some patients receive maintenance therapy with lenalidomide following transplant, though studies are still investigating the long-term benefits of this approach. While myeloma remains an incurable disease, the median progression-free survival in some studies has exceeded 46 months with median overall survival not yet reached.[1]

For patients otherwise in good health, transplant is currently possible in the United States up to the age of 75.

For patients who are not transplant candidates, there are several chemotherapy regimens built upon the efficacy of bortezomib and lenalidomide. Even in elderly patients, three year survival now approximates 70% with a combination of lenalidomide and dexamethasone.[2] When relapse does occur, still newer agents such as pomalidomide and carfilzomib offer new hope and extended survival for patients with progressive disease.

NORWOOD HOSPITAL PATIENT DATA:

Four patients received a diagnosis of multiple myeloma in 2010. There were four more new cases in 2011, seven in 2012, three in 2013, and nine in 2015

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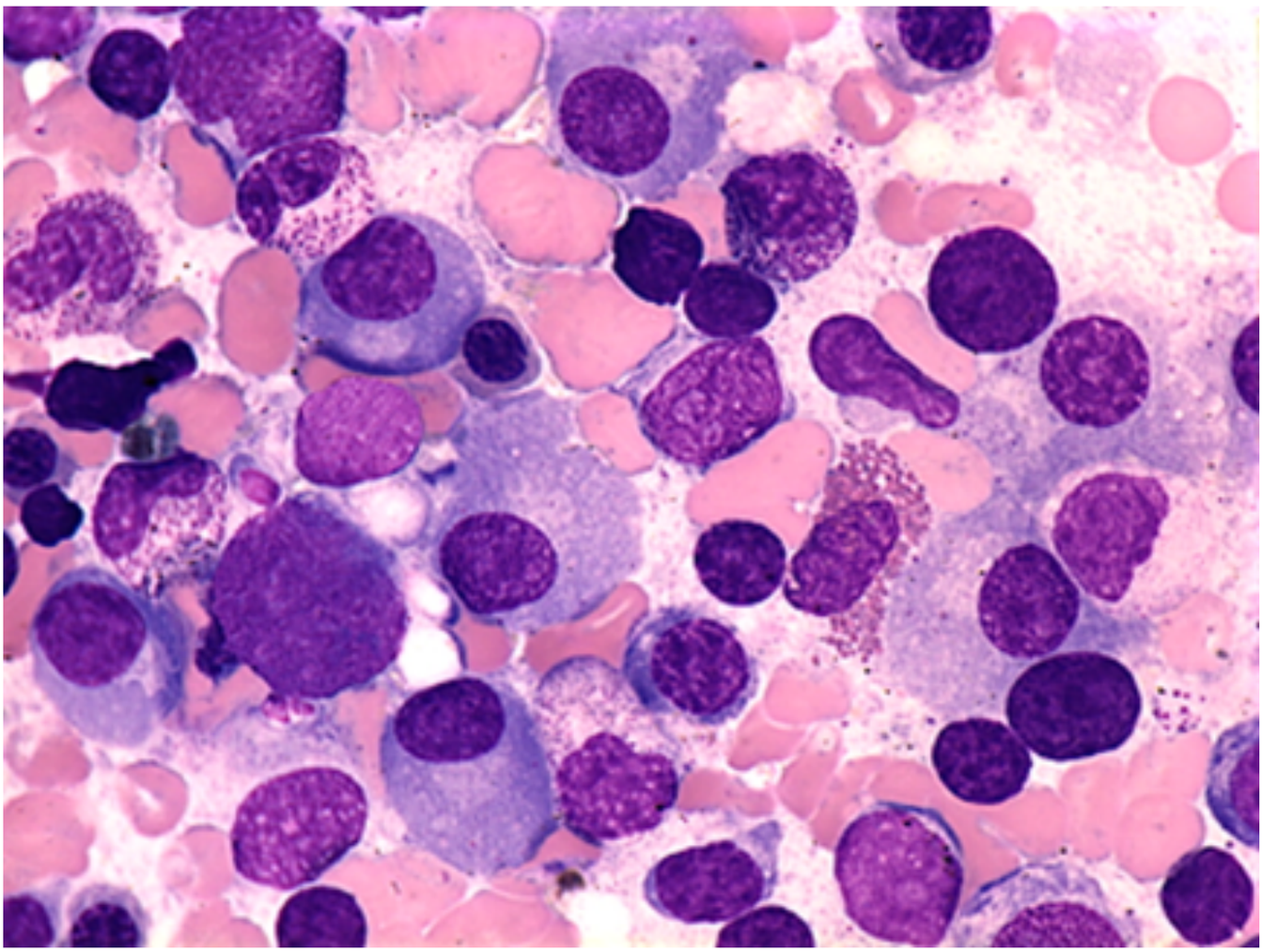

Myeloma Marrow

for a total of twenty-seven cases in the study years. Our average age at diagnosis was 73.9, older than the average age of 65 nationwide. Patients ranged from 52 to 93 at the time of diagnosis. This is fairly representative of the generally older age of the Norwood Hospital population.

Similarly, only four patients presented with Stage I disease. Another four had Stage II disease. Seventeen had Stage III disease. Two had smoldering, rather than frank, myeloma. The predominance of advanced disease at diagnosis here reflects our older population with extensive co-morbidities that often obscure the possibility of a plasma cell dyscrasia. Because fatigue and arthritic bone pain are common among the elderly, patients may not seek immediate evaluation for these symptoms.

Two patients did not undergo marrow biopsy because of advanced age and severe medical conditions that precluded therapeutic intervention. Because a diagnosis of myeloma requires marrow biopsy, these two do not, strictly speaking, have known myeloma. They are included in the study population for completeness' sake as they both had high levels of monoclonal protein and evidence of end-organ damage consistent with plasma cell dyscrasia.

Only two patients received autologous stem cell transplants. This is largely consistent with the older age, advanced stage, and presence of co-morbidities

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that typify the Norwood Hospital patient population. Both remain in continued remission and both are on maintenance therapy with lenalidomide.

Twelve patients continue treatment and follow-up with physicians at Norwood Hospital. Six have died from their disease. The fate of the remaining nine is not clear from data available in Meditech. While physician outpatient notes are not available in the hospital-based Meditech EMR, records of patients receiving intravenous therapy in Chemotherapy Clinic are accessible and provide valuable treatment information. Because the initial therapy of patients who are not transplant candidates can consist solely of oral medications however, Meditech does not necessarily capture a comprehensive record of patient treatment and follow-up.

One patient's primary care physician did not work within the Steward Healthcare system; that patient appears to have pursued oncologic care elsewhere upon hospital discharge. Three others indicated intent to seek care in Boston at tertiary care hospitals. The ultimate outcome for the remaining five patients originally diagnosed at Norwood Hospital between 2011 and 2014 is unknown. Of those patients treated by physicians at Norwood, all received chemotherapy regimens comprising combinations including bortezomib and/or lenalidomide as initial therapy in accordance with NCCN and ASCO guidelines.

Judicious use of high dose therapy with autologous stem cell rescue has led to tremendous improvements in progression-free and overall survival, with patients now living as long as ten years past original diagnosis.

CONCLUSION:

Multiple myeloma is an incurable and inexorable proliferation of plasma cells producing monoclonal paraproteins and marked by anemia, hypercalcemia, renal failure, and osteolytic bone lesions. While incurable, the development of newer immunomodulatory agents and proteasome inhibitors has revolutionized treatment. Judicious use of high dose therapy with autologous stem cell rescue has led to tremendous improvements in progression-free and overall survival, with patients now living as long as ten years past original diagnosis. Even for those who are not transplant candidates, these newer drugs have led to greatly improved survival and improved quality of life for our patients. Review of the Norwood Hospital experience with multiple myeloma between 2010 and 2014 time confirms our physicians appropriately and expertly employ the most modern therapies currently available for the benefit of our patient population.

NOTES:

1. McCarthy PL, Owzar K, Hofmeister CC et al., Lenalidomide after stem cell transplantation for multiple myeloma, *New England Journal of Medicine.* 2012; 366:1770-1781.

2. Jacobus S, Callander N, Siegel D, et al., Outcome of elderly patients 70 years of age and older with newly diagnosed myeloma in the ECOG randomized trial of lenalidomide/high dose dexamethasone (RD) vs lenalidomide/low dose dexamethasone (Rd). *Haematologica.* 2010; 95-149 (suppl 2; abstr 0379).

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