1-1-2009

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Moira Stephens
University of Wollongong, moiras@uow.edu.au

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Abstract

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Keywords

multiple, clinical, treatable, myeloma, update, cancer, rare

Disciplines

Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Stephens, M. (2009). Multiple Myeloma; clinical update on a rare and treatable cancer. Australian Journal of Cancer Nursing, 10 (2), 19-24.

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Multiple myeloma: clinical update on a rare and treatable cancer

Moira Stephens • RN MsC Cert Oncology Cert HIV/AIDS PGCert Ed
Research Academic, Centre for Values, Ethics & the Law in Medicine, Lecturer/Coordinator Cancer & Haematology Nursing Programme, Faculty of Nursing and Midwifery, University of Sydney NSW.

Abstract

Multiple myeloma is a rare cancer, contributing 1% of cancers and 15% of haematological malignancies. Myeloma is an incurable, yet increasingly treatable cancer with people often living in a chronic (controlled) state of relapse, i.e. living with a low level of disease for many years. Survival with myeloma varies from a few months to decades. Nurses play a valuable role in caring for people with myeloma and with their specialist knowledge of the pathophysiology of myeloma and the effects of treatment, together with their therapeutic relationship with the patient and the family, are in an important position to influence care for people with myeloma.

Introduction

Multiple myeloma is a clonal B cell malignancy of the bone marrow characterised by the accumulation of plasma cells that secrete an abnormal immunoglobulin (paraprotein or M Protein). As a result, patients may also develop bone lesions, hypercalcaemia, anaemia, immunosuppression and renal impairment. Myeloma is not curable; however, current treatments slow disease progression, allowing people to live with myeloma in a chronic state of relapse, if not in a remission. Nurses have a wide, varied and influential role in managing the complications of both disease and treatment.

This paper provides a clinical update about the management of myeloma and discusses implications for medical and nursing management. It describes the incidence and mortality of myeloma; explores the risk factors, characteristics and presenting symptoms; examines the diagnostic process and treatment options and explores the psychosocial and nursing implications of myeloma.

A brief historical note

Multiple myeloma is not a new disease. Lytic lesions, characteristic of multiple myeloma have been described in Neolithic man c 4,000BC [1] *and in Egyptian mummies. The first recorded description of what was probably a case of myeloma was by Samuel Solly FRS* [2]*. A record of his examination and treatment of Sarah Newbury was detailed in his paper* Pathology of Mollities Ossium *in June 1844. Sarah was a 39-year-old woman who presented 4 years earlier with progressive bone pains and spontaneous fractures. Despite treatment with orange peel infusions, daily stout, opiates and rhubarb pills, she died. In September of 1844, a wealthy London grocer developed severe pains in his chest and back, which were accompanied by oedema and a "peculiar reaction" of his urine when heated and cooled. Mr McBean was examined by Dr William Macintyre and his urine was sent to Dr Henry Bence-Jones for analysis. Mr McBean died on 2 January 1846. At autopsy, his bones were examined by John Darymple and found to be soft, fragile and could be cut by a knife, also described as "mollities ossium". The cause of death was recorded as "atrophy from albuminuria"* [3]*. All three physicians thought the disorder to be one of malignant bone disease. In 1873 von Rustizky described the particular pathological features, seen as multiple tumours of the bone marrow, as multiple myeloma* [4]*.*

Incidence and mortality

Myeloma accounts for 1.2 % of all cancer diagnoses in Australia and 10-15% of all haematological malignancies. In 2005, the incidence rate population was 6.8 per 100,000 in men and 4.7 in women, with a ratio of 1.7 men to women [5]. The incidence increases with age, with a mean age at diagnosis of 70 years, compared to 67 years of age in 1982. Some data suggests that myeloma is being diagnosed in younger patients with increasing frequency [6, 7] although it remains relatively rare in younger people with 2% less than 40 years old and 5% less than 50 years old. There was an 45% increase in the reported incidence in Australia from 1992-2001 [5].

In the US the incidence rate is 5.6 per 100,000 men and women per year [8]. The incidence rate is similar in Europe, with 6 per 100,000 people per year, a median age at diagnosis of between 63 and 70 years and a mortality rate of 4.1 per 100,000 people per year [9]. The rarity of this type of cancer impacts its management, perception and experience by both patients and healthcare workers.

Trends over the last 20-30 years

The pattern of disease of myeloma has changed over the last 2 decades [10, 11] with younger people presenting with the disease, earlier presentations and up to 25% of those diagnosed being asymptomatic at presentation [6, 7, 12]. The incidence of myeloma appears to primarily be increasing as the median age of the population in Western societies increases [13]; however, there are data demonstrating some varying trends supporting an overall increase in incidence [7, 14, 15]. Survival has increased over the last 20 to 30 years in concert with developments in diagnosis, treatment and supportive therapy.

The median duration of survival in the 1990s was less than 3 years. Recent improvements in treatment and care have increased the median survival to 7.5 years in patients under 50 years and 5.7 years in older patients, with 43% of younger patients and 29% of older patients alive 10 years after their diagnosis [16]. An improvement in 1-year survival in all age groups and improvements in 5- and 10-years survival in younger patients (60- and 70-years-old) has recently been reported [17].

Survival of people with myeloma varies from some months to several decades [18] and major improvements in long-term survival have recently been reported since the introduction of novel agents [19].

Tumour detail

Multiple myeloma is a clonal B cell malignancy of the bone marrow, characterised by the accumulation of plasma cells that secrete paraproteins and impairment of normal immunoglobulin production. Myeloma cells proliferate uncontrollably, causing a number of systemic complications including: skeletal destruction due to interaction with osteoclast activity and lytic lesions; overcrowding of the bone marrow leading to bone marrow failure and its attendant risks of anaemia and infection; the presence of paraproteins leading to increased plasma viscosity and renal insufficiency; and interaction with and adhesion to, bone marrow stromal cells and increased vasculature within the bone marrow microenvironment.

All cases of myeloma are now thought to be characterised by the presence of genetic abnormalities [9] and some of these changes are useful in prognosis. Hyperdiploidy (an increased number of chromosomes) is associated with a better prognosis; however, deletion of part of chromosome 17 (17p13) or translocation of 14 and 4, or 14 and 16 are all thought to confer a poor prognosis[9]. Myeloma is commonly described as a monoclonal plasma cell disorder. Monoclonal plasma cells (myeloma cells) produce abnormal immunoglobulins in most cases, with the appearance of monoclonal protein in the blood and/or urine (Para protein, M Protein) together with an increased number of plasma cells in bone marrow (more than 10%).

Risk factors

The aetiology of myeloma is unknown and, despite advances in clarifying the biological mechanisms of multiple myeloma, there are no established risk factors other than male gender, older age, African American ethnicity, a positive family history of lymphato-hematopoietic cancer (LHC) and a pre-existing diagnosis of monoclonal gammopathy of undetermined significance (MGUS) [20]. A small number of studies have suggested an association between obesity and the subsequent development of myeloma [21]; however, the strongest associations, although not conclusive, are with radiation and exposure to agricultural herbicides and pesticides [22]. Early studies [23] suggested a higher incidence of myeloma among people exposed to radiation in Hiroshima and Nagasaki following the atomic bomb blast in 1945; however, subsequent studies have found no increased incidence [24].

Characteristics

Myeloma is an incurable, treatable, malignant plasma cell disorder. It is characterised by the proliferation of a single clone of plasma cells derived from B cells in the bone marrow. The single clone of plasma cells produces a monoclonal protein: an abnormal immunoglobulin [25]. Due to invasion of the bone by malignant plasma cells and the production of excessive amounts of light chains, lytic bone disease and renal failure are often present. Immunity is commonly compromised due to the production of excessive amounts of the malignant immunoglobulin together with a deficit in production of the other normal immunoglobulins. Drug resistance is also a major characteristic of myeloma and this is due to a number of reasons: as plasma cells divide infrequently, they are relatively resistant to the cytotoxic effects of chemotherapy; Interlukin-6, a cytokine or messenger protein associated with myeloma, inhibits drug-induced apoptosis and; the interaction of myeloma cells with bone marrow stromal cells, other proteins and osteoblasts, osteoclasts and endothelial cells also contributes to the pathophysiology and resistant properties of myeloma [9].

Presenting symptoms

Twenty-five per cent of people with myeloma present asymptomatically and are diagnosed on a routine blood test [12]. The most common presenting symptoms are fatigue and pain [26]. Other frequently occurring presenting symptoms are: infection, pathological fractures, symptoms of renal failure and spinal cord compression. Less common symptoms include confusion, carpal tunnel symptoms and hyperviscosity syndrome. The sometimes ordinary (back pain, for example), often ambiguous and varied nature of presenting symptoms can lead to missed opportunities for early diagnosis. Early symptoms may appear benign and initially be discounted by patients, family and healthcare professionals.

Diagnostic process

The disease definition for myeloma has undergone a number of revisions since first described (although not defined) by Solly in 1844 [2]. The current definition requires the following three diagnostic criteria to be present: more than 10% monoclonal plasma cells in the bone marrow and/or the presence of a biopsy-proven plasmacytoma; monoclonal protein present in the serum and/or urine and the presence of one or more criteria describing myeloma-related organ dysfunction, know as CRAB (calcium, renal function, anaemia and bone lesions) [11, 27]. Symptomatic myeloma is differentiated from other plasma cell disorders such as monoclonal gamopathy of undetermined significance (MGUS) and smouldering or asymptomatic multiple myeloma (SMM) based on the presence or absence of end-organ damage attributable to the underlying disease [25]. A strategy for diagnosis, as suggested by the European Society of Medical Oncology (ESMO) is useful for such differentiation (Table 1).

Diagnosis should be based on the following tests:

Detection and evaluation of the monoclonal (M) component by serum and urine protein electrophoresis (concentrate of 24-hour urine); quantification of IgG, IgA and IgM immunoglobulins; characterisation of the heavy and light chains by immunofixation; serum-free light-chain measurement for identifying and monitoring nonsecretory multiple myeloma (MM).

Evaluation of bone marrow plasma cell infiltration. Bone marrow aspiration and biopsy are the standard option to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells.

Evaluation of lytic bone lesions. Full skeleton x-ray survey is recommended. Optional magnetic resonance imaging (MRI) provides greater details and is recommended if a spinal cord compression is suspected.

Biological assessments to differentiate symptomatic and asymptomatic MM: haemoglobin (and full blood cell count), serum creatinine and calcium level (CRAB classification).

These tests allow the differential diagnosis between symptomatic MM, smouldering (or indolent) MM and MGUS.

Table 1. ESMO clinical recommendations for diagnosis [28].

Staging

Historically three systems of evaluation of newly diagnosed myeloma have guided therapy decisions and prognostic speculation. The Durie-Salmon staging system primarily categorised patients using five factors: amount of paraprotein in the blood or urine; amount of serum calcium; haemoglobin; renal function and number of lytic bone lesions [29]. This system does not include assessment of either β2 microglobulin nor albumin. The International Prognostic Index (IPI) may provide more useful prognostic information to guide treatment decisions [27] as represented in the International Staging System (ISS) (Table 2) or functional staging system [10], as it includes reproducible parameters of albumin and β2 microglobulin and categorises patients into three 'risk groups'. The three groups are high, intermediate or low risk, which is useful both prognostically (as there appears to be a clear difference in outcome between the three) and it facilitates comparison across data sets in clinical trials.

Stage	Risk	Criteria
I	Low	serum β2 microglobulin <3.5mg/L & serum albumin ≥3.5g/dL
II	Intermediate	serum β2 microglobulin <3.5mg/L & serum albumin <3.5g/dL or serum β2 microglobulin 3.5-5.5mg/L irrespective of serum albumin
III	High	serum β2 microglobulin >5.5mg/L

Table 2. The International Staging System [27].

Current treatment options

The aims of treatment in multiple myeloma are to: induce remission or response of varying degrees (Table 3); to preserve the function of the major organs and, in doing so, maintain functionality and quality of life. Therapy is increasingly becoming a 'risk adapted' choice, where the treatment choice is determined by: aggressiveness of disease and tumour burden; age and general health of the patient; access to clinical trials and newer agents and patient choice.

International Myeloma Working Group Response Criteria	
Complete Response (CR)	No M protein in serum, loss of plasmacytoma & <5% plasma cells in bone marrow
Very Good Partial Response (VGPR)	Detectable M protein but≥90% reduction
Partial Response (PR)	Detectable M protein but ≥50% reduction
Stable Disease (SD)	Not CR, VGP, PR or PD
Progressive Disease (PD)	>25% increase in M protein

Table 3. International Myeloma Working Group Response Criteria Summary [25].

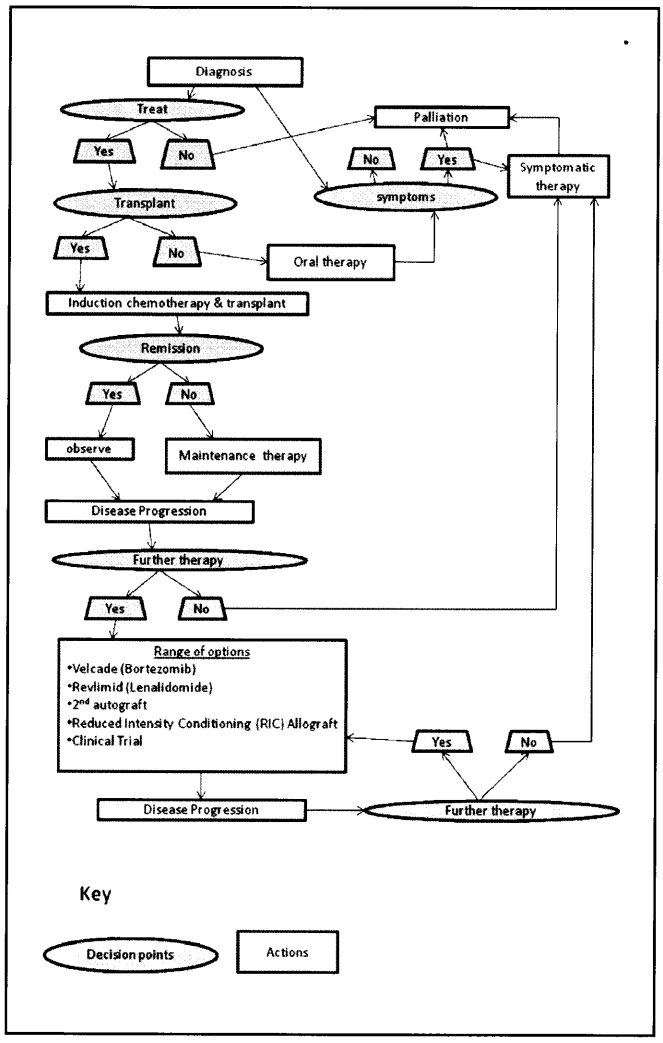
Chemotherapy, immunomodulatory therapies (otherwise known as 'novel agents'), with or without the high-dose therapy and stem cell rescue (autologous transplant) are the keystones of treatment.

The addition of thalidomide, lenolidomide and botezomib, often combined with dexamethasone, have substantially changed the landscape of myeloma treatment by inducing improved overall and duration of response and progression-free and overall survival, for patients with newly diagnosed and relapsed and refractory myeloma [30]. Melphalan and prednisolone remain an option for transplant ineligible patients but novel agents appear safe and beneficial in this group also.

Treatment of myeloma requires supportive management of complications associated with the disease. For example, management of bone disease (primarily with bisphosphonates) and renal impairment are as essential an antimyeloma treatment itself. Multiple myeloma remains an incurable cancer. However, complete and partial remissions are attainable in most patients for varying lengths of time and the focus in treatment aims are shifting from remission being the only option for quality of life to one of attaining durable complete or partial remission, that is, people living with their disease in a controlled state of relapse. Of importance in managing myeloma is that it appears to have a heterogeneous biology [31] and this impacts on the prognosis, clinical course and response to therapeutic interventions in different people [12]. This is becoming increasingly apparent as the meaning of variations in gene profiling, differences in response to treatment and variations in time to progression are evaluated.

Management of myeloma is focused on the concepts of inducing remission, extending durable remissions of varying degrees and maintaining quality of life and functionality in relapse. As cure is often not an attainable outcome, focusing on these concepts facilitates the patient to live with myeloma in a chronic state of relapse.

Figure 1. Broad overview of the process of decision-making points and possible pathways in the treatment of myeloma.



The broader array of therapy choices, none of which offer a single magic bullet, but many of which offer varying degrees of response, has changed the way relapsed disease is both managed and perceived. The increasing knowledge of the way myeloma interacts in the bone marrow microenvironment and the understanding of signalling pathways therein has led to the development of a number of drugs that impact at this level, providing options of various lines of therapy. A lack of or limited response to one drug does not mean that there will be no response to other lines of treatment, thus altering the trajectory of the disease, particularly after initial relapse.

Initial myeloma treatment utilised agents which were systemic in action and one of the major developments in recent years has been the use of more targeted therapies that have specific action in the bone marrow microenvironment. Historically, melphalan, doxorubicin, glucocorticosteroids and vincristine have been used alone or in combination to provide the mainstay of myeloma therapy. More recently, new active agents such as thalidomide, bortezomib, lenalidomide and combinations of these, with or without conventional therapy, have increased options for therapy choices and in doing so have created a range of treatment choices at both diagnosis and relapse.

Relapse management, management of refractory disease, symptom control and quality of life are key considerations in myeloma management. So far, innovative salvage treatments have not been demonstrated to offer any advantage over standard treatments [32]. There is now a variety of drugs and combinations available. The use of these options for the individual patient is dependent on their response to initial treatment. The degree and length of each drug response may vary with individual patients. There is a need to evaluate the risk-benefit ratio with regard to best response and minimum side effects. There appears to be an important difference between responsiveness to therapy and time to subsequent disease progression after therapy and these are two very different endpoints, of which the latter may ultimately be more important [12, 32]. Therefore, the treatment goal for many people with myeloma is that of a living with disease in a 'control' paradigm rather than the achievement of cure.

The role of transplant

Guidelines from Europe, the USA and Australia recommend that high-dose chemotherapy with autologous stem cell transplant should be part of initial treatment for people with myeloma who are 65 years or younger and have an adequate functional status [33].

Stem cell transplant has arguably been the gold standard in consolidation for eligible patients [32] and a strategy of tandem transplant appears to demonstrate a survival advantage, but only in patients who did not achieve a very good response to the initial transplant [12, 34]. More recently, the role of transplant

has been disputed as being a required treatment modality for all potentially eligible patients. There may be a subgroup of people for whom their disease's natural history allows them to maintain a durable good partial remission without transplant [12].

The role of maintenance treatment

The role of maintenance therapy must be balanced by the effect on quality of life and the benefit achieved. Maintenance with drugs such as thalidomide and Interferon-α with their inherent side effects and impact on quality of life may have limited appeal. For standard risk patients, no therapy has yet been shown to prolong survival in a clinically important manner to justify associated adverse effects [35].

Management of myeloma relapse

The availability of a number of therapeutic options with varying individual responses and the potential for patients to be able to tolerate multiple lines of therapy to control relapse, means that a full exploration of response and toxicities of known therapies must be undertaken before abandoning hope of a good outcome in relapse [12].

Psychosocial and quality of life issues for patients and families

Multiple myeloma is an incurable cancer and often has a complex trajectory. The relentless nature of myeloma combined with phases of acute illness (such as sepsis, acute renal failure or fractures) contribute to uncertainty. The main aims of treatment are, therefore, to control the disease, to secure remission and to maximise quality of life. The median duration of survival in the 1990s was 2.5 years [36]. Recent improvements in treatment, notably the availability of novel agents and care have increased the median survival to 5-7 years [37]. Many patients now survive 10-15 years. With few exceptions, most patients die from their disease, despite onerous and often complex regimens involving multidisciplinary support and a number of different treatment modalities.

Although little is known about how people manage their illness, it is clear that they are now living longer with myeloma. Myeloma is a disease that transgresses accepted categories of acute, chronic and terminal illness and, as such, creates uncertainty among patients, families and healthcare professionals. At initial diagnosis, myeloma has often never been heard of, which exacerbates the fear, upheaval and biographical disruption associated with a cancer diagnosis. Loss of income may be a major issue as frequently, but not always, people with myeloma are unable to work due to both the effects of the disease and treatment and the demands of treatment. The incurable nature of myeloma requires psychological and social adjustment and support.

The impact of the so called 'novel agents' has been to provide much improved survival for many patients; however, this is not without cost. The side effects of these treatments have a profound impact, particularly on quality of life. People with myeloma are living longer but they are living differently. Peripheral and autonomic neuropathy, profound fatigue, infection and pain are reported effects that impact on quality of life and therefore require recognition, assessment and proactive intervention.

Nursing implications

Key areas for nurses to engage with patients and their families are in the management of pain and in prevention, early recognition and monitoring of complications such as spinal cord compression, infection, hypercalcaemia, renal impairment, fatigue, constipation and peripheral neuropathy. Pain is primarily due to bone disease and requires an expert and multidisciplinary approach. Pain assessment tools are readily available and provide a benchmark against which an assessment of efficacy of treatment can be measured. The World Health Organization analgesic ladder [38] continues to provide a useful resource. Myeloma pain, particularly bone pain, frequently requires management with opiates. Nurses are in a position to provide therapy, advice and referral with nonpharmacological pain interventions.

Nurses have a key role in coordinating care and providing a therapeutic, supportive relationship across the trajectory from the bewilderment of diagnosis through to palliative and end of life care. The nurses' role is crucial in providing a motivated, knowledgeable and realistic approach for the person with this rare, incurable but treatable cancer.

Effective care requires understanding of the nature of myeloma and the range of treatment options available; early detection, recognition and support of the major complications of myeloma and treatment; the provision of a specialised resource for information, education and support for patients, families [39] and other healthcare professionals.

Conclusion

Myeloma is a rare haematological cancer, accounting for 1% of malignancies and 15% of haematological malignancies. It is characterised by excess plasma cells in the bone marrow, renal disease, osteolytic bone disease, a monoclonal paraprotein and immunodeficiency.

Treatment is aimed at inducing remission or a response and preserving functionality and quality of life by maintaining organ function and reducing tumour burden.

The introduction of autologous transplant in the 1980s and of 'novel agents' in recent years has changed the landscape of myeloma treatment and has consequentially improved survival. Many people now live with myeloma for longer, managing

their disease and treatment complications along a trajectory of chronic and acute illness phases. As people are living longer with myeloma, nurses have an important role in recognising the changes apparent in the management of the disease and by providing expert care through recognition, assessment and intervention.

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Editorial information