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## Management of the Older Patient with Multiple Myeloma

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### ABSTRACT

More than 50% of patients with multiple myeloma are over the age of 60 years at the time of presentation. The presenting features in the elderly are the same as for younger patients, with bone lesions and pathological fractures, hypercalcaemia, anaemia and renal impairment. Some patients are asymptomatic with a paraprotein found incidentally. Fit patients up to the age of 70 years without cardiovascular or significant renal disease may be managed in the same way as younger patients by firstly having their tumour load reduced with combination IV chemotherapy, followed by high-dose chemotherapy with peripheral blood stem cell rescue. In younger patients this aggressive approach has been shown to afford a survival advantage of approximately 18 months. Patients of more advanced age or with significant co-morbidities may achieve a good response with judicious administration of oral chemotherapy, commonly melphalan and prednisolone. With dose adjustments to reduce toxicities patients can have durable disease responses and relief of symptoms even in the very elderly. The median survival without high-dose chemotherapy is 3 to 5 years. This prognosis is not age-specific, but age-related co-morbidities may limit treatment options and hence affect the prognosis adversely. Some patients have indolent disease with a superior prognosis, requiring treatment only with progression and development of symptoms. Prophylaxis with bisphosphonates has been shown to reduce the incidence of fractures and radiotherapy can afford excellent palliation. The introduction of thalidomide to routine care has given a further palliative treatment, with a third of patients refractory to chemotherapy responding. Clinical studies addressing the use of thalidomide earlier in treatment are being undertaken. Dose reduction is often required in older patients because of increased somnolence and constipation. Withdrawal may be required because of neurotoxicity. Newer agents with similar properties to thalidomide but with fewer toxicities are eagerly awaited.

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### INTRODUCTION

Multiple myeloma is a disseminated clonal malignancy of plasma cells. In the majority of cases, a complete immunoglobulin or portions of immunoglobulin, for example, light chains are secreted. Current treatments improve survival and provide palliation, but are not curative. Despite advances in therapy, the median survival remains between 3 to 5 years.

### PREVALENCE

The median age at diagnosis of multiple myeloma is approximately 62 years.<sup>1</sup> More than 25% of newly diagnosed patients are older than 70 years of age. This malignancy is the second most common haematological malignancy in the US, with a frequency of 1% of all cancers and 10% of haematological malignancies.<sup>2</sup> The crude incidence figures from the Victorian State Cancer Register in 2001 were 7/100 000 for males and 5/100 000 for females, suggesting a similar incidence in Australia.<sup>3</sup>

### CLINICAL FEATURES

The unique clinical features of multiple myeloma relate both to expansion of plasma cells in bone and the physicochemical properties of the immunoglobulin (paraprotein or M band) produced. Plasma cells infiltrate bone marrow and bone causing lytic lesions. The paraprotein can cause renal impairment from tubular deposition, feedback to reduce normal immunoglobulin production, form amyloid deposits and rarely cause hyperviscosity. The paraprotein is a useful tumour marker and allows easy monitoring of disease response.

The presenting features of patients over the age of 75 years are the same as for younger patients, with the exception of an increased rate of infection.<sup>4</sup> In some patients, the paraprotein is found incidentally. In contrast some patients present as a medical emergency with hypercalcaemia or acute renal failure. Some older patients may have a delay in diagnosis as the symptoms may be attributed to other age-related problems such as osteoporosis. Significant co-morbidity is seen in unselected patients that present over the age of 75 years, most frequently cardiovascular disease.<sup>4</sup>

Bone disease may be asymptomatic or result in generalised osteoporosis, pathological fractures and hypercalcaemia. A normochromic anaemia is often present at diagnosis, but other cytopenias are unusual until the late stages of the disease or may be complications of treatment. Renal impairment at diagnosis (abnormal creatinine) can be found in 31% of patients presenting with multiple myeloma from all ages and 49% if defined by an abnormal creatinine clearance.<sup>5</sup> A smaller proportion of patients present with acute renal failure, which is most often due to light chain nephropathy. Acute renal failure may be precipitated by dehydration, hypercalcaemia, hyperuricaemia, contrast medium and sepsis. Amyloidosis is a rarer complication and is occasionally the major feature at diagnosis, causing proteinuria and renal impairment, as well as deposition in other organs, most importantly a restrictive cardiomyopathy. Infectious complications are a major feature of multiple myeloma. Recurrent bacterial infections, particularly from gram-positive organisms are seen secondary to immunoparesis, chemotherapy and steroid use.

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## DIAGNOSIS

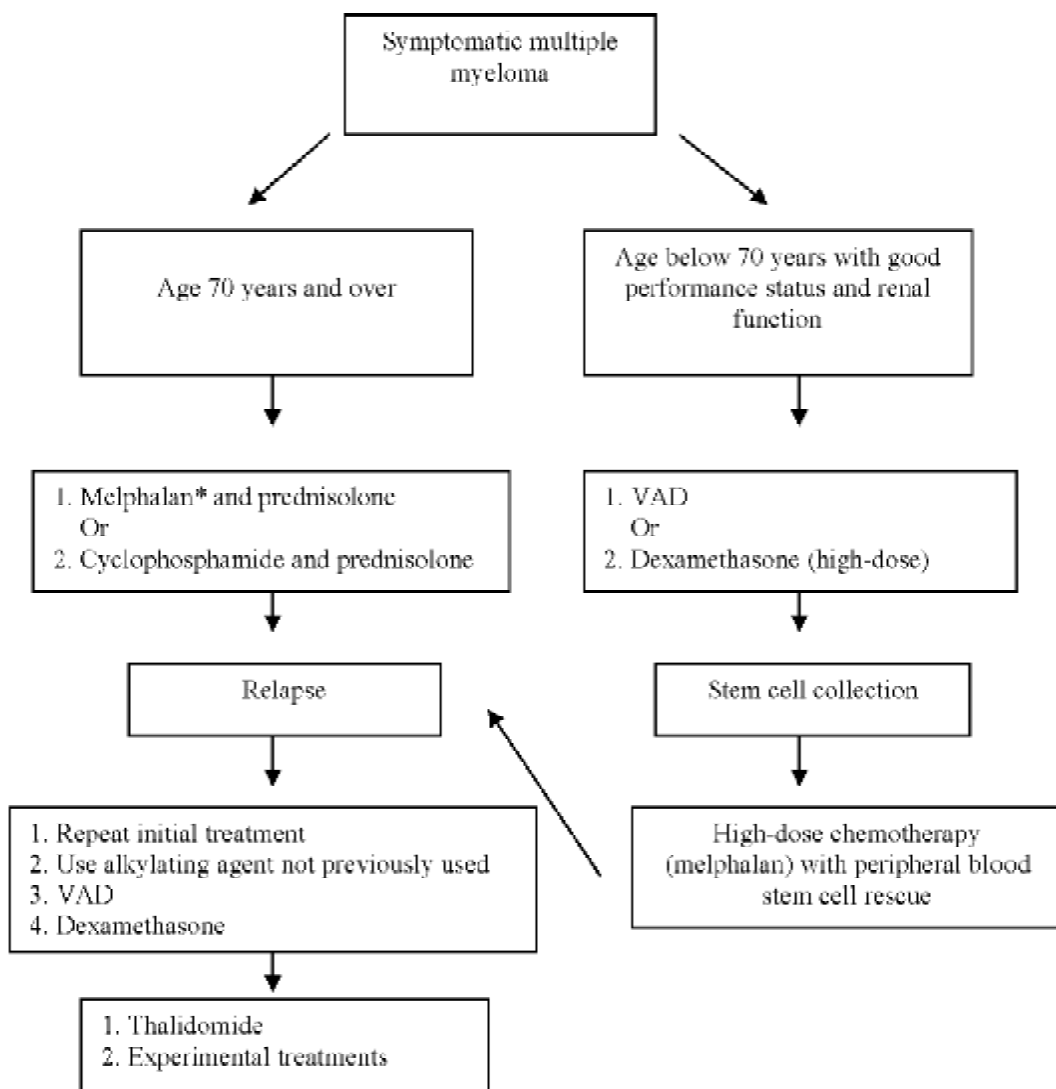
The minimum criteria for diagnosis of multiple myeloma include a bone marrow plasmacytosis of greater than 10% or a plasmacytoma, with at least one of the following: a paraprotein in the serum (> 30 g/L); light chains in the urine, and/or lytic bone lesions.<sup>1</sup> The diagnosis of multiple myeloma is most likely to require distinction from monoclonal gammopathy of uncertain significance, where these criteria are not met. Smouldering myeloma is defined as having a marrow plasmacytosis of >10%, paraprotein > 30 g/L, without bony lesions and very slow disease progression.

## MANAGEMENT

Treatment is commenced with symptomatic or progressive myeloma, but is not indicated in smouldering or indolent myeloma where there is absence of anaemia, renal impairment or bony lesions.<sup>6</sup> Many patients with smouldering myeloma do not progress over many months, and treatment, with its potential complications can be delayed until progression. An increasing paraprotein in serum or urine indicates that therapy will be required in the near future. Significant anaemia, hypercalcaemia, renal

impairment, lytic lesions or extramedullary plasmacytomas are indications to start treatment.

The goal of treatment is primarily that of palliation, but for younger patients and older patients without co-morbidities, the aim of treatment is to improve survival with an autograft. An autograft consists of high-dose chemotherapy with peripheral blood stem cell rescue. Achieving complete remission is rare in multiple myeloma, but may be associated with a survival advantage. The majority of patients have a partial response with continuing detectable paraproteins, even after autografting. A partial response is defined as 50% improvement in serum or urine paraprotein and clinical improvement. Patients are treated until the paraprotein becomes stable and reduces no further over three months. This plateau phase is a cytogenetically quiescent state similar to monoclonal gammopathy of uncertain significance or smouldering myeloma. Continuing treatment at this stage does not improve outlook<sup>7</sup> and may increase the risk of long-term treatment-related toxicities such as myelodysplasia, acute myeloblastic leukaemia and bladder tumours.<sup>8</sup> An approach to treatment is shown in Figure 1.



VAD = vincristine, doxorubicin, and dexamethasone; \*Melphalan is dose reduced or avoided in renal impairment.

VAD or dexamethasone is given for 3 to 6 cycles to rapidly reduce tumour burden. Treatment with alkylating agents is continued until plateau phase (no further reduction of paraprotein for 3 to 6 months).

**Figure 1. Initial treatment and treatment of multiple myeloma based on age, co-morbidities and renal function**

### Alkylating Agents

Oral melphalan and prednisolone are the traditional treatments for multiple myeloma and result in overall response rates in 50 to 60% of patients. This treatment results in a median survival of 2 to 3 years as determined by meta-analysis of trials including more than 6000 patients.<sup>8</sup> This combination is the first choice for patients older than 65 years who are not considered eligible for an autograft. Melphalan is given as a single daily dose, on an empty stomach to improve bioavailability. A mid-cycle neutrophil count is recommended to prove absorption and consider dose adjustment. Filgrastim or lenograstim may be given for severe neutropenia, but dose reduction is most often preferred. Generally, this regimen is well tolerated, even in those with a poor performance status and is conveniently administered without cytokine support. Melphalan is not recommended for patients with a pre-treatment neutrophil count below  $1.0 \times 10^9/L$  and platelets below  $75 \times 10^9/L$ . The dose of melphalan is 6 to 8 mg/m<sup>2</sup> daily and prednisolone 40 to 60 mg/day for four to seven days.<sup>1</sup> Cycles are repeated every six weeks. Dose reductions may be considered in the elderly and are recommended with renal impairment. Reduction of melphalan by 25% with creatinine > 0.177 mmol/L is recommended or with clearance < 50 mL/min.<sup>9</sup> Alternatively, cyclophosphamide, high-dose dexamethasone or combination chemotherapy could be considered. Melphalan is slowly effective and may require three cycles to be given for measurable effect. Overall response rates of 50% are seen with this regimen, but complete response rates are less than 10%.<sup>10</sup> The duration of the response is usually less than one year, with patients then requiring further treatment.<sup>11</sup> Melphalan may be given alone in those with diabetes, or alternatively prednisolone may be given at a low continuous dose.

Cyclophosphamide may also be given in low dose orally, usually in combination with prednisolone.<sup>12</sup> Disease that is refractory to melphalan may respond to cyclophosphamide. Cyclophosphamide can be used with caution in renal failure. Intravenous cyclophosphamide is used most often in doses of 1.5 to 4 g/m<sup>2</sup> to mobilise peripheral blood stem cells from marrow.

Anti-emetics, allopurinol or mouth care are not routinely given with oral chemotherapy. Proton pump inhibitors or H<sub>2</sub>-receptor antagonists may be given with oral steroids.

### Aggressive Therapies

VAD (vincristine, doxorubicin, and dexamethasone) or similar multi-agent chemotherapy is given either as initial treatment or at relapse. Vincristine and doxorubicin are delivered by infusion over four days, with intensive doses of intermittent oral dexamethasone. Although giving higher response rates than melphalan (60 to 70%), no overall survival benefit has been shown using VAD.<sup>8</sup> As well as having a superior response rate, the response to VAD is also more rapid than melphalan, which may improve symptom control. Infusional treatment is inconvenient and usually administered via a SC port to avoid extravasation. Some centres administer the infusion by a portable pump to allow ambulatory management. VAD may also be given to patients with renal impairment. Stem cell collections are not compromised and therefore VAD, or high-dose dexamethasone are the initial treatments of choice for patients suitable for autografting. A significant cardiac history, in particular reduced cardiac

ejection fraction and poor diabetic control are contraindications. Eighty percent of the effect of VAD relates to dexamethasone.<sup>11</sup> The adverse effects from VAD other than those related to steroids include cardiotoxicity, alopecia, cytopenias and infections.

High-dose dexamethasone induces responses in 43% of newly diagnosed patients, with a 4% incidence of serious adverse effects and rapid response.<sup>11</sup> The most common adverse effects are increased appetite, weight gain and insomnia. In the elderly, more serious adverse effects may occur more frequently with confusion, steroid-induced diabetes, osteoporosis and proximal myopathy possible. This treatment is suitable for patients with severe pancytopenia and for those presenting with renal failure.

A French randomised trial of 200 patients showed a significantly improved survival with high-dose chemotherapy using melphalan and total body irradiation followed by transplantation of autologous bone marrow, when compared with conventional chemotherapy. Five year survival rates of 52% were seen with high-dose chemotherapy compared to 12% for conventional chemotherapy.<sup>13</sup> The patients in this study were below the age of 65 years. Most units performing high-dose chemotherapy with peripheral blood stem cell rescue only consider patients older than 65 years, if they have a good performance status and normal renal function. However, age has not been shown to be a prognostic variable in the outcome after high-dose chemotherapy.<sup>14</sup> Currently, there is no evidence of a survival advantage for the 60 to 70 year old age group undergoing high-dose chemotherapy, although a small study of patients with a median age of 67 years has shown no difference in mortality with younger pairs,<sup>15</sup> suggesting that the advantage from this treatment is still seen in the older age group.<sup>1</sup> The use of autologous peripheral blood stem cell rescue rather than bone marrow as the source of stem cell rescue allows earlier recovery with reduced morbidity and mortality. A subsequent French randomised study has shown that compared to high-dose melphalan alone, the addition of total body irradiation increased toxicity and did not give a survival benefit.<sup>16</sup> Thus, conventional high-dose chemotherapy in most transplant units consists of melphalan (200 mg/m<sup>2</sup>) followed by rescue with peripheral blood stem cells. As melphalan is renally excreted, dose adjustments may be required in renal impairment,<sup>17</sup> and patients with significant renal impairment may be precluded from this treatment. One study of high-dose therapy using melphalan 100 mg/m<sup>2</sup> in elderly patients suggested that this treatment is superior to standard treatment and appeared to be better tolerated.<sup>18</sup> Preparation for high-dose therapy includes three to six cycles of induction treatment to reduce tumour burden using a regimen that does not reduce stem cells, such as VAD. Stem cells are mobilised from marrow using a combination of chemotherapy (most often cyclophosphamide) and cytokines (filgrastim or lenograstim). They are collected from peripheral blood by apheresis and cryopreserved. The majority of patients will relapse as this procedure is not curative.

Allogeneic transplantation using stem cells from a histocompatible sibling leads to prolonged disease-free survival in a relatively small percentage of patients.<sup>19</sup> There is some evidence of a graft versus myeloma effect, but

continuous relapse occurs, suggestive that cure is unlikely. The high treatment-related mortality associated with this procedure limits its use in younger patients. In an attempt to reduce mortality, more immunosuppressive, but less myeloablative conditioning regimens have been trialled.<sup>20</sup> These 'mini-allografts' remain experimental, but may allow allogeneic transplantation of patients in their 70s if tolerance and efficacy are proven.

### Supportive Care

To reduce gastric irritation, nonsteroidal anti-inflammatory drugs are avoided in multiple myeloma, particularly in those with renal impairment, but also in those having corticosteroids. Long-acting morphine preparations or transdermal fentanyl are commonly used if codeine/paracetamol preparations are insufficient for pain relief. Particular care is required in managing opiates in older patients and in those with renal impairment.

Randomised studies have shown that monthly IV bisphosphonates prevent or delay skeletal events such as osteolytic lesions and vertebral compression fractures.<sup>20</sup> Initial studies used pamidronate but zoledronic acid has shown equivalence and is infused over 15 minutes compared to 90 minutes for pamidronate.<sup>22</sup> Daily oral clodronate has shown equivalence to pamidronate but may not be tolerated due to nausea.<sup>23</sup> Many centres recommend that all patients with myeloma-related bone disease receive bisphosphonate therapy for an indefinite period.<sup>10</sup> In addition to hydration and steroids, bisphosphonates are used effectively to treat hypercalcaemia and relieve bone pain.

The principle organisms causing infections in patients with multiple myeloma are *Streptococcus pneumoniae*, *Haemophilus influenzae* and Herpes zoster. Although vaccination with pneumococcal, haemophilus and influenza vaccines is prudent, immunoglobulin production is defective in patients with multiple myeloma and efficacy of vaccination in this patient population reduced.<sup>10</sup> Symptomatic infections should be treated early with antibiotics. Currently, prophylactic antibiotics, or antiviral and antifungal agents are only used by some centres, particularly after high-dose therapy. Pneumocystis prophylaxis should be considered in those receiving high-dose steroids. Monthly immunoglobulin infusion has been shown to reduce infections, but is usually given to those with hypogammaglobulinaemia and recurrent infections.<sup>23</sup>

Anaemia is a common occurrence in multiple myeloma, compared to other cytopenias and may improve after chemotherapy, but an ongoing transfusion is often required. Erythropoietin is well tolerated and may be effective in multiple myeloma,<sup>25</sup> but due to cost considerations is most often used in those with renal impairment, meeting the criteria for government reimbursement in Australia.

Radiotherapy is usually reserved to control local pain that is unresponsive to cytoreductive treatment, bisphosphonates or steroids. Radiotherapy is most often used to treat acute spinal cord compression in multiple myeloma rather than surgery and incipient spinal cord compression may be averted by radiotherapy. Vertebral surgery or kyphoplasty may be considered in patients with vertebral instability or localised deformity. Plasma exchange is used to treat symptomatic hyperviscosity and may increase the chance of reversal of acute renal failure from light chain nephropathy.

### Maintenance Therapy

Few patients achieve a complete remission, even with high-dose treatment, but the majority of patients achieve a stable or plateau phase. Chemotherapy has not been shown to prolong the duration of this phase and may induce multi-drug resistance or treatment toxicities such as bladder tumours. The most common maintenance treatments used are either interferon or prednisolone. Many centres do not give maintenance therapy routinely due to toxicity, but combinations of low-dose thalidomide with prednisolone are being explored.

Although individual randomised studies have shown conflicting results, two meta-analyses have shown that interferon prolongs the duration of remission or plateau phase, with an improvement of survival of seven months in both studies.<sup>26,27</sup> Fatigue, depression and insomnia are prevalent adverse effects and may be more pronounced in the elderly. Due to the considerable adverse effects, cost considerations and modest survival advantage, interferon is not used routinely in most centres. Maintenance therapy with alternate day prednisolone 50 mg compared with 10 mg showed an improved overall survival of 37 versus 26 months for the higher dose of prednisolone.<sup>28</sup> Complications of increased osteoporosis, diabetes and infections may be anticipated and are more likely in older patients.

### Relapsed Disease

The majority of patients will relapse after the plateau phase and may respond to re-treatment with the initial regimen. Re-treatment with anthracycline-based regimens will be limited by the total anthracycline dose due to the risk of cardiac toxicity. Multi-drug resistance usually develops and alternative treatments sought. High-dose dexamethasone may be effective, particularly if previous regimens contained lower doses of steroids. Those patients with a long duration of remission after stem cell autograft may be considered for a second stem cell autograft, if fit and if sufficient stem cells have been collected to support a second transplant.

Thalidomide was originally used empirically to treat multiple myeloma based on its anti-angiogenic properties and an observation of increased angiogenesis in bone marrow. Response rates of 32% were seen in patients with refractory myeloma<sup>29</sup> and have been confirmed in other studies. Unfortunately, somnolence, fatigue, constipation, rash, peripheral neuropathy and deafness are common adverse effects and many patients, particularly the elderly, are unable to tolerate this medication. The starting dose is 200 mg daily, increased after two weeks to 400 mg daily, with some patients requiring up to 800 mg daily to sustain a response.<sup>10</sup> Adequate contraception must be used by males and females, if appropriate, due to the risk of teratogenicity. An incidence of venous thromboembolism of 1 to 2% is seen in patients receiving thalidomide alone, but the incidence may be as high as 25% when used in combination with chemotherapy, particularly anthracycline containing regimens.<sup>30</sup> Regimens with lower doses of thalidomide show some promise and more acceptable adverse effects.<sup>31</sup>

### New Experimental Treatments

Bortezomib (Velcade) is a boronic acid dipeptide and a reversible proteasome inhibitor (formerly known as PS-

341) that promotes apoptosis in multiple myeloma cell lines. Proteasome is a multi-enzyme complex that degrades cell-cycle progression proteins, activates nuclear factor  $\kappa$  and is present in all cells. A Phase I study of bortezomib included patients up to the age of 84 years, with some responses seen. The major adverse effects were myelosuppression, fatigue and peripheral neuropathy.<sup>32</sup> CC-5013 (revemid), an immunomodulatory drug, is a derivate of thalidomide. A Phase I study suggests that this drug gives some responses, is well-tolerated and is free of the adverse effects of somnolence, constipation and peripheral neuropathy that complicate the use of thalidomide.<sup>33</sup>

## CONCLUSION

Elderly patients may be treated for multiple myeloma, even into advanced age, for symptom control. Standard treatment with oral alkylating agents and steroids, such as melphalan and prednisolone, are simple and effective agents which can be dose reduced for elderly patients and for renal impairment. Many will reach a stable plateau phase where chemotherapy may be withheld. Younger and fitter patients, particularly younger than 70 years, may be eligible for more aggressive treatment that has been shown to improve survival. A good performance status and renal function is required to undergo the rigours of high-dose chemotherapy and peripheral blood stem cell rescue. Cytoreduction with combination chemotherapy with regimens such as VAD is given prior to high-dose chemotherapy and stem cell collection. Oral or IV bisphosphonates such as clodronate and pamidronate are used routinely to prevent fractures and reduce bone pain. Supportive care of pain control with analgesia and radiotherapy may greatly benefit quality of life. Erythropoietin may reduce transfusion requirements. Maintenance therapy with interferon or prednisolone is controversial. Treatment of relapse may include high-dose dexamethasone or thalidomide, drugs that are to be used with care in the elderly. Newer agents such as bortezomib and revimid may be as effective as thalidomide and have more tolerable adverse effects. The median survival of multiple myeloma remains between 3 to 5 years.

**Competing interests:** None declared

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