Multiple myeloma

Updated approach to management in 2018

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Background
Multiple myeloma is an uncommon haematological cancer of plasma cells. Improvements in understanding of this disease have lead to drastic changes regarding diagnosis, management and its prognosis.

Objectives
The aim of this article is to provide a concise update regarding the current management of myeloma in Australia, and important management issues for general practitioners.

Discussion
With the advent of new treatments, the outcomes of myeloma have changed drastically in the past decade, and it is now a disease that requires long-term monitoring by both haematologists and general practitioners.

MYELOMA, a malignant disease of the plasma cell, accounts for approximately 10% of all haematological malignancies. Recent population statistics indicate an incidence of four per 100,000, with a median age at diagnosis of approximately 70 years for both males and females. As age increases, so do the incidence of myeloma and the mortality rates associated with the disease. It was estimated that in 2017, 1816 new diagnoses of myeloma would be made, and the condition would cause 971 deaths across Australia.[1]

The diagnosis of myeloma uses an integrated approach of clinical findings, laboratory investigations and imaging techniques. A spectrum of disease exists, starting with monoclonal gammopathy of undetermined significance (MGUS), which can progress to smouldering and symptomatic multiple myeloma. MGUS occurs in approximately 3% of people aged 50 years or older. The risk of progression from MGUS to myeloma is dictated by the type of paraprotein, total paraprotein level and serum free light chain ratio. Rates of progression vary and are estimated to be 7–30% over a 20-year period.[2]

Signs and symptoms

An easily remembered acronym, CRAB (calcium, renal disease, anaemia, bone disease), aids in the diagnosis of myeloma, and each element is a disease-defining event (Box 1).

Investigations

History, physical examination and blood tests are the key to the detection of myeloma.[3] Tests include:

- complete blood count with differential and peripheral blood smear review
- urea, electrolytes, creatinine and calcium
- serum protein electrophoresis, immunofixation
- routine urinalysis, 24-hour urine collection for proteinuria, electrophoresis and immunofixation.

Additional tests and investigations arranged by haematologists include:

- a bone marrow aspirate to detect the degree of plasma cell infiltrate and for fluorescent in situ hybridisation to detect cytogenetic changes.
- imaging of the skeleton with either magnetic resonance imaging, low-dose whole body computed tomography (skeletal survey) or positron emission tomography scan to detect lytic lesions and fractures.

Prognosis

Prognosis for myeloma is based on serum albumin, beta 2 microglobulin levels and cytogenetic changes (Tables 1, 2).

Treatment

Treatment is offered when the patient has established symptomatic myeloma. Treatment varies and takes into account

Box 1. The CRAB (calcium, renal disease, anaemia, bone disease) acronym for diagnosis of myeloma

Calcium
- Hypercalcaemia, presenting with abdominal pain, constipation, polyuria

Renal failure
- Uraemic symptoms, fluid overload

Anaemia and other cytopenias
- Leukopenia/neutropenia, with increased risk of infections
- Thrombocytopenia with increased risk of bleeding

Bone pain and bone fractures

the comorbidities and performance status of patients. The options are summarised in Table 3. In Australia, current first-line treatment for transplant-eligible patients with myeloma includes induction with bortezomib-based therapy followed by autologous bone marrow transplantation. There is no specific age cut-off for therapies, and first-line therapy with bortezomib can be well tolerated in elderly (age >80 years) patients. Eligibility for autologous transplantation is assessed on age, comorbidities and frailty. The upper age limit for transplantation is generally 70–75 years in Australia.[4]

Bortezomib

Bortezomib is a proteosome inhibitor delivered intravenously or subcutaneously, generally in combination with an alkylator and steroid, on a weekly or bi-weekly basis. It is approved for all new diagnoses and relapsed multiple myeloma irrespective of age or cytogenetics.

Traditionally, bortezomib is used in combination with cyclophosphamide (orally) and dexamethasone (orally), with a number of international trials showing overall response rates of 91% and complete remission rates of 46%.[5] The significant toxicities of bortezomib-based therapy include thrombocytopenia (48%), neutropenia (12%) and peripheral neuropathy (6%). Painful peripheral neuropathy is a considerable side effect, more common in the elderly, and is a cause for dose reduction or cessation.[6]

Lenalidomide

Lenalidomide is an immunomodulatory drug that is derived from thalidomide, with anti-tumour effects through inhibition of angiogenesis and immunomodulation. It is an oral medication that is generally given in combination with dexamethasone in 21-day cycles, with seven-day break. Treatment is ongoing until disease progression or unacceptable toxicity.

Combination therapy with lenalidomide and dexamethasone results in overall response rates of 60% and complete remission rates of 15%. In a large international trial, combination therapy resulted in significantly improved overall survival of 60 months compared with 21 months in the dexamethasone monotherapy group.

Significant toxicities included higher rates of venous thromboembolism (15% versus 5%), neutropenia (35% versus 3%) and thrombocytopenia (13% versus 6%).[7] Lenalidomide is excreted through the kidneys; renal impairment results in drug accumulation and increased myelosuppression. Careful dosing and monitoring of renal function is necessary.[8]

Pomalidomide

Pomalidomide is a derivative of thalidomide and lenalidomide, with a similar mechanism of action. It is currently approved for use in Australia in patients with relapsed refractory myeloma. It is an oral therapy generally used in combination with dexamethasone in 21-day cycles, with a seven-day break. Treatment is ongoing until disease progression or unacceptable toxicity.

Trials for pomalidomide have largely taken place in the relapsed refractory setting, after treatment with bortezomib and lenalidomide. The overall response rates in these heavily pretreated groups are 30–60%, with a median overall survival of 12–16 months.[9]

The most frequent adverse effects associated with pomalidomide are haematological (neutropenia 48%) and infection (30%). There were low rates of peripheral neuropathy.

Carfilzomib

Carfilzomib is a modified proteosome inhibitor similar to bortezomib. It reversibly and irreversibly inhibits proteosome mechanisms of the cell, inducing apoptosis of malignant plasma cells. It is available on the Pharmaceutical Benefits Scheme (PBS) for relapsed refractory multiple myeloma after one line of therapy. It is used in combination with dexamethasone and delivered intravenously as an outpatient procedure on days 1, 2, 7, 8, 15 and 16.

Table 1. International Myeloma Working Group Revised International Staging System (R-ISS)[19]

Revised International Staging System (R-ISS)	Criteria
R-ISS 1	• Serum beta 2 microglobulin <3.5 mg/mL and serum albumin >35 mg/dL • No high-risk cytogenetic abnormality • Normal lactate dehydrogenase (LDH) level
R-ISS 2	• Not R-ISS 1 or 3
R-ISS 3	• Serum beta 2-microglobulin level >5.5 mg/L • High-risk cytogenetic abnormalities or high LDH level

Table 2. Cytogenetics risk stratification[20]

Risk stratification	Cytogenetics	Median overall survival (years)
Standard risk	Trisomies t(11;14) t(6;14)	8–10
Intermediate risk	t(4;14) Gain(1q21)	4–5
High risk	Del(17p) t(14:16) t(14;20) Del(1p)	3

In one landmark trial, carfilzomib was used in conjunction with dexamethasone and compared with bortezomib and dexamethasone. Carfilzomib and dexamethasone doubled the median progression-free survival (18 months versus nine months). Median overall survival improved by seven months in the carfilzomib group (47 months versus 40 months).[10] Anaemia, hypertension, pneumonia and thrombocytopenia were all more common in the carfilzomib group.

Daratumumab

Daratumumab is a human immunoglobulin G (IgG) monoclonal antibody that binds to CD38, a unique plasma cell surface marker. Its mechanism of action includes complement-mediated and antibody-dependent cell-mediated cytotoxic effects, and apoptosis.[11] It is not currently available on the PBS but is available by a compassionate access scheme. It is delivered intravenously weekly, with the first dose having an infusion time of approximately eight hours. Patients are monitored closely for evidence of infusion reactions.

Daratumumab was analysed in a population of patients who were heavily pretreated with multiple different therapies. These include those refractory to proteosome inhibitors and previous transplantation. The overall response rate was 30%, the median duration of response was 7.4 months, and the 12 month overall survival was 64%. When used in combination with first-line therapy, response rates increase to approximately 90%.[12]

Therapy was well tolerated, with anaemia and fatigue being the prominent adverse effects. There were significant infusion reactions observed in approximately 45% of patients, with 98% of those within the first infusion.[13] Most were grade 1–2, requiring additional steroids and antihistamines. There were no grade 4 infusion reactions.

Autologous stem cell transplantation

Autograft in an upfront setting is still considered the standard of treatment for newly diagnosed myeloma. It is generally performed after 4–8 cycles of induction chemotherapy (with bortezomib) and takes place at a specialised transplantation centre. After stem cell mobilisation with granulocyte colony-stimulating factor (G-CSF) with or without cyclophosphamide, patients have their stem cells collected and re-infused after high-dose chemotherapy (melphalan-based). They remain in hospital until their bone marrow recovers and are then followed up regularly in the clinic. The purpose is to deliver a high dose of chemotherapy for its antimyeloma effect and rescue the patients from marrow aplasia with their own stem cells. Trials indicate an improved progression-free survival (43 months versus 28 months) and better three-year overall survival (86% versus 73%).[14]

Complications from autologous transplantation include significant cytopenias, infection and mucositis. There is no graft versus host disease post-autograft, as the stem cells are the patient's own. The mortality rate is 1–5%. Recovery after transplantation generally takes 3–6 months and requires close monitoring in the community. Infection and re-admission to hospital post-transplantation is not uncommon.

Table 3. Summarised treatment for myeloma

Treatment	Mechanism of action
Imids	
• Thalidomide	Immunomodulatory
• Lenalidomide	Anti-angiogenic
• Pomalidomide	Anti-tumour effect
Proteosome inhibitors	
• Bortezomib	Interruption of cellular protein assembly
• Carfilzomib	Directly inhibit proliferation and induce apoptosis in multiple myeloma cell[19]
Monoclonal antibodies	
• Daratumumab	Complement-mediated and antibody-dependent cell-mediated cytotoxic effect, and apoptosis[11]
Autologous stem cell transplantation	High-dose chemotherapy for anti-myeloma effect Followed by patient's own stem cell 'rescue'

Additional treatment

Radiation

Radiation has a key role in the treatment of multiple myeloma and is used as a definitive therapy for solitary plasmacytoma;[15] it is also used at palliative doses for painful bony lesions or bones at risk of spontaneous fracture.[16]

Bisphosphonates

Bisphosphonates are used intensively in multiple myeloma to reduce skeletal-related events (pathological fracture, spinal cord compression, necessity for radiation of bone or surgery to bone). The chosen drug, commonly either zoledronic acid or pamidronate, is administered every four to six weeks for at least two years. After two years, those who have achieved complete remission or very good partial remission can discontinue therapy, but those with a partial remission or active disease should continue therapy.[17] Physicians and general practitioners should be mindful of the increased rate of osteonecrosis of the jaw, and careful dental review is needed prior to initiation of treatment and with ongoing bisphosphonate treatment.

Thromboembolism

Rates of thromboembolism are increased in multiple myeloma for a variety of reasons. Higher rates are attributable

not only to the malignancy, but also to the therapy. Thalidomide and lenalidomide, in combination with dexamethasone, increase thrombotic rates to 12–26%.[18] Current recommendations include an individualised approach, taking into account prior history, disease status and therapy to guide prophylaxis. Approximately 5–8% of patients on prophylaxis will still have a thromboembolic event.[18]

Follow-up

Follow-up varies for different patients in different states of disease activity. Patients with low-grade MGUS can be monitored every 6–12 months in the clinic, depending on its estimated risk of progression. Smouldering myeloma is generally seen every three months in the clinic, with repeated measurement of paraprotein and light chain levels. Active symptomatic myeloma is seen monthly in the clinic to monitor for disease response with full blood counts and paraprotein measurements, as well as monitoring for toxicity of therapy.

A variety of allied health and other speciality teams are fundamental for proper care. Dietitians, physiotherapists, pharmacists, palliative care teams and orthopaedic specialists are all essential for holistic care.

Key points

- Myeloma management is a rapidly changing field of haematology.
- Myeloma can be preceded by more indolent forms (MGUS and smouldering multiple myeloma).
- The incidence of myeloma increases with age, and symptoms are defined by CRAB criteria.
- Basic investigations in an outpatient clinic, as well as bone marrow aspirate and imaging, are used for diagnosis.
- Management often involves combination therapy, with numerous cycles and potentially stem cell transplantation.
- Adjunct therapies are often needed, including bisphosphonates and radiation.
- Multidisciplinary teams are necessary with allied health, general practitioners and palliative care doctors essential for appropriate management.
- Follow-up is generally lifelong, with ongoing monitoring of blood counts, paraprotein, bone health and other comorbidities.

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