# Biology and therapy of multiple myeloma

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## Summary

- Genetic sequencing of the myeloma genome has not revealed a specific disease-determining genetic alteration.
- Multiple disease subclones exist at diagnosis and vary in clinical importance with time and drug sensitivity.
- New diagnostic criteria have identified indications for early introduction of therapy.
- Autologous stem cell transplantation remains an essential component of therapy in young and fit patients.
- The use of continual suppressive (maintenance) therapy has been established as an important component in therapy.
- Immune therapies and the harnessing of the innate immune system offer great promise for future treatments.
- Since 2005, quality of life, supportive therapies, and survival have dramatically improved over a decade of remarkable progress.
- The common manifestations of multiple myeloma, such as bone pain, fatigue and weight loss, may be non-specific and are often initially ignored or missed by patients and medical practitioners.


Multiple myeloma is a malignancy of plasma cells originating from the bone marrow; it is a clonal plasma cell disorder that produces excess monoclonal immunoglobulin. The disease most commonly presents with hypercalcaemia, renal failure, anaemia and bone lesions (CRAB features) (Box 1).[1] Myeloma accounts for about 10% of all haematological malignancies. The annual incidence of myeloma in Australia is about five cases per 100 000 population, and there are about 1200 new patients diagnosed each year; the median age of diagnosis is the mid-60s.[4] There is variation in incidence among the different ethnic groups, with myeloma being twice as common in African Americans than in white people and less common in Asians.[1,5] Myeloma is preceded by an indolent phase termed monoclonal gammopathy of undetermined significance (MGUS), which is defined by the presence of a monoclonal protein (< 3 g/dL) without any end organ damage or features of myeloma. The cause of MGUS is currently unknown, but this disorder can evolve into symptomatic myeloma. The risk of progression to myeloma is about 1% per year, with risk factors being a high monoclonal protein level, high percentage of plasma cells in the bone marrow, presence of IgA monoclonal protein, and an abnormal free light chain ratio.[6] The prevalence of MGUS increases with age, with 3.2% of cases presenting in persons aged over 50 years, and 5.3% of cases in persons aged over 70 years.[7] From the early 1960s until the early 2000s, melphalan chemotherapy with addition of steroids (prednisone or dexamethasone) formed the basis for treating multiple myeloma. Melphalan was also used both in conditioning chemotherapy, which ablates the bone marrow before autologous stem cell transplantation, and for the treatment of patients deemed unsuitable for transplantation. There has recently been progress in the treatment of myeloma with the development of new targeted therapies, which include thalidomide, lenalidomide and bortezomib (Box 2). These newer agents have significantly changed the treatment strategies (Box 3).

In the decade following 2005,[1] there have been remarkable advances in therapy, which have resulted in improved survival rates in all age groups, but especially in younger patients (aged < 65 years), with median survival rates in a real-world situation of 7–8 years.[8,9] This evolution in understanding of myeloma has led to new diagnostic criteria for myeloma and high risk smouldering multiple myeloma and to the development of concepts of continual suppressive therapy akin to protocols used in acute lymphoblastic leukaemia, with induction, consolidation and maintenance phases of treatment.

This progress has been made possible by high dose therapy and stem cell transplantation, the development of novel drugs, targeted therapies, and the ability to harness the patient's immune system. There has been a progressive evolution of novel immunomodulatory drugs from thalidomide to lenalidomide and pomalidomide, proteasome inhibitors from bortezomib to carfilzomib and ixazomib, and targeted monoclonal antibodies (elotuzumab and daratumumab) as well as the bone-protective agents zolendronic acid and denosumab.

In addition, new immunomodulatory therapeutic endeavours using chimeric antigen receptor T cells (CAR T cells), bispecific T cell engagers and immune checkpoint inhibitors are under active investigation overseas and in Australia. In 2017, the United States granted approval to CAR T cell-based therapies for acute lymphoblastic leukaemia and lymphoma, together with checkpoint inhibitors, which may herald their future possible use in myeloma.

In this Narrative Review, we discuss new concepts of the biology of myeloma, including the process of clonal evolution and the new criteria for introducing therapy, as proposed by the International Myeloma Working Group. We performed a search of online databases including MEDLINE, PubMed and BMJ Clinical Evidence, using the term "myeloma", and searched recent conference proceedings from 2005 until the present.

## Myeloma genomics

The sequencing of the myeloma genome in 2011[10] failed to identify a specific defect such as is seen in Waldenstrom macroglobulinaemia.[11] Instead, a wide range of molecular abnormalities was found. In addition, all patients at diagnosis demonstrated multiple different subclones, including mutations in the driver genes *KRAS*, *NRAS* and *BRAF*,[12,13] and whole exome sequencing revealed similar findings.[14] Clones undergo varying prominence with disease progression and response to therapy. This finding has changed our concept of myeloma as a linearly progressive disease with increasing resistance to treatment to one in which a "Darwinian" or "branching" process occurs, such that some clones may be suppressed by chemotherapy but, eventually, new clones resistant to chemotherapy dominate.[15–17]

Mutations in myeloma are complex and the median missense mutational load is about 60 per patient.[17] The myeloma genome has fewer mutations compared with those observed in carcinogen-induced tumours such as melanoma and lung cancer.[18] The clinical relevance of this is that it may explain the relatively poor response of myeloma to the newer immunomodulatory

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**1 International Myeloma Working Group's diagnostic criteria for multiple myeloma and related plasma cell disorders***

| Disorder | Definition (all of the criteria must be met) |
|---|---|
| Monoclonal gammopathy of undetermined significance (MGUS) | Serum monoclonal protein (paraprotein) < 30 g/L<br>Clonal bone marrow plasma cells < 10%<br>Absence of end organ damage attributable to the plasma cell disorder — hypercalcaemia, renal impairment, anaemia, lytic bone lesions (CRAB) |
| Light chain monoclonal gammopathy of uncertain significance | Abnormal free light chain ratio (< 0.26 mg/L or > 1.65 mg/L)<br>Increased level of the appropriate involved light chain (ie, increased kappa light chains in patients with ratio > 1.65 mg/L, and increased lambda light chains in patients with ratio < 0.26 mg/L)<br>No immunoglobulin heavy chain expression on immunofixation<br>Absence of end organ damage attributable to the plasma cell disorder<br>Clonal plasma cells < 10%<br>Urinary monoclonal protein < 500 mg/24 hours |
| Smouldering multiple myeloma | Serum monoclonal protein level ≥ 30 g/L or urinary monoclonal protein level ≥ 500 mg/24 hours and/or clonal bone marrow plasma cells 10–60%<br>Absence of end organ damage attributable to the plasma cell disorder or amyloidosis |
| Multiple myeloma | Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma<br>Any one or more of the following myeloma-defining events:<br>• Evidence of end organ damage attributable to the plasma cell disorder (CRAB):<br>▸ hypercalcaemia — serum calcium > 2.75 mmol/L (RI, 2.10–2.60 mmol/L);<br>▸ renal impairment — creatinine clearance < 40 mL/min or serum creatinine > 177 µmol/L (RI, 45–90 µmol/L);<br>▸ anaemia — haemoglobin > 20 g/L below the lower limit of normal or < 100 g/L (RI, 120–150 g/L);<br>▸ bone lesions — one or more osteolytic lesions on skeletal radiography, computed tomography or positron emission tomography<br>• Clonal bone marrow plasma cells ≥ 60%<br>• Involved/uninvolved serum free flight chain ratio ≥ 100 mg/L (RI, 0.26–1.65 mg/L), with involved free light chain level ≥ 100 mg/L<br>• More than one focal lesions on magnetic resonance imaging scan at least 5 mm in size |

RI = reference interval. * Adapted from: Rajkumar et al[2] and Rajkumar.[3]

checkpoint inhibitors, which rely on immune recognition of cancer neoantigens by cytotoxic T cells compared with melanoma and lung cancer, in which such drugs play an important therapeutic role.[19]

## Classification

Patients are currently classified into high risk and low risk genetic groups based on simple cytogenetic and fluorescent in situ hybridisation analysis, with implications for expected length of survival (Box 4). The Revised International Staging System (R-ISS) risk stratification model forms the basis for this classification.[22] High risk cytogenetic features include the presence of t(14;16), t(14;20) and del(17p), while patients with t(4;14) and amp(1q) have intermediate risk. Other anomalies, such as hyperdiploidy (which occurs in about 50% of patients), are considered standard risk. The term "good risk" in myeloma is still an oxymoron.[20] Gene expression profiling can also identify significant prognostic groupings. While gene expression profiling may provide more detailed insight into an individual patient than standard fluorescent in situ hybridisation analysis, these analyses are complex and infrequently used in standard practice in Australia.[23]

## Diagnosis: smouldering multiple myeloma and active myeloma

Traditional diagnostic criteria for the diagnosis and indications for the introduction of therapy in myeloma have defined active myeloma by the presence of end organ effects (Box 1). These have now been expanded by the International Myeloma Working Group from the analysis of the risk of progression in large cohorts of patients with smouldering multiple myeloma[2] (Box 1). These new criteria have extended the diagnostic criteria to include the presence of free light chain abnormality (ratio of involved free light chain to non-involved free light chain > 100 mg/L; reference interval, 0.26–1.65 mg/L), bone marrow involvement demonstrating more than 60% plasma cells and the presence of more than one lytic lesions on magnetic resonance imaging (MRI) scan, in addition to the previous standard criteria.

The new criteria have facilitated the introduction of therapeutic concepts relating to smouldering multiple myeloma, which can now be subdivided into a group with high risk smouldering multiple myeloma, with an expected transformation rate to active myeloma of over 80% in the next 2 years. This is based on a marrow infiltration of more than 10% malignant plasma cells and one of the following: paraprotein level greater than 30 g/dL or increasing paraprotein, free light chain ratio greater than 8 mg/L but less than 100 mg/L, immunoparesis of non-involved immunoglobulins, 50–60% bone marrow plasma cells or circulating plasma cells, abnormal plasma cell phenotype, high risk genetics (Box 4), and positron emission tomography (PET) and MRI scans abnormalities.[24,25]

With the availability of new novel agents, the question of whether patients with high risk smouldering multiple myeloma should be treated is now legitimately being tested in controlled clinical trials. For example, the Spanish Myeloma Group found that early treatment with a combination of lenalidomide and dexamethasone, compared with standard therapy of close monitoring, resulted in a significant benefit in delaying progression to myeloma and improved overall survival without unexpected toxicity.[26] The Spanish group has taken this finding further with a study that attempts to cure high risk smouldering multiple myeloma. Patients are enrolled to receive maximal therapy with the newest available agents, including carfilzomib, and ongoing lenalidomide maintenance. Treatment in this trial has shown high remission rates, with 85% of patients who completed therapy remaining progression-free.[27] However, overall survival data are still awaited but crucial to confirm the value of treatment in an asymptomatic phase. Other groups are following a similar line of treatment and used the newer monoclonal antibodies, such as daratumumab,[28,29] in an attempt to show whether disease progression can be delayed and survival prolonged.

**2 Currently available myeloma therapies in Australia**

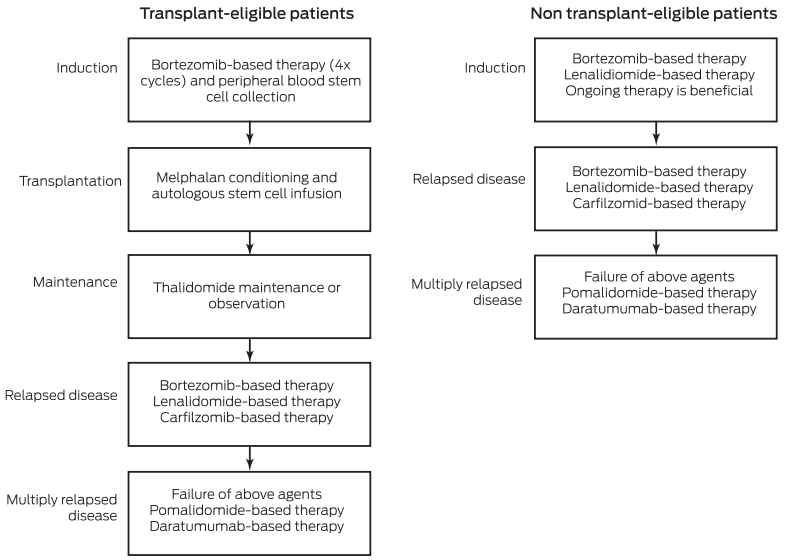
| Therapeutic class | Agent | Mode of delivery | PBS approved for use at which time |
|---|---|---|---|
| Proteasome inhibitor | Bortezomib | Intravenous or subcutaneous | First line onwards, re-treatment |
| | Carfilzomib | Intravenous | Second line onwards, no re-treatment |
| Immunomodulator | Thalidomide | Per oral | First line onwards |
| | Lenalidomide | Per oral | First line onwards in non-transplant eligible patients, second line onwards in transplant eligible patients* |
| | Pomalidomide | Per oral | When bortezomib and lenalidomide failed |
| Monoclonal antibody | Daratumumab | Intravenous | Compassionate access currently when all PBS options failed† |

PBS = Pharmaceutical Benefits Scheme. * Lenalidomide maintenance after autologous stem cell transplantation currently under consideration by the PBS. † Daratumumab therapy for patients with multiply relapsed myeloma currently under consideration by the PBS.

## Minimal residual disease testing

Concomitant with these studies is the evolution of highly sensitive techniques for evaluating very small numbers of residual myeloma cells, termed minimal residual disease (MRD). MRD can be detected by next generation flow cytometry or by next generation sequencing with sensitivity in one to $10^{-6}$ malignant cells, allowing the definition of patients who have had an excellent response to therapy. While these techniques have important technical caveats and are highly dependent on the expertise of the operator, they are now being performed by specialised centres in the evaluation of the efficacy of novel agents in clinical trials. The attainment of MRD acts as a surrogate marker for progression-free survival and it is hoped it will predict overall survival. Therefore, testing for patients with MRD has considerable prognostic importance. In a recent phase 3 trial comparing autologous stem cell transplantation to novel agent therapy, the finding of MRD to a level of below one and $10^{-6}$ malignant cells was associated with significant better progression-free survival and overall survival compared with patients not achieving this level. In addition, the attainment of MRD to this level was associated with an excellent prognosis irrespective of whether the patients had an autologous stem cell transplantation or novel agents.[29] Thus, the attainment of MRD offers significant prognostic formation and maybe a valuable adjunct to patient management.[30–32] The potential use of PET scanning as an additional modality of detection of MRD continues to be investigated.[33]

**3 Overview of therapeutic options for Australian patients with myeloma***




* Always consider clinical trials when available.

## New agents for myeloma

The advent of new and more potent proteasome inhibitors (carfilzomib) and oral proteasome inhibitors (ixazomib) together with more potent immunomodulatory drugs (pomalidomide) and the development of a new class of monoclonal antibody therapies have revolutionised the treatment of relapsed refractory disease and are now being introduced into newly diagnosed multiple myeloma (Box 2 and Box 3). Monoclonal antibodies directed against CD38 (daratumumab) and SLAMF7 (elotuzumab) have already been successful when used in combination with an immunomodulatory agent in phase 2 clinical trials[34] and in large phase 3 trials.[35] Additional anti-CD38 antibodies in combination with proteasome inhibitors or immunomodulatory drugs are in phase 2 and phase 3 clinical trials.[36] They offer great hope for the eradication MRD as they act independently of genetic mutations that do not affect surface phenotype.

Revolutionary T cell therapies are undergoing expedited development in myeloma and other haematological malignancies. CAR T cells, which target an activated T cell to a defined antigen present on malignant cells, are undergoing phase 1 trials in myeloma.[36] In addition, the development of bispecific T cell engagers[37] — which are composed of a single-chain immunoglobulin variable component providing cancer specificity bound to a T cell receptor so as to bring the T cell and tumour in apposition to produce an immunological synapse — shows great promise. The most promising specific myeloma target is the B-cell maturation antigen, which is universally present on plasma cells. Clinical trials of these agents are underway both internationally and in Australia.[38,39] It is hoped that T cell therapies may play a most useful role in the eradication of MRD. However, of potential concern is their susceptibility to the same immune suppressive effects caused by myeloma, which allows the tumour to suppress and evade innate immunity. The prospect for the reactivation of innate natural antimyeloma immunity with vaccination is another possible avenue for eventual cure, and active immunisation

**4 Revised International Staging System for myeloma***

| Stage | Definition (all criteria must be met) | 5-Year overall survival |
|---|---|---|
| Stage I | • Serum albumin > 35 g/L<br>• Serum β-2 microglobulin < 3.5 mg/L<br>• None of the following high risk cytogenetics:<br>▸ t(4;14)<br>▸ t(14;16)<br>▸ del(17p)<br>• Normal serum lactate dehydrogenase | 82% |
| Stage II | • Not fitting Stage I or III | 62% |
| Stage III | • Serum β-2 microglobulin > 5.5 mg/L<br>• High risk cytogenetics or elevated serum lactate dehydrogenase | 40% |

* Adapted from: Rajkumar,[3] Chng et al[20] and Palumbo et al[21]

protocols using hybrid fused plasma cells and dendritic cells are in progress.[40]

## Therapy paradigms

Patients can be divided in two main groups: patients who are considered eligible for autologous stem cell transplantation and those considered ineligible. This distinction is arbitrary, but age, frailty and comorbidities are part of the clinical decision making process. Frailty scores, as proposed by the European Myeloma Network, are helpful when making this decision.[41] Patients older than 75 years of age are considered, in general, ineligible for transplantation.[42] Overall treatment schedules and Australian guidelines have also been published by the Medical and Scientific Advisory Group of Myeloma Australia[42–44] and are summarised in Box 3.

## Transplant-eligible patients

Patients considered eligible for stem cell transplantation undergo an induction period with a proteasome inhibitor-based regime (induction) followed by a stem cell transplant and maintenance therapy with thalidomide. Autologous bone marrow transplantation using high dose melphalan has been available for over 20 years and its safety and tolerability have dramatically increased.[45] Recent studies have compared transplantation with novel agents in order to avoid the cytotoxicity associated with high dose melphalan. These studies have confirmed the place of transplantation a beneficial procedure, showing improved progression-free survival and higher rates of MRD.[27]

Allogeneic stem cell transplantation from a sibling or human leucocyte antigen-matched donor is rarely used, but may have a place in young patients with high risk myeloma or who have had an early relapse after autologous stem cell transplantation. A recent large study from the United States showed no advantage in allogeneic transplantation compared with sequential autologous stem cell transplantation, but there remains disagreement in the literature concerning its value.[45–47]

## Maintenance therapy

Maintenance therapy after stem cell transplantation has shown significant benefits in a number of studies. Lenalidomide is considered appropriate maintenance therapy in most patients,[48] although bortezomib may be more beneficial in high risk patients with the t(14;16) and t(14;20) translocations, or del(17p).[6,16,49] However, neither lenalidomide or bortezomib maintenance therapy are available routinely in Australia. Lenalidomide has recently been combined with elotuzumab and oral proteasome inhibitor ixazomib.[50] Encouraging results from these studies suggest that maintenance therapy may be intensified, especially in patients who do not obtain a significant MRD reduction with high dose therapy.

## Newly diagnosed patients who are not eligible for stem cell transplantation

Dramatic changes have occurred in the group of patients who are not suitable for stem cell transplantation. The use of lenalidomide and dexamethasone as initial therapy has been definitively established in a large international study in which lenalidomide and dexamethasone were compared with melphalan, prednisone and thalidomide.[49] Of significance is the rapid adoption of the use of daratumumab,[51,52] which has been added to the standard combination of melphalan, bortezomib and prednisone.[34] This resulted in a significant benefit in progression-free survival in all pre-specified patient subgroups, including patients who were aged over 75 years, were at an advanced disease stage and had high risk cytogenetics. While the addition of cyclophosphamide or melphalan to standard lenalidomide and dexamethasone induction did not appear to improve the overall survival, recent early data on the addition of ixazomib to lenalidomide and dexamethasone are exciting and confirmation of benefit is awaited.[53]

## Relapsed and refractory patients

Until recently, the prognosis for relapsed patients and patients who are refractory to lenalidomide and bortezomib has been very poor,[54] but a number of new drugs have now been introduced, including daratumumab, carfilzomib and pomalidomide. In a large phase 3 randomised controlled study, the greater efficacy of carfilzomib over bortezomib was documented,[55,56] with improvement in progression-free survival and overall survival.[57] Furthermore, it is now apparent that carfilzomib can be given successfully in a weekly schedule.[58] Similarly, pomalidomide has been shown to be effective in patients who are refractory to lenalidomide.[59,60] A new regimen combining pomalidomide, carfilzomib and dexamethasone in relapsed and refractory patients has shown improved results in this cohort.[58] Patients who have been heavily treated with multiple agents have the future possibility of the use of CAR T cells against B-cell maturation antigens and bispecific T cell engagers. It is hoped that these will be able to be used in newly diagnosed patients in the future, further enhancing the possibility of cure.

## Supportive therapies

One of the major advantages in myeloma care is the improvement in supportive care. Major strides have been made in the management of bone disease, both in diagnosis and assessment (MRI and PET) and in therapy, with the introduction of bone-strengthening agents, such as zolendronic acid and denosumab. Denosumab has potential benefits over zolendronic acid as it can be safely used in patients with renal failure, which is present in over 25% of patients at diagnosis.[61] However, both these agents may rarely cause osteonecrosis of

the jaw. Potential new agents, such as sclerostin inhibitors, are also being investigated.[62] It is now appreciated that proteasome inhibitors play a critical role in the therapy of cast nephropathy, and reversal from dialysis dependence to independence can be obtained with rapid reversal of light chain load.[63–65] The need for high cut-off filter dialysis to further reduce the light chain load is controversial, as a randomised controlled study did not find additional benefits when provided with a bortezomib-based chemotherapy regimen.[66] In addition, autologous stem cell transplantation can be performed safely in patients with renal failure, although a lower dose of melphalan is often used.[64]

A large clinical trial in the United Kingdom has shown that prophylactic levofloxacin given for the first 12 weeks of therapy reduces the incidence of infections during the induction phase of the therapy.[27] The routine use of antiviral agents has significantly lessened the incidence of herpes zoster, especially in patients treated with proteasome inhibitors. Intravenous immunoglobulin replacement has been shown to reduce the incidence of respiratory infections in patients with low immunoglobulin levels.[67] Finally, the control of pain has been improved with the use of new concepts of pain control and long-acting narcotics. Adverse events during therapy include febrile neutropenia, septicaemia and opportunistic infections, such as herpes zoster and fungal infections, whose management requires the use of broad spectrum antibiotics and antifungal agents in different centres.

## Conclusion

Improvements in our understanding of the pathophysiology of myeloma and the advent of novel and targeted therapies have heralded a remarkable decade of progress in myeloma, which has translated into better patient outcomes. Data from the Australian Institute of Health and Welfare show a dramatic improvement in survival rates between the period 1982–1987 and the period 2006–2010, when the 5-year survival rose from 26% to 43%.[68] However, outcomes for older individuals remain much poorer, with only a 19% 5-year survival rate in individuals aged 80 years or over. Care for these patients remains a pressing challenge. Notably, in Australia, there is now a growing myeloma and related disease registry,[69] which is collecting disease, treatment and outcome data on patients with myeloma from many treating hospitals around the country. The registry will provide a unique opportunity to monitor outcomes in an Australian context and in different areas of health care delivery. This large registry is now reaching the level of maturity in which survival data will be available.[70] We can confidently look forward to regimens that will predictably attain MRD, especially in patients who do not have high risk genetic disease, and to protocols that will allow the final eradication of residual disease and result in the cure of myeloma.

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