Multiple myeloma: the present and the future

Major advances continue apace in therapy and in understanding its molecular pathogenesis

Myeloma is a malignancy of plasma cells in the bone marrow and presents with bone lesions, renal failure, anaemia and hypercalcaemia. Back pain, often associated with vertebral body collapse, is the most common presenting feature. In Australia, about 1200 new patients are diagnosed with multiple myeloma each year, with a median age at diagnosis in the early 60s.

The aetiology of myeloma remains essentially unknown, although recent studies suggest links to agricultural exposures and lifestyle factors, such as low socioeconomic status and obesity.[1] The major risk factor is the presence of a monoclonal immunoglobulin (paraprotein) in the blood. The incidence of paraproteins increases with age, and they are found in up to 3%–5% of people aged over 80 years. They are termed "benign paraproteins" or, more commonly, MGUS (monoclonal gammopathy of undetermined significance). By definition, this condition is not associated with other myeloma abnormalities. A patient with this type of gammopathy has an annual risk of about 1%–1.5% of developing active myeloma.[2]

A variant of myeloma — smouldering or indolent multiple myeloma — is associated with an infiltrate of over 10% monoclonal plasma cells in the bone marrow, but no organ dysfunction. Patients with this variant can be safely monitored for the onset of increasing paraprotein levels or organ dysfunction, suggesting transformation from smouldering myeloma to active disease.

Melphalan chemotherapy was introduced in the 1960s, but there was little further change in our ability to affect the natural history of myeloma until the past decade, which has witnessed dramatic therapeutic advances. Currently, all patients aged under 65 years are offered autologous stem cell transplantation, using bone marrow stem cells harvested from the peripheral blood, unless precluded by other comorbidities. Stem cell transplantation is usually preceded by 3–6 months of induction therapy aimed at reducing tumour load and contamination of stem cell harvests by malignant cells.[3] The role of a second stem cell transplant 3–6 months after the first is under investigation; it appears to benefit patients who do not have a full response to the initial transplant.[4] The effect of a second transplant is also being compared with the new targeted drug therapies (see below). While allogeneic transplantation is usually precluded by age at presentation of myeloma, new techniques that require less intensive chemotherapy and gain their efficacy from the immunological effect of the stem cell graft on the malignant plasma cells (so-called "non-myeloablative" transplants) are now being used for patients who have a suitable matched sibling donor, are young, and have relapsed after autologous stem cell transplantation. The role of ongoing chemotherapy after transplant is unknown at present and the subject of a number of clinical trials.

Lytic bone disease, bone pain and hypercalcaemia are major clinical manifestations of myeloma. In the past, no effective therapy was available for bone disease, but now all patients with myeloma receiving chemotherapy are also treated with a bisphosphonate. This reduces the number of skeletal events, such as vertebral collapse and pathological fracture of long bones, and reduces bone pain. Despite the increasing recognition of the uncommon side effect of osteonecrosis of the jaw, bisphosphonate therapy continues to be a standard intervention for all patients with myeloma who are receiving active chemotherapy.[5,6]

Of great interest are the new targeted therapies. Currently, three drugs — thalidomide, its analogue lenalidomide, and the proteasome-inhibitor bortezomib — are available for use in North America and are undergoing clinical trials in Australia. Extensive clinical experience with these drugs in refractory disease shows that they have a response rate of about 30%, which rises to 60%–70% when combined with dexamethasone.[7] Major side effects include neuropathy (thalidomide and bortezomib) and myelotoxicity (lenalidomide). Current investigations are assessing the value of these drugs at initial diagnosis and as maintenance therapy after stem cell transplantation.[7-9]

Thalidomide and dexamethasone have been shown to be as effective for induction before stem cell transplantation as standard therapies. However, as they may be administered orally they are considered more convenient than therapies requiring venous access. Current studies involve the use of lenalidomide and bortezomib in induction therapy, while a recent French study has shown that thalidomide taken after stem cell transplantation both prolongs event-free survival and prevents relapse compared with no therapy.[10]

In April this year, the 10th International Myeloma Workshop in Sydney was attended by over 1000 experts in myeloma, indicating the current research interest in this condition. Abstracts and presentations of the meeting are available at the *Haematologica* website (www.haematologica-thj.org/supplements.html). The work presented at the meeting offered great hope for the future, both in our understanding of the molecular pathogenesis of multiple myeloma and, more importantly, in new therapies for our patients.

Douglas E Joshua
Head, Institute of Haematology, Royal Prince Alfred Hospital, Sydney, NSW
Douglas.Joshua@email.cs.nsw.gov.au

Competing interests: I am an advisory consultant to Pharmion, Janssen-Cilag and Novartis, and received assistance from Novartis to attend the 2004 meeting of the American Society of Haematology.

1 Baris D, Lan Q, Zhang Y, et al. Epidemiology of multiple myeloma [abstract]. *Haematologica* 2005; 90 Suppl 1: 11.
2 Kyle RA, Therneau TM, Rajkumar SV, et al. Long-term follow up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. *Mayo Clin Proc* 2004; 79: 859-866.
3 Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996; 335: 91-97.
4 Attal M, Harousseau JL, Facon T, et al; InterGroupe Francophone du Myelome. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003; 349: 2495-2502.
5 Roodman GD. Mechanisms of bone metastasis. *N Engl J Med* 2004; 350: 1655-1664.
6 Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001; 91: 1191-1200.
7 Singhal S, Mehta J, Desikan R, et al. Antitumour activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999; 341: 1565-1571.
8 Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* 2002; 100: 3063-3067.
9 Richardson PG. Bortezomib — first in the class of proteasome inhibitors and an important advance in the treatment of multiple myeloma [abstract]. *Haematologica* 2005; 90 Suppl 1: 23-24.
10 Attal M, Harousseau JL, Leyvraz S, et al. Maintenance treatment with thalidomide and pamidronate after autologous transplantation for myeloma: second analysis of a prospective randomized study of the Intergroupe Francophone du Myelome [abstract]. *Haematologica* 2005; 90 Suppl 1: 17.