



New drugs for multiple myeloma

Michael Osborn, Haematology Registrar, Noemi Horvath, Haematology Specialist, and Luen Bik To, Clinical Professor, Division of Haematology, SA Pathology, Adelaide

Summary

Multiple myeloma is a plasma cell neoplasm that is currently incurable. Older patients are managed with melphalan and prednisolone. Younger patients have induction chemotherapy followed by high-dose melphalan and autologous stem cell transplantation. Recent insights into the biological basis of myeloma have resulted in several new drugs becoming available. Thalidomide, bortezomib and lenalidomide have each improved the response to therapy, but they are expensive. Future challenges include optimising the sequence of these drugs, refining their combination with standard drugs and high-dose therapy, and identifying the subgroups of patients most likely to benefit from them.

Key words: bortezomib, lenalidomide, thalidomide, transplantation.

(Aust Prescr 2009;32:95–8)

Introduction

Multiple myeloma is a malignant proliferation of plasma cells that characteristically secrete a monoclonal protein. This is measured in the laboratory as paraprotein or free light chains in blood, or Bence-Jones protein in urine.¹ Clinically the disease is associated with a combination of hypercalcaemia, renal failure, anaemia and lytic bone lesions. While multiple myeloma remains incurable in the majority of cases, the considerable developments in our therapeutic armamentarium over recent years have significantly improved survival.

Treatment overview

Oral melphalan and prednisolone have been the backbone of myeloma therapy for many years. This combination, with or without newer drugs, remains the standard of care for older patients. Younger patients who are eligible for transplantation have induction chemotherapy followed by high-dose melphalan with autologous stem cell rescue. This approach has led to an improvement in median overall survival from 42 to 54 months.² While there are a number of induction regimens, the combination of vincristine, doxorubicin and dexamethasone

has been most frequently used. An oral induction regimen containing cyclophosphamide, idarubicin and dexamethasone is increasingly being used.

Currently, the treatment approach for newly diagnosed myeloma is guided by the patient's eligibility for autologous haematopoietic stem cell transplantation (Fig. 1). Most Australian centres will consider transplantation in patients aged up to 65 years depending on their general health. Autologous stem cell transplantation for myeloma has a treatment-related mortality of 1–2%.

Supportive care

Both before and during treatment attention must be given to supportive care. This includes management of renal impairment, control of steroid-induced hyperglycaemia, transfusion support, aggressive management of febrile illnesses and effective pain relief to help maintain mobility. Cotrimoxazole is frequently used as prophylaxis against *Pneumocystis jirovecii* pneumonia throughout treatment. Prophylactic famciclovir or aciclovir, norfloxacin and often an antifungal drug are administered for the period of immunological compromise following autologous stem cell transplantation.

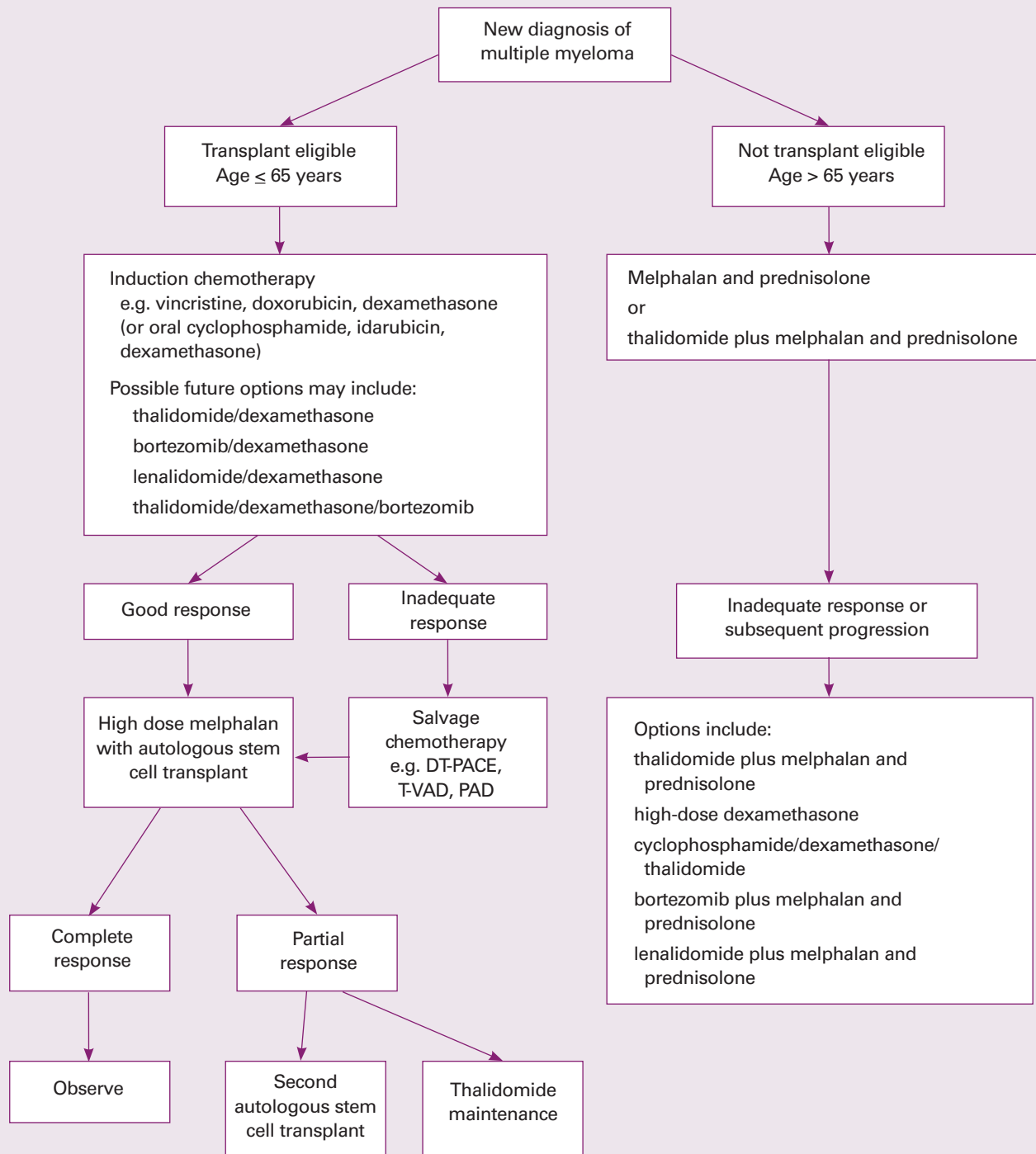
Radiotherapy and surgery, such as vertebroplasty, should be considered for established or imminent fractures and soft tissue plasmacytomas that pose an immediate threat (for example extradural plasmacytoma). Bisphosphonates can be given to patients with myeloma-related bone disease to reduce the risk of pathological fractures, hypercalcaemia and other skeletal-related events. While both intravenous and oral bisphosphonates are effective, the intravenous route is often preferred. Bisphosphonates have been associated with an increased incidence of osteonecrosis of the jaw. A dental review is therefore warranted before treatment and the bisphosphonate should be ceased if this complication develops.

New drugs

In recent years, evidence supporting a survival benefit for thalidomide, bortezomib and lenalidomide has resulted in their inclusion, in combination with older drugs, in the management of younger and older patients. Each of these new drugs has multiple mechanisms of action, targeting both intracellular signalling pathways and the tumour micro-environment. Their optimal sequence and combination is still being refined by ongoing clinical trials.

Fig. 1

A suggested approach to treatment of patients with newly diagnosed multiple myeloma



DT-PACE dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide
 TVAD thalidomide, vincristine, doxorubicin, dexamethasone
 PAD bortezomib, doxorubicin, dexamethasone

Thalidomide

Despite its notorious history, thalidomide emerged as the first important new drug treatment for myeloma following recognition of its anti-angiogenic effects in the 1990s. It is given orally, but its precise mechanism of action is unclear. Thalidomide also has immunomodulatory and anti-inflammatory effects. Initial studies in patients with relapsed or refractory myeloma showed a response rate of 32% when thalidomide was used as a single drug, with a considerably higher response rate (41–65%) when it was combined with dexamethasone with or without cyclophosphamide.³ Numerous subsequent studies have confirmed thalidomide's efficacy in a range of settings.

In elderly patients not eligible for transplant, randomised controlled trials show that the addition of thalidomide to melphalan and prednisolone results in response rates that are superior to melphalan and prednisolone alone. The partial response rate was 76% with melphalan, prednisolone and thalidomide compared with 48% in the melphalan and prednisolone group. However, an updated analysis found no survival advantage when thalidomide was added, probably because many of the patients in the control group later received thalidomide or other new drugs on relapse.⁴

In the younger patient group, thalidomide combined with dexamethasone is an effective pre-transplantation induction regimen.³ It has also been used as 'maintenance' following high-dose therapy and autologous stem cell transplantation.³ Maintenance therapy with thalidomide increased four-year overall survival from 77% to 87% in studies of patients after autologous stem cell transplantation.³ The Therapeutic Goods Administration (TGA) has approved thalidomide in first-line treatment and for relapsed or refractory myeloma, but Pharmaceutical Benefits Scheme (PBS) funding is currently only available for relapsed or refractory myeloma.

Adverse effects

The most frequent adverse effects seen with thalidomide are constipation, fatigue, somnolence and peripheral neuropathy. As thalidomide significantly increases the risk of venous thrombosis, prophylaxis should be considered (aspirin, warfarin or low molecular weight heparin is recommended).

Thalidomide use is strictly regulated due to its teratogenicity. In Australia, patients, prescribers and dispensing pharmacists must be registered with the Pharmion Risk Management Program. They have to complete phone questionnaires emphasising the importance of effective contraception before receiving authority for each 28-day prescription. Distribution of the drug is carefully controlled and tracked.

Lenalidomide

Lenalidomide is an oral thalidomide analogue and acts by similar mechanisms, targeting both signalling pathways

within the malignant plasma cell and the bone marrow micro-environment. After promising initial results as a single drug, trials comparing lenalidomide plus dexamethasone with dexamethasone alone found superior response rates (60% vs 24%) and improved median overall survival in relapsed myeloma.⁵ Trials involving newly diagnosed patients have shown an 81% response rate when combined with melphalan and prednisolone in elderly patients, and a 91% response rate when combined with dexamethasone in younger transplant-eligible patients.^{6,7} Lenalidomide is frequently effective even in patients whose myeloma is resistant to thalidomide.

Although approved by the TGA for relapsed disease, lenalidomide is not presently subsidised by the PBS. Haematologists can currently access lenalidomide through a temporary expanded access program established by the drug company.

Adverse effects

Unlike thalidomide, lenalidomide is not associated with somnolence, constipation or peripheral neuropathy, but causes neutropenia and thrombocytopenia. Thromboembolic events occur at an increased rate, hence antithrombotic prophylaxis is recommended. Effective contraception is also required given its teratogenic potential.

Bortezomib

Just as the use of thalidomide arose from an understanding of the importance of angiogenesis in myeloma, the development of bortezomib followed new insights into the importance of the proteasome. This is the intracellular structure responsible for orderly degradation of intracellular proteins. Proteasomal inhibition by bortezomib results in cellular apoptosis, particularly in malignant and proliferating cells.

Early studies showed that intravenous bortezomib had a higher response rate and a six-month survival advantage over high-dose dexamethasone in relapsed myeloma. The median overall survival was 29.8 months with bortezomib versus 23.7 months with dexamethasone.⁸ In newly diagnosed elderly patients, bortezomib used with melphalan and prednisolone resulted in a response rate of 89%, with overall survival being 90% at 16 months versus 62% in those treated with melphalan and prednisolone alone.⁹ Younger transplant-eligible patients had similarly impressive response rates when bortezomib was included in induction regimens.¹⁰

In Australia, bortezomib is currently subsidised by the PBS for patients who have progressive disease after at least one prior treatment, who have undergone or are ineligible for stem cell transplant and who have failed thalidomide. Ongoing therapy requires documentation of an adequate response. In contrast, for newly diagnosed patients its use is currently limited to those enrolled in clinical trials.

Adverse effects

The major adverse effects of bortezomib include fatigue, gastrointestinal upset, painful peripheral neuropathy, anaemia, thrombocytopenia and neutropenia. There is also an increased incidence of herpes simplex and herpes zoster infections.

Related conditions

Monoclonal gammopathy of undetermined significance is an asymptomatic clonal plasma cell proliferation, but 1% of patients progress to myeloma every year. These patients require careful monitoring, but treatment is not indicated.

Smouldering myeloma refers to an intermediate pre-malignant phase with no end-organ damage. Although these patients have a greater risk of progression to myeloma, treatment may still be reserved until there is evidence of systemic effects.

Challenges for the future

Thalidomide, lenalidomide and bortezomib are advances in the treatment of myeloma, but their exact place in therapy is yet to be fully defined. While these drugs have survival benefits, the challenge is to determine their optimal sequence and combination with other drugs. Another important challenge is to determine which subgroups of patients would benefit most from these drugs. Debate continues as to whether these new drugs ought to be used as part of initial therapy to improve the initial response, or whether equivalent survival benefits and quality of life can be obtained, with less toxicity, by deferring them until disease progression occurs. Until these questions are answered by future clinical trials, PBS restrictions dictate that most Australian patients will receive these drugs only when their disease progresses.

The efficacy of these new drugs has also challenged some of the paradigms of myeloma treatment. For example, while maintenance therapy has not previously been used in myeloma, it may have a role in future. Furthermore, regimens containing the new drugs might provide the same benefits as an autologous transplant, thus obviating the need for transplantation. However, if the two approaches are found to be equally efficacious, the high cost of the new drugs and the low transplant-related mortality may ensure that autologous transplantation still has a role.

Allogeneic stem cell transplantation has been trialled in myeloma with both myeloablative and reduced intensity conditioning. A plateau in long-term survival has been demonstrated suggesting that this may be a potentially curative approach. Nonetheless, it is associated with considerable transplant-related mortality and morbidity, and currently should be regarded as an experimental treatment.

While myeloma remains incurable, these new therapies are substantially changing our approach to this disease. More importantly, they have the potential to further improve

survival as we continue to determine their optimal place in the management of this common haematological malignancy.

References

1. Firkin F. Abnormal laboratory results. Screening for multiple myeloma. *Aust Prescr* 2009;32:92-4.
2. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003;348:1875-83.
3. Palumbo A, Facon T, Sonneveld P, Bladè J, Offidani M, Gay F, et al. Thalidomide for treatment of multiple myeloma: 10 years later. *Blood* 2008;111:3968-77.
4. Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. *Blood* 2008;112:3107-14.
5. Dimopoulos M, Spencer A, Attal M, Prince HM, Housseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;357:2123-32.
6. Palumbo A, Falco P, Corradini P, Falcone A, Di Raimondo F, Giuliani N, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA - Italian Multiple Myeloma Network. *J Clin Oncol* 2007;25:4459-65.
7. Rajkumar SV, Hayman SR, Lacy MQ, Dispenzieri A, Geyer SM, Kabat B, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood* 2005;106:4050-3.
8. Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007;110:3557-60.
9. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al; VISTA Trial Investigators. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008;359:906-17.
10. Housseau JL, Attal M, Leleu X, Troncy J, Pegourie B, Stoppa AM, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II trial. *Haematologica* 2006;91:1498-505.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 115)

3. Thalidomide increases the risk of venous thrombosis in patients with multiple myeloma.
4. Bisphosphonates are ineffective for the treatment of the hypercalcaemia associated with multiple myeloma.

Patient support organisation: Myeloma Foundation of Australia
see p. 107