Treatment for multiple myeloma aims to control the disease, maximise quality of life and prolong survival; this can be achieved through a combination of disease-specific therapies and supportive care.

**Multiple myeloma management**

By Nick Duncan, MSc, MRPharmS

Treatment options for multiple myeloma have increased considerably in recent years, with three medicines (bortezomib, lenalidomide and thalidomide) being licensed in the UK since 2004. In addition, there have been developments in the field of stem cell transplantation and, for the first time, the potential for supportive therapies to improve survival has also been demonstrated. Therefore, survival rates have increased dramatically in the past decade and the direction of travel is such that, in the near future, clinicians may begin to consider myeloma as a chronic disease.

**Initial treatment**

It is important to remember that there is no evidence to suggest that patients with asymptomatic myeloma require treatment unless their disease progresses to the symptomatic form.

Patients with symptomatic multiple myeloma should be assessed for suitability for autologous stem cell transplant (SCT). The age cut-off for this procedure is usually 65 years, although it can be considered for older patients who have good performance status (a measure of everyday functioning).

Comorbidities will also influence a patient’s suitability for autologous SCT. Whether or not a patient is deemed suitable for an autologous SCT will guide the choice of induction therapy, discussed below.

**Induction therapy**

**Patients not eligible for autologous SCT**

The combination of oral melphalan and prednisolone (MP) was, until recently, regarded as the standard of care for patients deemed unsuitable for autologous SCT. However, several randomised trials have demonstrated that the addition of thalidomide, at a dose of 100–200mg a day, improves response rates and, in some studies, overall survival.

Consequently, MP plus thalidomide (MPT) is usually considered to be the induction regimen of choice for these patients. Thalidomide is licensed, and approved by the National Institute for Health and Clinical Excellence and the Scottish Medicines Consortium, for this indication.

An alternative regimen is CTD, in which cyclophosphamide is used instead of melphalan and dexamethasone replaces prednisolone. An attenuated version of this regimen (CTDa) demonstrated superior response rates to MP in a recent Medical Research Council study, known as Myeloma IX.

Another option is to use a bortezomib-containing combination, usually bortezomib plus melphalan and prednisolone (VMP). This regimen, involving twice-
weekly bortezomib, was shown to be superior to MP in the VISTA study, although it was associated with relatively high rates of myelosuppression and neuropathy. More recent studies have demonstrated that weekly bortezomib significantly reduces the incidence of grade 3 and 4 toxicities without any loss of efficacy.  

Lenalidomide is not routinely used for induction therapy outside clinical trials, despite encouraging data for its use in combination with dexamethasone or with melphalan plus prednisolone. 

**Patients eligible for autologous SCT** Historically, regimens such as VAD (vincristine, doxorubicin and dexamethasone) were the mainstay of induction therapy for patients younger than 65 years and were associated with response rates of 50–60%. However, few patients achieved a complete response — defined as negative immunofixation (an absence of M-protein in the urine and serum), disappearance of any soft tissue plasmacytomas and <5% bone marrow plasma cells. It is now accepted that complete response is a key determinant of long-term outcome for patients with multiple myeloma. 

Better rates of response have been seen with regimens incorporating bortezomib, lenalidomide or thalidomide. For example, in the Myeloma IX study, CTd (cyclophosphamide, thalidomide and dexamethasone) was better than cyclophosphamide plus VAD (CVAD) in terms of overall response rate (82.5% vs 71%) and rate of complete response (13% vs 8%) in a large population of newly diagnosed patients. 

Other highly active regimens include: bortezomib plus dexamethasone (Vd); bortezomib, doxorubicin and dexamethasone (PAD); and lenalidomide plus dexamethasone (RD). One of the most potent combinations, with a reported response rate of 98%, is lenalidomide plus bortezomib and dexamethasone (RVD) but the cost of this combination means that it is unlikely to be used widely in UK practice.  

Generally, CTD is considered the current UK standard induction regimen for patients due to undergo autologous SCT: This combination is now being compared with a regimen of lenalidomide, cyclophosphamide and dexamethasone (RCD) in the recently opened MRC study Myeloma XI. This study is also investigating the role of a bortezomib-based regimen (bortezomib, cyclophosphamide and dexamethasone; VCD) for patients who have a suboptimal response to an induction regimen using thalidomide or lenalidomide. 

**Stem cell transplantation** 

Although not curative, high-dose chemotherapy (a “conditioning” regimen) followed by reinfusion of autologous stem cells can prolong overall survival by about 12 months compared with conventional chemotherapy. Intravenous melphalan (at a dose of 200mg/m²) is the most commonly used conditioning medicine. It was first shown to be effective in 1983 and remains the standard conditioning regimen. 

Research into the timing of autologous SCT is ongoing (see Box 1). The value of tandem autologous transplantation (ie, two successive autologous SCTs) has also been investigated by several groups. Although these trials have demonstrated an improved response rate with double SCT compared with single SCT, an overall survival advantage (42% alive at seven years compared with 21%) was only shown by one group. Importantly, the benefits of a second transplant appear to be restricted to those patients who only achieve a partial response after the first procedure, and this approach is now generally only considered for this specific sub-group of patients. 

An alternative strategy is to collect sufficient stem cells for two procedures but delay the second transplant until the patient has actually relapsed.

**Allogeneic SCT** 

To date, the only potentially curative treatment option for multiple myeloma is allogeneic SCT. Conventional myeloablative conditioning is associated with a transplant-related mortality of 30–50% and is only really an option for the 2% of patients who are younger than 40 years at diagnosis; transplant-related mortality for older patients undergoing allogeneic SCT is unacceptably high.

However, the introduction of reduced-intensity conditioning (RIC) schedules has been associated with lower transplant-related mortality, in the region of 10–20%, while maintaining a graft-versus-myeloma effect (an immune-mediated phenomenon in which the new immune system recognises and targets residual myeloma cells, thus reducing the likelihood of relapse).

A recent Italian study demonstrated improved overall survival for patients who received an autologous SCT followed by a RIC allogeneic SCT, compared with those who received a double autologous SCT. The former approach is now recommended for selected patients.

**Maintenance therapy** 

As data have accumulated on the benefits of novel medicines, for both newly diagnosed and relapsed myeloma, interest has grown in using them to maintain response after autologous SCT. Thalidomide has demonstrated a survival benefit for this indication — it was associated with a 10% improvement in survival over placebo. However, concerns have been raised over the toxicity of long-term thalidomide use (particularly with doses >150mg a day) and further studies are needed to determine the optimal dose and duration of therapy.

Likewise, encouraging data have recently emerged for the use of lenalidomide or bortezomib for maintenance treatment but, until long-term follow-up data become available, use of these medicines for maintenance therapy is not recommended outside clinical trials.
Relapse

All patients with myeloma (apart from a proportion of those who have undergone an allogeneic SCT) will eventually relapse and require further treatment. The choice of salvage therapy will be guided by a variety of factors, including previous therapy, duration of first remission, type of relapse, performance status of the patient and any previous drug-induced toxicities.\textsuperscript{27}

For these patients, bortezomib, lenalidomide and thalidomide all show activity as monotherapy, but their benefits are augmented by the addition of dexamethasone, with or without an alkylating agent. For example, lenalidomide monotherapy produces a response in less than 25% of patients with relapsed or refractory myeloma.\textsuperscript{27} However, when used in combination with dexamethasone, it achieves a response rate of 60% and has been shown to improve overall survival when compared with dexamethasone alone.\textsuperscript{28,29}

Current NICE guidance recommends bortezomib for first relapse and lenalidomide (plus dexamethasone) for second relapse.

Novel medicines

The introduction of bortezomib, lenalidomide and thalidomide into standard treatment pathways for multiple myeloma has revolutionised treatment for this disease (so too has an understanding of the need for supportive therapies — see Box 2).

**Box 2: Supportive treatments**

In addition to treating the underlying disease process, management of patients with multiple myeloma involves using supportive therapies to address the condition’s clinical manifestations.

**Thromboembolism** Patients with multiple myeloma have an increased risk of venous thromboembolism (VTE) — the absolute risk for these patients is around 9%.\textsuperscript{30} This is caused by a range of factors, including elevated immunoglobulin levels and an increase in blood viscosity. This risk is increased further (to 15–25%) for patients receiving treatment with thalidomide or lenalidomide in combination with corticosteroids or chemotherapy, particularly for first-line treatment.\textsuperscript{31} There does not appear to be a significant increase in VTE risk when these drugs are used as monotherapy.\textsuperscript{32}

All patients starting thalidomide- or lenalidomide-containing therapy should have their risk of VTE assessed, taking into account their number of thrombotic risk factors (eg, infection, immobility, previous VTE). For those considered to be at low risk of VTE, prophylaxis with low-dose aspirin (75–325mg a day) can be considered, unless it is contraindicated.

For higher-risk groups, either warfarin or low molecular weight heparin (40mg daily, or 20mg daily if glomerular filtration rate is <30ml/min) is advised.\textsuperscript{1} However, there are currently no data from randomised trials to determine whether warfarin or low molecular weight heparin is preferable. There is no evidence to support the use of fixed, low-dose warfarin schedules in this setting.\textsuperscript{33}

Thromboprophylaxis should be given to at-risk patients for at least the first four to six months of treatment.

**Infection** Patients with multiple myeloma are at an increased risk of infection (due to the disease’s effect on immune response and the use of high-dose corticosteroids). Despite patients’ increased susceptibility to infections caused by organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, broad-spectrum antibiotic prophylaxis is not currently recommended. A large UK trial investigating the benefits of prophylactic levofloxacin (the TEAM M study) is due to open soon.

For patients receiving high-dose corticosteroids, most centres recommend co-trimoxazole (at a dose of 960mg three times a week) as prophylaxis against *Pneumocystis jirovecii* pneumonia. In addition, patients receiving bortezomib-based treatment should receive prophylactic aciclovir due to an increased risk of *Varicella* zoster infection.

**Skeletal effects** Bone disease is an extremely common feature of multiple myeloma, affecting up to 90% of patients, and is associated with fractures, spinal cord compression and hypercalcaemia.

The bisphosphonates sodium clodronate, zoledronic acid and disodium pamidronate have been shown to reduce skeletal related events (SREs) in patients with symptomatic multiple myeloma.\textsuperscript{34} Recently, a beneficial effect of monthly zoledronic acid infusions on overall survival was demonstrated by the MRC Myeloma IX study.\textsuperscript{35} Compared with oral sodium clodronate, zoledronic acid had a greater impact on SREs and significantly increased overall survival (50 months compared with 44.5 months, P=0.04).

However, it was also associated with an increased risk of osteonecrosis of the jaw, a rare but potentially serious complication of all bisphosphonates, particularly when given intravenously. Because of this, it is recommended that all patients should be reviewed by a dentist, and that any necessary dental procedures are completed, before starting treatment with an IV bisphosphonate.

It is also important to monitor renal function closely for all patients using bisphosphonates and ensure that doses and administration rates are adjusted appropriately for patients with renal impairment.

**Anaemia** Anaemia (haemoglobin <12g/dl) is a common complication of myeloma, occurring in 75–85% of patients. It is recommended that patients with anaemia associated with renal failure, or with symptomatic anaemia and haemoglobin <10g/dl, should be considered for treatment with recombinant human erythropoietin (eg, epoetin beta 30,000u once weekly).\textsuperscript{36}
Bortezomib

Bortezomib was the first proteasome inhibitor to be introduced into clinical practice. Proteasomes are large protein complexes whose role in breaking down intracellular proteins is vital for key cellular processes, such as the cell cycle and gene expression. Inhibition of proteasomes leads to apoptosis (programmed cell death).

Bortezomib is licensed as monotherapy for advanced myeloma (although it is routinely given in combination with dexamethasone) and in combination with melphalan and prednisolone for first-line treatment of patients ineligible for autologous SCT. It is approved by NICE for both indications but is only recommended as induction treatment for patients who are intolerant of or not suitable for a thalidomide-containing schedule.

The licensed dose of bortezomib is 1.3mg/m², given intravenously, on days 1, 4, 8 and 11 of a 21-day cycle. It is metabolised via the cytochrome P450 enzyme system, so dose reductions are recommended for patients with moderate-to-severe hepatic impairment. No dose modifications are needed in renal impairment but, for patients receiving dialysis, the drug should be given after a dialysis session.

Thrombocytopenia is a common adverse effect of bortezomib, but neutropenia and anaemia are uncommon. Other significant toxicities are summarised in Box 3. Data have recently been published demonstrating that subcutaneous administration appears to be clinically equivalent to intravenous administration but is associated with a lower incidence of adverse effects, particularly peripheral neuropathy.¹ In this study, rates of grade 2–4 peripheral neuropathy were 24% for subcutaneous bortezomib compared with 41% when the drug was given intravenously (P=0.01). It is expected that the product licence will be updated to include subcutaneous administration later in 2012. Moderate peripheral neuropathy necessitates a dose reduction of bortezomib and the drug may need to be discontinued permanently in the event of severe neuropathy.

Thalidomide

Thalidomide was used as a sedative and treatment for morning sickness in the late 1950s but was withdrawn from the UK market in 1961 after it was shown to be highly teratogenic. However, in 1998 it received regulatory approval in the US as a treatment for leprosy and in 2008 it was relaunched in the UK for treatment (in combination with melphalan and prednisolone) of multiple myeloma in patients unsuitable for autologous SCT. Because of its teratogenicity, the strict requirements of the “Thalidomide Celgene pregnancy prevention programme” must be followed for all patients taking thalidomide.

Although the mechanism of action in myeloma is not known, thalidomide is believed to have antiangiogenic and pro-apoptotic properties and can also inhibit tumour necrosis factor-alpha.

The standard dose of thalidomide is 100–200mg daily (given at night because somnolence is a common side effect). Although dose modifications are not generally required for patients with renal or hepatic impairment, active metabolites are excreted via the urine, so close monitoring for side effects is advised in patients with severe renal impairment.

Thromboprophylaxis with warfarin or low molecular weight heparin is usually required due to an increased risk of thromboembolic events. Other common toxicities are summarised in Box 3.

Lenalidomide

Lenalidomide is an immunomodulatory thalidomide analogue that possesses antiangiogenic, direct antitumour, anti-inflammatory and immune stimulatory properties. It has been shown to be more potent than thalidomide in vitro and has a different side effect profile to its parent compound. Although there is no evidence to date of human teratogenicity, lenalidomide is structurally related to thalidomide and has been shown to be teratogenic in animals. Consequently, the manufacturer’s pregnancy prevention programme must be followed for all patients receiving this drug.

Lenalidomide was licensed in the UK in 2007 for use, in combination with high-dose dexamethasone, for patients with multiple myeloma who had received at least one previous therapy. NICE approval was granted in 2009 based on the manufacturer’s guarantee that the drug would be provided free of charge for all patients who

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**Box 3: Adverse effects of novel treatments**

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<th>Bortezomib</th>
<th>Lenalidomide</th>
<th>Thalidomide</th>
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<tr>
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<td>No</td>
</tr>
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<td>Somnolence</td>
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continued treatment beyond two years (ie, from cycle 27 onwards). Importantly, the NICE approval was only for patients who had received two prior therapies although there are emerging data that the drug is more effective if used at first relapse.16

The starting dose of lenalidomide is 25mg daily for 21 days of a 28-day cycle (with dexamethasone 40mg daily on days 1–4, 9–12 and 17–20 for cycles 1–4, then 40mg daily on days 1–4 from cycle 5 onwards). A recent trial demonstrated that a lower dose of dexamethasone (40mg once a week) appeared to be better than the high-dose dexamethasone schedule, in terms of overall survival, and this has led to the weekly schedule being increasingly preferred, especially for older patients.3

Lenalidomide undergoes minimal metabolism and most of the dose is excreted unchanged in the urine. Therefore dose modifications are necessary for patients with renal impairment. Dose reductions are also required for patients who develop significant neutropenia or thrombocytopenia during treatment. Other common side effects of lenalidomide are listed in Box 3 (p130). Although lenalidomide does not share the classic thalidomide side effects of neuropathy, constipation and somnolence it appears to have a similar risk of thromboembolic events when used in combination with corticosteroids, with or without chemotherapy.

The next generation of novel agents with activity in multiple myeloma are currently being investigated, primarily in combination with more established therapies (see Box 4).

Pharmacist input

As the complexity of treatment pathways for multiple myeloma has increased, so too has the need for specialist clinical pharmacy input into the management of these patients. The need is recognised in the latest UK guidelines for the management of multiple myeloma, which state that “chemotherapy prescribing should be undertaken . . . with input from a specialist chemotherapy-trained pharmacist”.17

Given the high incidence of myeloma-induced kidney damage, it is important for clinical pharmacists to advise on dose modifications for chemotherapy and supportive therapies. Pharmacists should also be involved in counselling, particularly since these patients are often taking oral anticancer medicines and multiple supportive therapies (eg, antiocoagulants, antiemetics and anti-infectives). Pharmacists should provide written and verbal advice to promote adherence, either at the point of dispensing or through specialist pharmacist-led oral chemotherapy clinics.

**Box 4: Future therapies**

The following are four drugs that may receive licensing approval in the next 12–18 months.

**Carfilzomib** Carfilzomib is a second-generation proteasome inhibitor that has shown promising activity for patients with multiple myeloma, including those who are resistant to bortezomib.18 It also appears to be less likely to cause peripheral neuropathy than bortezomib. Phase III trials of the drug are under way in Europe and a licence application has been filed in the US.

**Pomalidomide** Pomalidomide is an oral immunomodulator, related to thalidomide and lenalidomide. In combination with dexamethasone it has been shown to produce response rates of >30% for patients with myeloma who are refractory to both bortezomib and lenalidomide.19

**Panobinostat and vorinostat** Panobinostat is an oral histone deacetylase inhibitor that, in in vitro studies, has been shown to act synergistically with bortezomib. A large international phase III trial (PANORAMA 1) is currently investigating the efficacy of this combination for patients with relapsed myeloma.20 Another drug in this class — vorinostat — has shown encouraging activity in heavily pre-treated patients refractory to bortezomib and lenalidomide or thalidomide.21

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References

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Multiple myeloma

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Questions

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The information in the Box (below) is there to help you identify knowledge gaps and undertake continuing professional development. This online module will close on 12 July 2012.

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● How has it added value to your practice?
● What will you do now and how will this be achieved?

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Consider making this activity one of your nine CPD entries this year

Reflect on your gaps in knowledge

● What are the common clinical features of multiple myeloma?
● What medicines are used for the treatment of multiple myeloma?

Act to enhance your practice

● Read the CLINICAL FOCUS articles in this issue (pp123–32)
● Test your knowledge by completing the questions at www.clinicalpharmacist.com

Answers from the March module

Gout

1 (a) T, (b) F, (c) T, (d) T, (e) F
2 (a) T, (b) F, (c) F, (d) T, (e) T
3 (a) F, (b) T, (c) T, (d) T, (e) E
4 (a) T, (b) T, (c) F, (d) T, (e) F
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6 (a) F, (b) F, (c) T, (d) F, (e) F
7 (a) F, (b) F, (c) T, (d) F, (e) F
8 (a) T, (b) F, (c) F, (d) T, (e) T
9 (a) T, (b) F, (c) T, (d) T, (e) F
10 (a) T, (b) T, (c) T, (d) F, (e) F

38 Richardson P, Siegel D, Vij R, et al. Randomised, open label phase 1/2 study of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib: phase 2 results. Blood 2011 (ASH Annual Meeting abstracts);118:634.