

NOVEL DRUG FOR RELAPSED OR CHEMO-RESISTANT MYELOMA

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Bortezomib, a proteasome inhibitor, is a new treatment option recently granted a UK licence. This article, part of an occasional feature of drugs reviews, examines the evidence

Multiple myeloma is a disorder in which malignant plasma cells accumulate in the bone marrow and produce an immunoglobulin (Ig), usually monoclonal IgG or IgA. Common complications of overt multiple myeloma include recurrent bacterial infections, anaemia, osteolytic lesions and renal insufficiency.¹

Although conventional chemotherapy and high-dose therapy with haematopoietic stem-cell rescue can prolong survival, few if any patients are cured. Salvage therapies for relapsed disease are equally disappointing and although thalidomide has shown promise, new treatments are urgently needed.²

Bortezomib is the first in a new class of drugs that inhibit proteasomes. Proteasomes play a pivotal role in the balance of important intracellular enzymes, the ubiquitin-proteasome pathway being responsible for degrading more than 90 per cent of all intracellular proteins. By inhibiting these enzymes bortezomib can disrupt normal cellular processes and promote apoptosis.

Fundamental to its activity in myeloma is its ability to inhibit the anti-apoptotic influence of nuclear factor κ B (NF- κ B), the activation of which is proteasome-mediated. In addition to its ability to stimulate the production of anti-apoptotic factors, NK- κ B, also plays a pivotal role in the production of cell adhesion molecules and inflammatory cytokines, both of which are essential in the pathogenesis and progression of myeloma.²

Bortezomib is administered by intravenous bolus injection (over 3–5 seconds). The usual dosage is 1.3mg/m² on days one, four, eight and 11 of a 21-day cycle.

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EFFICACY

An open-label, non-randomised, phase II trial of 202 patients (193 evaluated, ie, 96 per cent follow-up) was published in 2003: 35 per cent of patients had a response to bortezomib alone (10 per cent had a complete [or near complete] response, 18 per cent had a partial response and 7 per cent had a minimal response). Twenty-four per cent of patients showed no change, ie, disease stabilised.² Although the authors claim an overall response rate of 35 per cent, more than two-thirds of these responses were either “partial” or “minimal” — terms the authors failed to define. However, many other papers on myeloma treatments are also not explicit in their definition of a “partial” or “minimal” response.

The median time to progression of disease in patients receiving bortezomib was seven months compared with three months during their last treatment before enrolment ($P=0.01$). The median time to progression among patients with a complete or partial response was 13 months. The median overall survival was 16 months (with a median duration of response of 12 months). Achievement of a complete or partial response after two cycles was associated with a significantly longer survival than in all other patients ($P=0.007$). Median overall survival in patients without a response was eight months. Responses were also associated with increased haemoglobin levels, decreased transfusion requirements, an improved quality of life and improved levels of normal Igs.

The US Food and Drug Administration (FDA) approved the use of bortezomib partly based on the above phase II data. However, due to the fact that the study was open-label and non-randomised, it could be argued that it is difficult to quantify accurately the size of the apparent treatment benefit due to the lack of a control group. FDA-approval was contingent on post-marketing study commitments, including completion of an ongoing randomised phase III study.

An interim analysis of the randomised controlled phase III trial data comparing bortezomib with dexamethasone was presented at the American Society of Clinical Oncology (ASCO) earlier this year. In this study, patients with relapsed or chemo-resistant myeloma (treated with one to three prior therapies) were randomised to bortezomib ($n=327$) or dexamethasone ($n=330$). Median time to progression (the primary end-point) in the bortezomib arm was 5.7 months (95 per cent confidence interval [CI]: 5.0,7.9) and 3.6 months (95 per cent CI: 3.2,4.8) for dexamethasone-treated patients ($P<0.0001$).³ This yielded an apparent absolute benefit increase of 2.1 months.

Thirteen deaths were reported in the bortezomib arm compared with 24 deaths in the dexamethasone arm ($P=0.038$). However, median survival was not reached in either group. A non-significant reduction in grade three or grade four infections was also reported for bortezomib treated patients (6.7 per cent bortezomib; 10.6 per cent dexamethasone; $P=0.096$). No differences were demonstrated in the “time to skeletal event”, eg, osteolytic lesions ($P=0.954$).

ADVERSE EFFECTS

The most clinically significant adverse event, demonstrated in phase II studies was cumulative, dose related peripheral sensory neuropathy. However, only one patient that did not have neuropathy at baseline developed grade three peripheral neuropathy. Thrombocytopenia was the most common severe adverse event. However, thrombocytopenia developed primarily in patients with a low platelet count at baseline and was often transient and without serious bleeding complications. Details on the adverse effects during the phase III trial should become apparent following the full publication of the data.

SUMMARY

Phase II data have shown that bortezomib can induce clinically significant responses, with manageable toxic effects in

full treatment benefit beyond the interim analysis will not be known because patients randomised to dexamethasone were switched to bortezomib.

Another important consideration when reviewing the cost of treatment with bortezomib is the available presentation of the drug. As seen in Panel 2, bortezomib (Velcade) is available as a 3.5mg vial. Considering the licensed dose is 1.3mg/m², nearly 40 per cent of the active ingredient would be wasted for an average adult patient. Therefore centres may opt to co-ordinate treatment sessions for patients to ensure complete use of the vials and thus reduce wastage. Such an approach could save up to one third on drug costs.

In summary, bortezomib appears to have robust evidence supporting a treatment benefit over dexamethasone in patients with relapsed or refractory myeloma. The treatment benefit, although small, is a significant advancement for this difficult-to-treat patient group. A major issue surrounding the use of this drug is its cost and subsequent funding. The perceived treatment benefit of bortezomib needs to be balanced against the cost implications of approving this therapy. The best approach to this important issue is currently the subject of local discussions between primary and secondary health care organisations.

However, to ensure equity of access to treatment nationally, a National Institute for Clinical Excellence appraisal would be welcomed.

A case such as this highlights the necessity for Drugs and Therapeutics Committees to review cost implications in parallel with the clinical evidence.

Two phase II studies are currently investigating the use of bortezomib in previously untreated patients and a separate trial in the UK is investigating its use alongside dexamethasone or doxorubicin. Preliminary results appear promising which hopefully should drive phase III trials in early stage myeloma treatment.

Further reading on this topic is suggested in Panel 3.

Panel 2: Product details

- Velcade (bortezomib as mannitol boronic ester) 3.5mg vial
- Cost: £895.80 (inc VAT) per vial
- Dose: 1.3mg/m²
- Dosage for patient with a body surface area of 1.7m²=2.21mg
- Wastage for patient with a body surface area of 1.7m² is 37 per cent

Panel 3: Further reading

A recent article (Schrag D. The price tag on progress — chemotherapy for colorectal cancer. *New England Journal of Medicine* 2004;351:317–9) discusses the ethical and moral issues of approving high cost drug therapies.

REFERENCES

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