

# Bortezomib economic evaluation limited

From Dr A. Haycox and Mr K. Tolley

The article by Grosso *et al*<sup>1</sup> provides an excellent and balanced summary of the phase II and III trial evidence on bortezomib (Velcade) efficacy that is available in the public domain. The authors are positive about the efficacy and importance of the clinical benefits derived from bortezomib. In addition, they state: "Bortezomib appears to have robust [phase III] 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."<sup>1</sup>

However, the authors, quite rightly, also emphasise that the treatment benefits derived from bortezomib must be evaluated in the context of the cost of providing the therapy. Health economic assessments are a fundamental necessity in balancing the costs and benefits of new therapies and are now essential to complement the clinical case for introducing a new drug into the NHS. In this regard, the authors are correct in calling for an early evaluation by the National Institute for Clinical Excellence (NICE) to evaluate independently and scientifically the costs and benefits derived from this novel drug.

Unfortunately, the method the authors have used for assessing the cost-benefit balance has significant limitations and is likely to have produced a biased assessment. They have calculated the numbers needed to treat (NNT) to prevent an additional death with bortezomib compared with dexamethasone and then determined the total cost of treating that number of people with bortezomib. Based on a difference in deaths between the two arms reported in an interim analysis of the phase III trial, Grosso *et al* have calculated the NNT as 31 to prevent one additional death. They have then applied an assumed cost for 11 cycles of bortezomib of £39,415 (including VAT) to report a cost per death prevented of over £1.2m. Such a calculation exhibits a number of limitations which may provide a misleading impression of the cost-effectiveness.

The calculations were based on data from an interim analysis, which due to the importance of the initial results were presented at the earliest possible opportunity at the American Society of Clinical Oncology (ASCO) meeting in June 2004.<sup>2</sup> This analysis, however, was not designed for health outcomes assessment and so any such analysis based on these data is tentative and has to be treated with extreme caution. Efficacy results from the final phase III data analysis were to be presented at the American

Society of Haematology meeting in December 2004.<sup>3</sup>

The cost assessment is based on the maximum dosing schedule as specified by the protocol of 11 cycles of treatment (eight induction followed by three maintenance), although the authors recognise that a shorter length of treatment (six to eight cycles) is more likely. The mean duration of scheduled treatment in the phase II study (which specified a maximum of eight cycles) was 5.25 cycles, indicative of the actual length of treatment that might be expected. Non-adherence (ie, missed doses) was 10 per cent in the phase II study producing an actual treatment received equivalent to 4.71 cycles per patient, representing an average cost of just under £16,900 (including VAT). The phase III study has an additional objective of investigating whether the addition of up to three months maintenance therapy produces significant clinical benefits over induction treatment. To be justifiable in cost-benefit terms an additional gain in survival will be required, and so the extra cost of maintenance would not be incurred in actual clinical practice unless justified by sufficient additional survival benefits. The Research Prescribing Group at Liverpool University is currently analysing the full phase III dataset, and will be able to report the median and mean duration of treatment in due course.

## Full economic evaluation

The authors considered acquisition costs only. However, a rigorous health economic evaluation must consider the additional costs associated with adverse events. These data were not available from the interim analysis but it is likely that the incremental costs associated with bortezomib compared with dexamethasone will be lower due to an expected worse serious adverse event profile for patients in the dexamethasone arm (eg, neurological complications, chronic infection and diabetes onset).

The use of observed deaths in this context is too crude to provide a meaningful assessment of the cost-benefit ratio. Given the nature of the patient set treated, ultimately all patients are likely to die from multiple myeloma whether on bortezomib or dexamethasone and hence the cost per additional death prevented becomes essentially meaningless. Such a measure takes no account of survival time or quality of life. Economic evaluations of cancer treatments estimate the incremental cost per life year and quality adjusted life year (QALY) gained which take into account the additional months of survival for each patient, and the quality of that survival. Such measures pro-

vide a more robust approach for assessing relative cost-effectiveness.<sup>4</sup>

A full health economic evaluation of bortezomib versus best supportive care/standard therapy for relapsed or refractory multiple myeloma at third-line and beyond has been conducted by the Prescribing Research Group using the phase II data. The expected benefit was estimated to be an additional mean survival of nearly 10 months in the base case (range 7.75–12.09). Using extensive survival modelling, this has demonstrated an incremental cost per life year gained of £17–31,000, based on a mean additional survival benefit over current expectations of 8–12 months, with good quality of life.<sup>5,6</sup>

Data on cost-effectiveness were submitted in 2004 to a health technology assessment body, the Scottish Medicines Consortium (SMC). An estimate for bortezomib of £30,379 per QALY gained was included in the submission to the SMC. The outcome was that the SMC has recommended bortezomib for use in Scotland.<sup>7</sup> Based on conventional benchmarks for assessing cost-effectiveness of new or novel cancer therapies the evidence generated so far suggests that bortezomib has good cost-effectiveness when used in patients with relapsed and refractory multiple myeloma at third-line and subsequent treatment stages, which is the current licensed indication.

The cost-effectiveness of bortezomib for second-line use has yet to be established. However, additional health economic modelling using the full phase III dataset is now under way to support this earlier use of bortezomib in multiple myeloma. This is being conducted by the Prescribing Research Group, and is intended for publication during 2005. Bortezomib is not yet licensed for this use, but if and when a licence is granted (expected in 2005), this modelling will provide a firmer basis than crude NNT calculations for determining whether the expected survival and quality of life benefits bortezomib provides justifies the additional cost.

In conclusion, cost-effectiveness of bortezomib has been determined for the current licensed indication of third-line and subsequent treatment of relapsed or refractory multiple myeloma, and is currently being established for an extension of treatment to second-line use pending regulatory approval for this indication. Bortezomib is a novel first in class treatment and the available evidence has already been reviewed by a number of national bodies on behalf of the NHS. Due to issues of cost and funding there is a real likelihood of widespread post-code prescribing in the use of bortezomib

across the UK, and first indications are that this is already occurring in some areas. Therefore, we support the recommendation of Grosso *et al* that to ensure equity of access to treatment nationally, a NICE appraisal would be desirable.

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The economic evaluation of bortezomib mentioned is being undertaken through an unrestricted educational grant from Johnson & Johnson.

ANTHONY GROSSO replies: The evaluation of the evidence was based upon the preliminary data available at the time. The limitations surrounding these data were clearly identified in the original article. However it was considered valuable to summarise the available data to aid clinicians and therapeutics committees in their decision-making process. Although we agree that ideally the incremental cost per life year and QALY gained are optimal pharmacoeconomic parameters for assessment in the non-curative setting, such an evaluation was

beyond the scope of our remit even if the necessary data had been available at the time of publication, which was not the case.

The original article stated that the phase III data needed to be interpreted with caution for the reason stated by the reviewer and for many others. However, it was thought pertinent to include these data as this provided the most up-to-date mortality information at the time of publication.

The article included information based on intention-to-treat analysis, ie, on a protocol based on 11 cycles of therapy. As with all efficacy studies, it was considered essential to report the data as per the study protocol. The limitations surrounding the median number of cycles administered were also clearly outlined in the original article as the exact figure was unavailable at the time of publication.

Although we expressed clearly our concerns regarding interpretation of the phase III interim analysis data, we are of the opinion, that at the time of writing, this provided us with the most accurate indication of the treatment benefits associated with bortezomib. We do, however, agree that acquisition costs should not be viewed in isolation when assessing the cost-effectiveness of therapy, particularly in the non-curative setting.

The use of observed death was presented in absolute terms so as to take into account

the control event rate. The acquisition cost analysis was presented, as an example, because we hoped it would highlight the need for an independent pharmacoeconomic evaluation of the randomised, controlled phase III data (preferably by NICE).

In conclusion, the aim of the article was to present clearly the available phase II and phase III data available. This was expressed in absolute, intention-to-treat terms with the limitations surrounding this approach clearly documented. An economic evaluation surrounding the cost-effectiveness of bortezomib was not intended or implied. Bortezomib is an effective agent, however, the issues surrounding its cost-effectiveness will not be resolved until an independent, robust, economic evaluation of the full phase III dataset is available.

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