Background

In October 2007 NICE published guidance on the use of bortezomib in relapsed multiple myeloma as follows (1): Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances:

- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in people who have a complete or partial response (that is, reduction in serum M protein of 50% or more or, where serum M protein is not measurable, an appropriate alternative biochemical measure of response) and
- the manufacturer rebates the full cost of bortezomib for people who, after a maximum of four cycles of treatment, have less than a partial response (as defined above).

Therefore NICE do not currently support the use of bortezomib for 2nd, 3rd or subsequent-line treatment in patients that relapse. This guidance conflicts with previously issued guidance from the BCSH (2) which supported the use of bortezomib as a third-line therapy in patients with reasonable performance status and organ function and reasonable life expectancy. This guidance is due for review in October 2010 but at present it is unclear if NICE will revisit it.

Prior to publication of the NICE Guidance the BCSH guidance probably best reflected how bortezomib was used in the UK. Therefore since publication of the NICE Guidance there is now a population of patients with multiple myeloma who cannot get access to bortezomib at any stage of their disease as they had already had more than one relapse at the time of the NICE publication and therefore do not meet the treatment criteria.

Clinicians in London Networks have prioritised reconsideration of the role of bortezomib for this patient group for the last two years.

Evidence used by NICE

The primary evidence, and that considered by NICE, for the use of bortezomib comes from the APEX trial (3). In this trial 669 patients with relapsed myeloma were randomised to receive bortezomib or high-dose dexamethasone. Patients recruited had received a median of 2 previous therapies, with 56 and 58% receiving 2 or 3 previous lines of treatment and 4 and 7% receiving 4 or more previous lines of treatment in the two treatment arms. Overall it was shown that bortezomib was associated with a longer time to disease progression (6.22 months vs 3.49 months) and an improved 1 year survival rate (80% vs 66%). Subgroup analyses showed that patients that had only received one previous therapy had a median time to progression of 7 months when treated with bortezomib compared with 5.6 months if treated with dexamethasone. However in patients that had received more than one previous treatment the figures were 4.9 months and 2.9 months respectively.

At 22 months follow-up, the median overall length of survival in the intention to treat population was 29.8 months in the bortezomib arm compared with 23.7 months in the high-dose dexamethasone arm despite 62% of patients crossing over from dexamethasone to bortezomib.

NICE reviewed the cost-effectiveness of bortezomib based on a model derived from the APEX data and concluded that the most cost-effective approach to using bortezomib was to treat patients at first relapse, to measure serum M protein after four cycles, to discontinue and rebate treatment cost in people whose disease had responded less than partially, and to continue treatment only in those whose disease had responded at least partially. This approach resulted in an ICER of £20,700 per QALY gained. It was further noted from the Evidence Review Group that treating patients at second relapse only or at third relapse only would result in markedly increased ICERs of £77,000 and £107,000 per life year gained, respectively. The Committee therefore accepted that bortezomib monotherapy is not cost effective when used at second or subsequent relapse (1)
Evidence published subsequent to NICE decision

Mikhael et al has published the results of a multicentre, open-label, phase 3b trial in 638 patients with relapsed or refractory multiple myeloma (31.8% had received 2 or less therapies, 50.8% had received 3 prior therapies and 17.4% had received between 4 and 11 prior therapies) (4). In this programme dexamethasone was added to regimens in patients with progressive disease after 2 or more cycles of bortezomib and after 4 or more cycles of bortezomib in patients with stable disease. Responses were assessed based on M-protein changes and it is reported that overall response rate was 67% with 11% complete (100% M-protein reduction), 22% very good partial (75-99% reduction), 18% partial (50-74% reduction) and 16% minimal (25-49% reduction). Dexamethasone was added in 33% of patients of whom 34% showed improved response. The median time to best response was 84 days (approximately 4 cycles).

Jagannath et al have published an analysis after prolonged follow-up of the phase 2 study multicentre CREST study of bortezomib in relapsed or refractory multiple myeloma (5). In this study 54 patients who had relapsed or were refractory to front-line therapy (received between 1 and 3 previous treatments) were randomised to receive bortezomib either as a 1mg/m\(^2\) regimen or as a 1.3mg/m\(^2\) regimen. The median duration of treatment was 4.7 months and 3.9 months respectively and 61% and 27% completed all 8 cycles. After a median follow up of 61 months and 65 months in the low and high-dose groups it is reported that the median overall survival was 26.8 months vs 60 months (not powered to assess this end-point and not statistically significant). Overall it is reported that based on Kaplan Meier projections, 32% of patients that received low dose bortezomib and 45% of patients that received conventional dose bortezomib would be alive at 5 years.

Lee et al have published the findings of an assessment of quality of life that was run in parallel with the APEX study (6). They report that bortezomib was associated with better health related quality of life across many domains over 42 weeks of assessment. Specifically bortezomib was associated with better global health status, better physical health, role, cognition, and emotional functioning, and less dyspnoea and sleep disturbance over time compared with dexamethasone.

Toxicity

The data from the Mikhael report are probably the most relevant in terms of outlining the toxicity profile of bortezomib

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one event</td>
<td>64.7</td>
<td>30.4</td>
<td>95.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21.6</td>
<td>17.7</td>
<td>39.3</td>
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<tr>
<td>Neutropenia</td>
<td>12.9</td>
<td>3.3</td>
<td>16.2</td>
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<tr>
<td>Anaemia (NOS)</td>
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<td>1.7</td>
<td>12.2</td>
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<tr>
<td>Diarrhoea (NOS)</td>
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<td>Peripheral neuropathy</td>
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<tr>
<td>Fatigue</td>
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</tbody>
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Points for discussion

In 2007 NICE reviewed the evidence for bortezomib and concluded that it was not cost effective when used in patients that had received more than one prior treatment. When used in patients that had received three prior treatments they estimated that it cost over £100,000 per QALY gained.

Group agreed that it was difficult to justify use beyond first-line setting given these estimates of incremental cost effectiveness ratio (ICER)

Subsequent to that decision there has been little additional relevant information published that helps to clarify the robustness of that decision.

Group agreed that the data published subsequent to NICE appraisal did not significantly alter the evidence base.

There are a decreasing cohort of patients that cannot access bortezomib because their disease had progressed beyond first relapse when NICE issued this guidance – is there sufficient evidence or ethical considerations that would support contradicting NICE in defined circumstances? e.g. in cases where use of bortezomib may act as a bridging therapy to a transplant procedure or in cases where existing neuropathy or history of thromboembolism may contraindicate thalidomide (any other examples?)

The only groups of patients identified after discussion were patients that missed out on bortezomib at first relapse because they agreed to enter a clinical trial at this point instead and patients that experienced their first relapse before NICE approved it and did not receive bortezomib at that time. LCNDG felt that these groups of patients should have access to bortezomib at a subsequent point in their disease progression.

References

1. NICE: Bortezomib monotherapy for relapsed multiple myeloma (TA 129)