

Bortezomib and Thalidomide for the first-line treatment of myeloma Assessment report

Response from the UK Myeloma Forum

This report has been prepared by the UK Myeloma Forum in conjunction with representatives from the British Society for Haematology, the Royal College of Pathologists and the Royal College of Physicians, and contains our initial comments on the Assessment Report of the systematic review and economic evaluation of the clinical and cost effectiveness of Bortezomib and Thalidomide for initial treatment of multiple myeloma.

Overall we believe that the review is fair and balanced but we welcome the opportunity to raise a number of points we consider to be important.

There is an accurate description and understanding of underlying health problem and the inclusion criteria for study selection with regards to interventions, comparators, and populations were appropriate. Outcomes criteria were also appropriate but we note that use of OS to calculate the QALY in trials where patients are allowed to cross over to alternate therapy or, after subsequent relapse, receive other agents, is increasingly problematic.

Criteria for selection of studies, and eligibility of outcome data

Data extraction appears accurate but we are concerned to note that there appears to be a wide gap between the standards and qualities required by the assessment group to perform their evaluation, and what researchers conducting studies both in the UK and world wide consider necessary to produce well conducted and informative trials.

We note that this meant that only five RCTs met the criteria for inclusion in the systemic review of clinical effectiveness whereas a number of large studies with a potentially significant amount of important and relevant information were excluded. We feel that, as a consequence, potentially clinically important results may be excluded, thus affecting the cost effectiveness estimate of any one of the technologies being assessed.

We highlight this as an area of major concern and recommend that in future there should be a dialogue between NICE and clinical researchers as well bodies responsible for authorisation and funding of national clinical trials. This will ensure that clinical trials can deliver information that meets the needs of both clinical researchers and HTA's.

We are also concerned that data from the large UK Myeloma 1X study have not been taken into account because the trial included a randomisation to maintenance with thalidomide. It is our understanding that the study is large enough for a subgroup analysis of those not receiving maintenance could be undertaken and we would encourage the assessment team to explore this option.

SHTAC model

Although we do not have particular expertise in Health Economics, we were pleased to note that the choice of health economic model in this evaluation was one which appeared to us to be able to model the reality of a patient's progress through the various stages of Myeloma, and was therefore a particularly suitable choice for this evaluation.

Allowing for the caveats outlined above we feel that the benefits and risks of the technologies have been fairly represented.

Adverse events: incidence, effect on utility and clinical experience

We note a statement of concern from one of the clinical experts (pg 145 section 1.17 Uncertainties) that 'the incidence of AE's may be underestimated by the clinical trials'.

Whilst this may be possible we would point out that the trials were conducted at a time when experience with these technologies was limited. Since that time, UK clinicians have developed considerable expertise in monitoring for, and managing side effects. Local guidance is in place in many departments in the form of peripheral neuropathy and thrombosis risk assessment tools. We would be happy to supply examples of these on request. In addition comprehensive guidance is included in the revised UK Guidelines for management of multiple myeloma which are expected to be published shortly. Employment of such tools for these toxicities ensures early recognition of problems and implementation of strategies to prevent progression. This is not only better for patients but ensures prudent use of resources with resultant cost effectiveness benefits. We feel that there is greater awareness of all other AE's which are also managed more skilfully. We therefore suggest that there is less uncertainty about the impact of AE's than may have been the case in the early days of the use of the technologies.

Principle findings: Clinical effectiveness

We are pleased to note that the SHTAC report finds that the technologies are clinically effective, based on the five RCT's that were included in the review. Specifically, the complete response (CR) rates in patients receiving MPT, CTDa or VMP were higher than in the control groups of patients receiving MP. In some studies, this translated into superior progression free survival and overall survival. We note that not all the RCT's that were selected for review used ITT principles, and only one reported on time to progression. In addition, data from the Myeloma IX RCT are not sufficiently mature to produce robust estimate of OS benefit. The statistically significant increase in CR rate is important because our clinical experience with this group of patients is that being in CR correlates with improved quality of life.

Cost effectiveness results

We note that the SHTAC found that the cost effectiveness estimate of the MPT regimen vs. MP per QALY gained was cheaper at £9,174 compared with £29,837 and £33,216 for VMP and CTDa respectively. We were pleased that the assessment produced such a favourable outcome for MPT and feel that this regimen would be widely used in the patient population under consideration because of its ease of administration and

manageable side effect profile. We feel equally strongly, however, that the MPT regimen would not be suitable for all patients, in particular, those with a high thrombotic risk, the 10-15% who suffer with unacceptable thalidomide-related toxicity, e.g. somnolence, fluid retention, rash and severe constipation, and those with poor bone marrow reserve who would not tolerate Melphalan. For such patients, it is vital that MPV and CTDa are available and accessible.

In addition, we would argue that the ICER per QALY gained by **MPV** vs. MP has been overestimated because both in the VISTA trial, and also in everyday clinical practice, much less treatment is given than has been used in the economic model. The VISTA protocol that has been used in the economic model includes 4 initial cycles with 8 doses of Bortezomib each. This in practice equates to a total of 12 cycles of Bortezomib in the VISTA protocol. In clinical practice in the UK, treatment with Bortezomib rarely goes beyond 8 courses and is usually significantly less, often from four to six, either because patients have achieved complete responses within 3-4 cycles, or require dose reduction to manage toxicity.

The high cost effectiveness estimate for the **CTDa** regimen is clearly at odds with the corresponding figure for the related regimen, MPT. In our clinical experience, these regimens are fairly similar to administer, the active 'ingredient' being Thalidomide. Notably, previous MRC trials have not shown any differences in response or survival between Melphalan and Cyclophosphamide either alone or in combination with steroids. We understand that none of the time to event outcome data for the Myeloma IX RCT has been deemed eligible for inclusion, because of the randomisation to Thalidomide maintenance. Therefore we are concerned that the estimate of cost effectiveness does not reflect the reality of health economics of myeloma care. It is the experience of UK physicians that both MPT and CTDa regimens are equivalent in clinical effectiveness, ease of delivery and adverse events (mainly related to Thalidomide); hence we argue that the large disparity between the estimated ICER per QALY makes no clinical sense. We can see that this disparity has arisen because the incremental QALY for CTDa vs. MP is much smaller, and we feel strongly that this can only be because of lack of maturity of the Myeloma IX data. We fully expect that, in due course, CTDa will prove to be as effective as MPT.

This is important because whilst Melphalan has been used routinely in the UK in the elderly population, it is myelosuppressive and would therefore be contra-indicated in some patients with cytopenia. In addition it requires dose reduction in the 20% of patients with myeloma who present with renal impairment. It is therefore clear to us that a Melphalan containing regimen would not be suitable for a significant proportion of patients but CDTa could be used safely in these patients and thus would be clinically preferable to MDT. In situations where rapidity of response is essential, e.g. to prevent irreversible renal failure and dialysis-dependence, the MPV regimen may be more appropriate.

Uncertainties and limitations of the assessment

The SHTAC have noted that differences in Thalidomide dosing, scheduling and treatment duration between RCTs, and also between these European studies and UK practice. Uncertainties also exist regarding incidence of AE's (see above), and of

HRQoL data for the population of interest, and the effect of subsequent treatments. Furthermore, it is important to note that the patient populations are heterogeneous making it extremely difficult to draw comparisons between them. It is now very clear that myeloma is not a homogeneous condition and if we are to improve outcomes for this disease in the future it will be necessary to select treatment for individual patients taking into account the inherent disease heterogeneity, the patient population (elderly with co-morbidities) and the different toxicity profile of each of the technologies.

Thus, we strongly argue that it is important that all these technologies should be made available for the treatment of myeloma patients. Given the freedom to make these clinical decisions, physicians will act responsibly and in the context of a peer reviewed Multi-disciplinary team structure will utilise a risk-adapted approach to treatment. This will allow flexibility whilst at the same time taking into account cost effectiveness issues.

Finally we would like to endorse the Assessment group's views that research involving head to head trials of Bortezomib and Thalidomide containing regimens would have been useful to inform the assessment process. Learning from this, we would welcome the opportunity to discuss future clinical studies addressing new technologies, including the effect of sequencing, with NICE and the DH.



On behalf of the UK Myeloma Forum