

HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal - Assessment Report	
Bortezomib and Thalidomide for the first-line treatment of multiple myeloma	
TO: NICE	FROM: NHS Quality Improvement Scotland 15 March 2010

I have two comments to make in relation to the technology appraisal:

1. In establishing the comparative cost effectiveness of the VMP regime with that of MPT the analysis is limited because there are no studies which have directly compared these two regimes. The most recent data on bortezomib combinations as first line therapy in myeloma appear to show a better response rate and progression free survival in comparison with previous studies involving thalidomide based combinations. I agree with the authors of the appraisal that a RCT comparing VMP vs MPT (or similar thalidomide combination) would be of value although I suspect that this trial will never be undertaken given that US practice is to use lenalidomide as first line therapy and in continental Europe Bortezomib as first line therapy.

2. The appraisal did not look at cost effectiveness in the sub-group of patients with adverse cytogenetics. There is compelling evidence from studies that bortezomib abrogates the negative impact of adverse cytogenetics on treatment outcomes. I would suspect therefore that the QALY for bortezomib would be substantially lower in this sub-group of patients.



The report is well laid out, with clear descriptions of the methods used, the results obtained, the cost effectiveness analysis and the uncertainties that remain.

I note that additional data was provided by the clinical trials research unit relating to the Myeloma IX study comparing CTDa and MP. However, as this data was provided in academic confidence, the data is not included in this report for my perusal. I cannot therefore comment on any of the comments made relating to CTDa versus MP

VMP versus MP (VISTA study)

The clinical effectiveness data is clearly presented here indicating the higher rates of overall survival (72% at 3 y versus 59%), complete remission (30 v 4%) and at least partial remission (71 v 35%) with the use of VMP. It is also clear that the remissions obtained with VMP are of longer duration, and that there is a high rate of response to second line therapy (indicating that early use of bortezomib is not resulting in highly resistant disease).

A median of 8 courses of VMP and 7 courses of MP were delivered in this study. It is noted that the patients recruited to the study may be fitter than patients in the UK requiring treatment that have not been specifically selected for a trial. It is therefore not clear why the deterministic sensitivity analyses for VMP versus MP are based on an upper value of 10 and a lower value of 8.

The VISTA study did not use any prophylactic antibiotics or antiviral agents. It is not clear whether the addition of aciclovir prophylaxis (which is routine in the UK) would reduce the incidence of herpes zoster noted with the use of VMP and therefore impact on the quality of life of these patients.

The high incidence of anemia and thrombocytopenia with both VMP and MP is documented. However, it is not clear what proportion of patients experienced significant bleeding as a result or required platelet transfusions. A higher proportion of patients (35%) in the MP arm required red cell transfusions (versus 26% VMP arm). This needs to be taken into account in the quality of life studies and when considering the impact of services.

There is some discrepancy between the cost analyses submitted by the different drug companies. In practice, it is reasonable to assume that there will be vial sharing of bortezomib in a large proportion of cases as it is likely that there will be more than one patient receiving bortezomib at any one time in a given centre. The cost-analysis should therefore take this into account.

A number of uncertainties are mentioned with respect to VMP therapy in the UK.:

- Peripheral neuropathy reporting: there is a well documented incidence of peripheral neuropathy associated with bortezomib therapy. However, this is usually manageable if there is prompt reduction in the dose or frequency of bortezomib administration as per the SPC. The data also indicate here that the neuropathy improves significantly within a few months of stopping therapy.
- Second line therapy in the UK differs to the RCTs: the data from the VISTA trial indicate that 16% of patients treated with VMP first line received bortezomib or a bortezomib combination second line. A PR was achieved in 33% and CR in 6%. In addition, the use of bortezomib second line (or later) in the UK simply reflects the lack of availability of novel agents for first line therapy, and the lack of alternative agents such as lenalidomide for second line therapy or later.

MPT versus MP (IMF studies and GIMEMA)

The clinical effectiveness of these two regimens is clearly documented. However, the different doses and treatment protocols used make it difficult to know whether the cost effectiveness is based on the amount of drug that will be used in clinical practice. The analyses are based on a 6-week cycle, although it is noted that the GIMEMA protocol (and Myeloma IX for CTDA v MP) uses a 4-week cycle. In addition, the administration of 12 cycles of MPT or MP (as in the IMF study) is greater than unselected patients in the UK usually receive or tolerate. Table 38 states that the analyses here are based on 10-12 x 6-week cycles of MP. This is not the dose that those practitioners involved in the Myeloma IX study will be used to using.

However, it is clearly demonstrated here that MPT is more clinically effective than MP, although the rate of complete remission is lower in both arms than that reported in the VISTA study with VMP.

The data indicate that the trials reported here did not have sufficient power for subgroup analyses. The benefit of obtaining complete remission rather than just a partial remission remains to be proved and is one draw back of this report.

The MPT studies vary in their use of thromboprophylaxis (Facon did not routinely use thromboprophylaxis and Palumbo used enoxaparin for 4 cycles). Low molecular weight heparin prophylaxis or warfarin therapy is routinely used in the UK although the duration of treatment will be centre-dependent (3 months minimum; duration of thalidomide therapy maximum). This needs to be considered in the quality of life and cost-effectiveness analyses.

Cost-effectiveness

It seems clear that both VMP and MPT are clinically more effective than MP. In the SHTAC report, it appears that MPT is more cost-effective, although the above comments should be considered. A number of scenarios are analysed. It is unlikely that most patients will receive first line therapy and no subsequent therapy. However, scenario B is likely, with vial sharing. The role of thalidomide maintenance is not clear, and there are ongoing studies looking at this. However, pending results from Myeloma IX, thalidomide maintenance following first line therapy is not routinely being used in the UK. All analyses of cost-effectiveness need to take into account that, as a chronic condition, myeloma patients are highly likely to receive 2nd line therapy and will be given bortezomib-based regimens if they do not receive them first line. This needs to be counterbalanced against the increased complete remission rate achieved when bortezomib containing regimens are used first line. The impact of achieving complete remission on disease outcome is not yet known as the subgroup analyses were felt to be inadequate.

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The clinical and cost-effectiveness of bortezomib and thalidomide for the first line treatment of multiple myeloma: a systemic review and economic evaluation.

Thank you for asking me for my comments on this assessment report.

I found the report well written, detailed and informative. The literature discussed appeared reflective of my knowledge of the subject. Obviously I am not an expert in Health Economics but the conclusions appeared sound. The clinical discussion appeared appropriate.

The basic conclusion appears to be a recommendation for use of MPT as first line therapy in multiple myeloma for patients not eligible for stem cell transplantation, rather than VMP or CTDa. The trial of CTDa (Myeloma IX) still has to be reported in full so some caution is required.

However, I think this is a reasonable recommendation clinically for the NHS in Scotland. Access to Velcade (Bortezomib) would still be permissible as a second line agent in accordance with recent SMC advice.

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