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16th March 2010

Dear [REDACTED]

Re: 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’

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with regard to this assessment report consultation. We are pleased to be invited to comment and would like to thank our clinical expert nominee, Dr Steve Schey for coordinating this response. We would like to make the following points:

The review represents a fair and balanced overview of clinical trial activity in the world in the setting of the treatment of *de novo* myeloma. Scoping of the issue in respect to interventions, comparators, and populations seem appropriate. Caution, however, needs to be exercised when the estimation of cost effectiveness relies upon outcome data that is calculated from trials that allow cross over for patients who either do not respond or progress on treatment.

Study selection

We note that of 1436 records screened only 40 studies were retrieved for consideration for systematic review of clinical effectiveness and only 5 of these met the inclusion criteria for clinical effectiveness systematic review. The potentially significant amount of relevant information that may have been excluded and the bias that may have been introduced by these exclusions does, in our opinion, cast some doubt upon the cost effectiveness analysis.

This fact is in line with a number of reviews in the literature, underlining the need for a dialogue between clinical researchers and NICE to ensure that time, money and patient resources are utilised to maximum effect to ensure that important medical advances are introduced in a timely manner into standard clinical practice.

In particular, the exclusion of data from the UK Myeloma 1X study (the largest ever conducted in the world), because the trial included maintenance phase thalidomide should in our view be



reconsidered to allow analysis of the subgroup of patients not receiving maintenance. The need to include the Myeloma IX data is given added credence by virtue of the fact that one of the IFM studies that was included in the analysis for this evaluation included a population of patients that in all probability had a better performance status than the Myeloma IX trial population.

Health Economics Model

The model development is clearly delineated in the report and appears to be a robust and fair model. In particular, we applaud the fact that it reflects the changing effects on quality of life as the disease progressed through its different stages.

Adverse events:

Clinical trials in de novo disease have shown incremental improvements in outcomes for single, 2 drug and 3 drug combinations in all studies. However, this has been at the cost of an increased incidence of toxicity and side effects. The toxicity profiles of novel agents differ significantly from those of conventional chemotherapy. However, as experience with these agents has increased it has been our clinical experience that the incidence and severity of these complications has markedly decreased. This has been in line with the development of clinical guidelines for the management of thrombosis and peripheral neuropathy from expert consensus guidelines and increasingly from guidelines devised by individual institutions. Awareness of the early symptoms and signs of complications and a consensus on the management and treatment of these has resulted we believe in fewer problems that is likely to enhance cost effectiveness compared to early experience in clinical trials.

Clinical effectiveness:

We believe that response rates are accurately reported in the trials that have been evaluated. Although CR does not invariably impact post conventional chemotherapy, on OS and PFS, it does impact on quality of life and is therefore important in assessing QALY's. It is also of concern that at least 1 of the RCT did not analyse the data on an intention to treat basis thus skewing the survival data. Furthermore, the analysis of Myeloma IX is a complicated study that continues to undergo analysis and by controlling for confounding factors such as the use of a bisphosphonate, is now showing a clear benefit for CTD compared to the melphalan arm. Given the fact that previous MRC trials have not shown any differences in response or survival between melphalan and cyclophosphamide either alone or in combination with steroids, this we believe is more likely to be the true outcome for this study.

Whilst melphalan has been used routinely in the UK in the elderly population, it is myelosuppressive and there are no clear guidelines for its use in renal impairment. Since 20% of patient with myeloma will present with renal impairment, it is clear to us that a melphalan containing regimen would not be suitable for all patients and indeed would be contra-indicated in some patients with cytopenia or renal impairment. Similarly, patients at high risk of thrombosis, congested heart failure with peripheral oedema, rash or moderate or severe constipation might be considered contra-indicated for the use of a thalidomide containing regimen.

Cost effectiveness

The high cost effectiveness of CTDA compared with MPT is difficult to understand in clinical practice but is presumed to be due to low clinical efficacy reported in the initial analysis of the Myeloma IX data. We would advise that more time is allowed to elapse before drawing conclusions about the differences in the ICER per QALY for CTDA and MP and the impact this has on cost effectiveness in the UK. We believe that as the main difference between CTDA and MPT is the use of different alkylating agents which have been shown in previous MRC trials to

be equally efficacious, the current differences identified by this evaluation are anomalous, and will disappear as the data mature.

We doubt that the VISTA trial provides an accurate reflection of the true ICER per QALY in the UK where, in normal practice, most patients will receive 4-6 cycles of treatment and rarely beyond 8, rather than 12, as in the VISTA protocol.

Uncertainties and limitations of the assessment

We would submit that data relating to dosing, scheduling and treatment duration is highly variable between studies and that the patient populations are heterogeneous making it extremely difficult to draw comparisons between them. It is now 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 tailor treatment to individual patients taking note of differences in the disease and in patient characteristics.

We would strongly argue, therefore, that clinicians be given the freedom to select from a number of regimens to provide a risk adapted approach to treatment a allow flexibility whilst taking account of cost effectiveness.

To undertake a “head-to-head” phase 3 study of these agents would be highly desirable. However, it would require a large number of patients because of the high response rates in this setting, over a prolonged period of time and is unlikely to provide an answer for many years, particularly as it normally takes over 2 years to initiate such a study. If clinicians were to be allowed access to these protocols it is likely that a quicker answer could be obtained by facilitating a retrospective audit of clinical practice that may be able to be conducted by a specialist Society as an alternative.

Please feel free to contact me if the above poses any questions.

Yours sincerely

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