Response to NICE Single Technology Appraisal Consultation Document

Bortezomib for treatment relapsed & refractory multiple Myeloma

i) The evidence considered by the appraisal group is incomplete: Significant new abstracted evidence from International Workshop April 2005 & ASH Annual Conference December 2005, relating to

a) updated APEX trial at median 22 months follow-up confirms improved response rates (43% overall response & 16% complete response (IF-/+), as well as showing persistence of overall survival advantage for those first treated on bortezomib arm, even after cross-over [Richardson et al. Blood 2005].

b) combination usage of bortezomib in both relapsed/refractory setting (complete responses ranging from 3-36% & overall responses 50-73%) and as up-front treatment (e.g. PAD [Cavenagh et al. 2005] gives 95% overall response & 29% complete response, as well as permitting stem cell harvest; post SCT CR increases to 57%; for non-intensive patients bortezomib/mephalan/pred [Mateos et al. 2005] gives CR 42%, without SCT, & 92% OR, which is the best complete remission rate ever described without SCT, in a representative elderly patient group). These combinations exemplify the increased efficacy that can be achieved by using novel agents together with steroids & cytotoxics, often allowing lower dosage of the costly biological modifiers to remain effective.

The evidence is also inadequate in the lack of assessment of role of poor-prognosis cytogenetics in myeloma, especially as thalidomide has been shown not to be good salvage option for myeloma patients with poor karyotype [Barlogie et al. 2003], particularly deletions of chromosome 13 & translocations of 4 & 14; however these cytogenetic translocations do not preclude bortezomib response.

ii) Summary of clinical efficacy does not take into account the natural history of relapsing myeloma. This is a progressive & often painful condition, which when advancing reduces patients functional capabilities & quality of life. Hence stabilization of disease (which approx. 60% of patients achieved on Phase II/III bortezomib trials, even with only monotherapy) can be a clinically meaningful outcome.
To preclude combined bortezomib & dexamethasone from being the main regimen under assessment seems inappropriate as this is not only the most common way that bortezomib is used in U.K., it is also recommended in the British Committee on Standards in Haematology (BCSH) guideline for bortezomib [Morgan et al. 2005].

Summary of cost-effectiveness appears inaccurate, not only due to aforementioned reliance on monotherapy (the ICER estimate per LYG of HDD/bortezomib combination was £28K, but this should be lower if cessation after 3 cycles in non-responders is also carried out, possibly to below £25K). There has been no apparent account of the dose-reductions often required in bortezomib treatment courses, either for neurotoxicity, thrombocytopaenia or other toxicity. The ERG data interestingly confirms the increased cost-effectiveness of bortezomib used earlier in the disease process, suggesting best efficiency if used at 1st or 2nd relapse (as per BCSH guidelines).

Most importantly there has been no adjustment of cost to take account of vial sharing between patients. This has been performed very successfully within my own & many other institutions, due to the excessive vial size. From the ERG analysis the estimate of patient surface area is unrealistic. The median surface area of patients is 1.7m^2 (not 2.3 m^2 as ERG appendix implies), which equates to a dose of 2.2mg per administration; this makes a saving of 38% of the vial, which can be utilized by another co-treated patient. Hence the estimated cost per course should be reduced by 38% when vials are shared in the hospital pharmacy. This would therefore equate to ICER per LYG of £15.5K, if bortezomib is used with steroid & stopped after 3 cycles in non-responders.
It is also instructive to examine the data provided by ERG on varying the cost of bortezomib in the appendix. This implies that there should be strenuous efforts to both reduce the price negotiated for the drug & ideally the vial size also (if smaller practices are to avoid the need to co-schedule patients).

iii) On this basis the recommendation of the Appraisal Committee cannot be regarded as sound. Given that bortezomib has been investigated in the largest randomized controlled trial conducted in relapsed myeloma to date & this trial has been published in a preeminent peer-reviewed journal (NEJM), it is of concern that there has been no attempt by the Committee to compare this data to the alternatives that are mentioned in the documents. Thalidomide responses as a monotherapy for relapsed disease are almost universally incomplete, & range from 20-50% partial response. This option is not available for those patients who have been induced with thalidomide-containing regimens (e.g. CTD), have broken through thalidomide maintenance treatment (e.g. MRC Myeloma IX), or who have contra-indications to or intolerance of thalidomide. Repeat stem-cell transplant is only available to a small minority of patients, & retreatment with induction chemotherapy has results inferior to initial treatment [BCSH UK/Nordic Guidelines 2005].
Trials are ongoing into the use of bortezomib in induction (PAD & VISTA) as well as salvage (amendment to Myeloma IX), and enrollment into such Phase II & III trials should be facilitated, but many patients are precluded from such studies, particularly through geography &/or concomitant illness, & these individuals should not be disadvantaged in their access to licensed therapies that have proven efficacy.