

We write as the representatives of the Haematology community through the Royal college of Pathologists and the British society of Haematology. Haematologists organise the overall care of myeloma patients in the UK and organise the many facets of the care of this complicated disease.

We would like to formally express our disappointment with the preliminary recommendations for the use of Bortezomib in multiple myeloma in England and Wales as summarised in the recent appraisal consultation document. There has been a large response to this document from the Haematology community and the overwhelming (100%) response has been disappointment and concern.

The arguments we will present are very similar to those that will be presented by the UKMF and the patient representatives and this reflects the broad agreement between physicians, other health care professionals and patient groups that the findings in the appraisal document are disappointing and will deprive patients facing a very difficult malignant process of one of the most effective agents in the treatment of this disease – indeed there is no evidence that there is another treatment as effective as Velcade in the relapse setting.

In answer to the formal questions

1. We do not feel any major evidence has been taken into account but the whole context of myeloma care has not been fully considered.
2. We do not consider the clinical and cost effectiveness summaries are reasonable interpretations of the evidence – see below.
3. We do not consider the provisional recommendations of the appraisal committee to be sound – see below

We wish to put before the committee a number of arguments which we wish to be taken into consideration during this period of further consultation.

- Myeloma is currently an incurable disease, extremely variable in its biological basis and clinical expression, and that the aim of all treatments at the present time is to improve the quality and duration of life. The management approach to this disease is different to other haematological and non-haematological malignancies, where cure is the goal, and can be achieved with currently available therapy.
- There is no strong evidence base on which to approach the treatment of relapsed/ refractory myeloma. There are however clearly defined treatment pathways for myeloma and over the course of the disease patients will receive different combinations of treatment at different times. Myeloma care is well organised however and follows well established and up-dated guidelines.
- Until the publication of the Apex trial there was no robust, large, prospective randomised controlled trial to inform the decisions clinicians made at the point of relapse and it was appropriate that physicians chose the therapy which best matched the patients need. Initial treatment and patient's response to it, the inherent characteristics of the disease, patient's performance status and patient preferences all influence treatment choice. With the publication of the Apex trial physicians do now have evidence on which to base the treatment decision at relapse.

We believe that the position of Bortezomib in the pathway of care has now been established and that it should, in the group of patients we will define below, be the agent of choice for the treatment of first relapse.

- We note the Appraisal committee's recommendation that the position of Bortezomib is uncertain and that it should be established more clearly by the results of on going research, however we assert that further trials are unnecessary because the Apex trial data has unequivocally demonstrated the efficacy of Bortezomib. Indeed any further trials performed in relapsed patients would be unethical unless Velcade was chosen as the control arm i.e. the established best therapy against which other therapies could be compared.
- Such trials would not be supported by funding bodies nor would clinicians have enthusiasm for them as they see that the role of Bortezomib as monotherapy has been established. They are now interested in the question of how Bortezomib performs in combination with other drugs. Finally it is also very difficult to believe that in the current financial climate of the NHS such a trial would be funded by Trusts and PCTs.
- We wish to endorse the choice of High Dose Dexamethasone (HDD) as a suitable comparator. Often used in combination with other cytotoxic agents (e.g.VAD, CVAD, ZDEX etc) both for initial treatment, and at relapse, studies have shown that HDD alone is almost as effective as the combinations and is the most powerful component of the combinations. This knowledge has led to its widespread use as a single agent worldwide.
- That Bortezomib is more effective than High Dose Dexamethasone is highly significant. We feel it represents a major advance for patients who have commonly had both cytotoxic chemotherapy and recently also Thalidomide, as initial treatment. For these chemo- resistant patients the fact that Velcade acts by an entirely different mechanism is highly significant
- Further, on the question of the validity of HDD as the choice of comparator we believe it is important to be aware that 70% of patients with myeloma now receive a Thalidomide containing regime as initial treatment which markedly limits its use as an alternative comparator to Velcade at relapse. We believe that acknowledging the use of HDD as a valid comparator in this setting is important not only for this trial but also for future trials of new agents.
- We note that the appraisal committee concluded that Bortezomib had not been shown to be cost effective compared with current practice in England and Wales. However we believe that insufficient account has been taken of the following points which materially affect this conclusion.

We believe that physicians can and will stop therapy appropriately if patients are not responding to treatment. The majority of patients with myeloma have a tumour marker (either an entire monoclonal immunoglobulin or light chain) the measurement of which enables physicians to assess response to disease in a simple and timely fashion. Thus it would be clear after 3 courses of treatment if a patient had responded to Bortezomib, and that treatment could be stopped at that point if there had been no effect. This is already common practice amongst physicians using Bortezomib and could be enshrined in guidelines as will be discussed below. Clearly if treatment were limited in this way, overall cost per QALY would be reduced.

Similarly it is already common practice to use Velcade in combination with intermediate doses of steroids which studies have shown to increase response rates at minimal additional cost. This again reduces overall cost per QALY in practice.

Furthermore we believe it is possible to define the patient group for whom Bortezomib is most cost effective and restrict use to such patients thereby improving cost effectiveness. Such guidelines are already in operation in several regions in the UK. We believe that as a community we have mechanisms, both centrally throughout the UKMF/BCSH Guidelines committee, and locally via cancer networks to audit the application of guidelines on the cost effective use of Bortezomib, to measure outcomes and side effects. Such mechanisms are already in place in Northern Ireland and the Yorkshire Cancer Network.

- We also feel that by not using Bortezomib in the relapse setting physicians will be forced to choose potentially more expensive therapies, which have not been subject to randomised, controlled trials. The options will include, for a significant number, a second high dose therapy and stem cell transplant which may associated with considerable cost, morbidity and yet is of unproven benefit. Even for the small proportion of patients who have not already received Thalidomide either as initial treatment or maintenance, the thalidomide option is costly, unlicensed, unproven, has significant side effects and thus cannot be seen as a beneficial alternative to Bortezomib.

In summary we believe that

- The Apex trial does define the role of Bortezomib in the treatment of myeloma
- It is not necessary, nor feasible, to mount further clinical trials to establish the position of Bortezomib as a single agent in relapsed/refractory myeloma.
- That Bortezomib is an advance in the treatment of relapsed myeloma and can be used cost effectively for patients selected in the following way and defined in a national guideline

Patient characteristics

- Those at 1st relapse
- With Performance status 60
- With Peripheral neuropathy < grade 2
- With Life expectancy > 12 months with treatment
- Stopping rules should be
  - After 3 cycles if non-responder
  - Maximum of 8 treatment cycles for responders
- Bortezomib should be used
  - In combination with dexamethasone

**This summary has universal support amongst clinicians, health care professionals, patients and their carers without dissent.**