NICE Single Technology Appraisal: Bortezomib for induction in multiple myeloma before high-dose therapy and autologous stem cell transplantation

Patient/carer statement from Myeloma UK

Sources of evidence for inclusion in the statement

The patient perspective included in this submission is gathered from the day-to-day contact that Myeloma UK has with patients across the UK participating in and using our programmes and services.

These programmes and services include the Myeloma UK freephone Infoline, an 'Ask the Nurse' email service, Patient and Family Myeloma Infodays, Myeloma Support Group meetings, as well as regular user involvement questionnaires and evaluations.

Myeloma UK has conducted its own review of relevant published literature and has interpreted this very much from the perspective of patients.

We also work closely with a broad range of healthcare professionals involved in the treatment and care of myeloma patients, both nationally and internationally, informally and more formally, via a number of advisory boards and committees. We have sought input and opinions from these professionals in relation to this appraisal.

About myeloma

Myeloma is an incurable, complex and debilitating cancer of the plasma cells. Complications of myeloma include severe bone destruction, bone fractures, fatigue, frequent infection and kidney failure. The complexity and range of co-morbidities of myeloma set it aside from almost every other cancer.

Across the UK there are around 4,000 people diagnosed with myeloma each year, with around 14,000 myeloma patients at any one time. Myeloma occurs mostly in older people, with around 70% of patients over the age of 65.

Whilst survival rates for myeloma have historically been poor, the introduction of 'novel' drugs such as thalidomide, bortezomib and lenalidomide has transformed the treatment of myeloma and improved both the survival and quality of life.

Recent statistics show that the ten-year survival rates for myeloma have increased from just 5% in 1970 to over 17% in 2011.[1] The Office for National Statistics (ONS) in 2010 also showed that five-year survival rates in myeloma are increasing at one of the fastest paces among all cancer types in the UK with over one-third of myeloma patients surviving for at least five years.[2]

Due to the complex, relapsing and remitting nature of myeloma, patients require a range of treatment options and doctors need a degree of flexibility to pick the best and most appropriate treatment. This makes treating myeloma optimally for each patient in the UK extremely difficult due to the way in which treatments are researched, approved and commissioned.

Until these disconnects are fixed, we will never be able to do the best we can for patients in the UK. It should be the responsibility of all stakeholders to work together, outside of a NICE appraisal, to find solutions to these critical problems.

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[1] **Cancer Research UK (2011)** http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2010-07-12-deadly-cancer-survival-doubles

[2] **Office for National Statistics** - Five-year age-standardised relative survival (%) for adults (15-99 years) diagnosed during 2003-2007 and followed up to 2008: England, 21 common cancers, by sex, 16 April 2010

Appraisal technology treatment setting

Current practice

Patients who are young and fit enough, and in whom high-dose therapy and stem cell transplantation is indicated, typically receive a three drug combination 'known as 'induction' treatment followed by high-dose melphalan and autologous stem cell transplantation.

Current standard of care for 'induction treatment' in the UK is cyclophosphamide, thalidomide and dexamethasone (CTD). Evidence from the Myeloma IX trial showed improved survival rates for CTD when compared with the previous standard of care - cyclophosphamide, vincristine, dexamethasone and doxorubicin (CVAD) regimen[3].

Patients who do not achieve the desired response by the third or fourth cycle of CTD induction treatment (i.e. they have not achieved at least a 50% reduction in the paraprotein) would normally switch to a bortezomib-containing regime for a further two to three cycles, providing this was approved locally.

Current induction practice in the UK is clearly set out in national guidelines[4]:

Bortezomib-containing induction combinations

Consensus of expert opinion
There has only been limited use of bortezomib as an induction treatment on the NHS. However, whilst this is the case, consensus of expert opinion in the UK is overwhelmingly in favour of having bortezomib available to use in the induction setting.

Literature review
Our review of the literature provides strong evidence that bortezomib offers a safe and effective induction treatment prior to high-dose therapy and autologous stem cell transplantation. In all four of the main trials looking at bortezomib induction, the response rates, progression free survival (PFS) and overall survival (OS) rates were better in the bortezomib-containing arm.

In the **HOVON-65/GMMG-HD4 trial** 827 patients were randomised to receive induction therapy with vincristine, doxorubicin and dexamethasone (VAD) or bortezomib, doxorubicin and dexamethasone (PAD) followed by high-dose melphalan and autologous stem cell transplantation. Patients also received maintenance consisting of thalidomide 50mg (VAD) once per day, or bortezomib 1.3mg/m(2) (PAD) once every two weeks for two years.

The trial found that complete and near complete response (CR/nCR) were superior after the PAD induction and that after a follow-up of 41 months, progression free survival (PFS) and overall survival (OS) were superior in the PAD arm. The trial also found that in patients presenting with increased creatinine levels, bortezomib significantly improved PFS, which could be of significance to patients with renal impairment[5].

In the **IFM 2005-01 trial**, 482 patients were randomised to VAD and bortezomib and dexamethasone, with or without consolidation treatment, with dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP). The study concluded that bortezomib induction with dexamethasone compared with VAD significantly improved CR and nCR rates, very good partial response rates and resulted in a trend for longer PFS[6].

Finally, the PETHEMA/GEM Trial[7] and the GIMEMA trial[8] both assessed bortezomib, thalidomide and dexamethasone (VTD) compared to thalidomide and dexamethasone (TD) and found that the response rate was superior in the VTD arms.

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[3] **Morgan et al 2012.** Haematologica' March; 97(3): 442–450.
[4] BCSH and UKMF Guidelines on the Management and Diagnosis of Multiple Myeloma Sept 2010
[5] **Sonneveld et al 2012.** J Clin Oncol Oct 10; 30(29): 3654.
[6] **Harousseau et al 2012**. J Clin Oncol. Oct 20;28(30):4621-9
[7] **Laura Rosinol 2011.** ASH Oral/Poster Presentation 3962
[8] **Cavo et al 2010.** The Lancet, Volume 376, Issue 9758, Pages 2075 - 2085, 18 December

Potential advantages and disadvantages

Taking the published evidence, together with knowledge derived from consulting with our clinical experts and a wide range of patients, the following provide a strong case for the approval of bortezomib as an induction treatment.

Below you will find our opinion on the potential advantages and disadvantages of bortezomib as an induction treatment.

(a) Potential advantages

Importance of obtaining and initial complete response

Our understanding from the literature and from our clinical experts is that obtaining the best possible response to initial treatment is a major factor in determining long-term improved outcomes for patients. To that end, a treatment with data that supports an improvement over currently available treatments is in the best interests of patients, especially when its toxicities appear to be more than acceptable.

Potential to overcome the issue of renal impairment

Recent data suggests that around 1 in 4 patients present with mild to moderate renal impairment at the time of diagnosis[9]. Renal impairment can greatly impact on a patient's ability to tolerate treatment and ability to function in daily life. Patients with severe renal impairment or who require dialysis have a particularly poor prognosis.

Although maybe not entirely clear cut, results of the HOVON[10] study, along with data from other recent studies in both newly diagnosed and relapsed myeloma patients, have shown that bortezomib has the potential to reverse or improve renal dysfunction and avoid the need for dialysis[11] [12].

Bortezomib therefore potentially offers a valuable treatment for newly diagnosed patients, who are eligible for high-dose therapy and stem cell transplantation and who have presented with kidney impairment.

Subcutaneous out-patient administration

Bortezomib is usually administered in the outpatient setting and does not require a hospital stay. The administration time has been made shorter by the recent approval of a subcutaneous licence for bortezomib by the European Medicines Agency (EMA).The licence has led to bortezomib being quicker and easier to administer.

Both these factors are important from a patient perspective and have made a positive impact on overall patient experience of their treatment.

(b) Potential disadvantages

Peripheral neuropathy

This is a well reported side-effect of bortezomib treatment that needs to be closely monitored.

However, as mentioned above, bortezomib has recently been granted its licence to be provided subcutaneously, which is associated with less debilitating side-effects and in particular reduces the level of peripheral neuropathy in the patient's experience[13].

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[9] **Ludwig et al 2007,** haematologica 92(10):1411,1414
[10] **Sonneveld et al 2012.** J Clin Oncol Oct 10; 30(29): 3654.
[11] **Asher et al 2007.** Blood 109:2604-2606
[12] **Kama Malani et al 2006.** Acta Haematol 116:255-258
[13] **Moreau et al 2011.** Lancet Oncology, published online April 19

The increasing use of subcutaneous bortezomib will reduce the potential of negative side-effects associated with the treatment and improve patient experience.

Although the administration time for bortezomib has been greatly reduced, a potential disadvantage is that when it is administered either subcutaneously or intravenously it requires a visit to the hospital either once or twice a week during the treatment cycle (depending on the dose the patient receives).

We know from a recent Myeloma UK survey that some patients would prefer to have a treatment that they could receive at home (preferably in tablet form) due to ease, convenience, the fact it reduces hospital visits and allows patients to avoid invasive procedures such as infusions[14].

However, in the same survey, some patients reported that they preferred treatments which allow them regular visits to the hospital as it gives them confidence in the quality of care and means that there is medical support available when they are receiving their treatment. Some patients also reported problems with committing to oral dosing schedules.

Summary

Myeloma UK believes there is a very strong case to support the approval of bortezomib as an induction treatment for myeloma patients who will go on to receive an autologous stem cell transplant.

The data are compelling and the potential advantages to patients significantly outweigh any disadvantages.

The approval of bortezomib in this setting would represent a major and much needed step forward in the treatment pathway for myeloma in the UK.

[14] Myeloma UK Survey 2012