NICE Multiple Technology Appraisal: Bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma

Statement from Myeloma UK
Supported by Leukaemia CARE and Macmillan Cancer Support

About myeloma

Myeloma is an incurable, complex and debilitating cancer of plasma cells. Complications of myeloma include severe bone disease, bone fractures, fatigue, frequent infection and kidney failure. Its multiple, complex mechanisms of action and range of co-morbidities sets it apart from almost every other cancer. All aspects of its management are underpinned by difficult treatment decisions, along with unpredictable side-effects and treatment outcomes.

The causes of myeloma are not fully understood, but exposure to pesticides, atomic radiation and petroleum products are thought to be possible trigger factors. Causes are likely to be individual to each patient.

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

Myeloma is considered an 'orphan' disease as its UK prevalence lies within the EMEA designation criteria of less than 5 per 10,000 of the population.

Historically treatment options for myeloma were limited and survival prospects poor. However, after decades of limited research and innovation, the last few years have seen a number of significant developments.

A greater understanding of the genetics and biology of myeloma together with the development of novel treatments are providing hope. The introduction of novel drugs, alongside advances in supportive care, has improved the outlook for patients and new drugs in development promise significant further improvements.

In the past decade the overall survival of myeloma patients has increased from around 29% to almost 35% at 5 years, and from 11% to 17% at 10 years. Newer drugs such as Thalidomide, bortezomib and lenalidomide can provide substantial benefit to patients in improving their overall survival and helping them lead an increasingly independent life.

The introduction of novel drugs has particularly helped patients who are not candidates for high-dose therapy and stem-cell transplant, and for whom alternative treatment options were historically very limited.

It is no longer uncommon for patients in this group to experience a complete response to treatment. Active myeloma disease can cause various complications (for example, bone disease and kidney damage) which in turn affect quality of life. The magnitude of response is therefore

extremely important to patients both in terms of experiencing longer remission periods and an improved quality of life.

Crucial to achieving these outcomes is patient access, within reasonable bounds, to a sensible and evidence-based clinical pathway which includes novel drugs.

Sources of evidence for inclusion in submission

Much of the patient perspective is garnered from regular contact with patients through the Myeloma UK freephone Infoline, email correspondence, communication at Patient and Family Myeloma Infodays, feedback from Myeloma Support Group meetings and regular user involvement questionnaires and evaluations. Myeloma UK also works closely with many consultant haematologists, nurses and other key workers involved in the treatment and care of people affected by myeloma.

Thalidomide

Thalidomide represents a significant advance in the treatment of the older and / or less fit patient group.

Patients in this group commonly receive Thalidomide in the UK in combination with cyclophosphamide and dexamethasone (CTD), both as part of the MRC-funded trial and as standard clinical practice outside the trial. UK clinicians have vast experience of this use in clinical practice and show overwhelming support for this use to continue.

Thalidomide was recently approved in combination with melphalan and prednisolone (MPT) by both the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) in 2009 as a standard first-line treatment for this group. Although most clinicians in the UK have less experience of using this combination, the trial evidence supports the use of this combination and clinicians have told us that it offers them a welcome further option to treat patients according to their individual circumstances.

Feedback from clinicians and patients about both CTD and MPT suggest that the combinations are on the whole very similar in their effects and outcomes.

(a) Advantages

Thalidomide is undoubtedly an important drug for patients, and there is good data supporting its use as part of first-line treatment for myeloma.

Patients tell us that advantages of Thalidomide include that it is taken orally, has flexible administration and the side-effects tend to be manageable.

Thalidomide is already used throughout the UK as a standard first-line treatment for patients who are unsuitable for high-dose therapy and stem cell transplant.

After years of compassionate use, the licensing of Thalidomide in April 2008 has helped to impose better regulation, ensure safety and prevent unregulated supply. Licensing has also helped to improve patient access to Thalidomide in the UK and address any inconsistent approaches to prescribing.

Data from the pivotal licensing trial (IFM 9906[1]) of newly diagnosed patients over 65 years and those ineligible for transplant has shown increased overall survival in older patients with a melphalan-prednisolone-thalidomide (MPT) regimen compared with an melphalan-prednisolone (MP) combination. The study showed MPT out-performing the MP arm by an average 18 month survival advantage with a median overall survival of 51.6 months. This data is similar to that of data supporting use of high-dose therapy (HDT) and stem cell transplant (SCT) in younger patients.

The role of Thalidomide in newly diagnosed patients was also explored in the multicentre MRC Myeloma IX trial, in combination with cyclophosphamide and dexamethasone. This is the standard first-line Thalidomide-containing combination this group of patients receive on the NHS. The full data set is yet to be reported but preliminary findings suggest that this is an effective combination for the treatment of myeloma. Clinical practice of this combination in this setting would also support its effectiveness and appropriateness in this group of patients.

(b) Disadvantages

From our communication with patients they generally find a Thalidomide-containing regimen to be a well-tolerated, oral regimen with a manageable side-effect / toxicity profile. The most commonly reported side-effects to our Infoline is peripheral neuropathy and gastrointestinal upsets which in most cases can be managed with dose reduction.

All adverse events that we have heard of are in line with those reported in the trials.

Bortezomib

Bortezomib also represents a significant advance in the management of myeloma. However there has only been very limited use of bortezomib as a first-line treatment in the NHS to date. For the vast majority of patients, bortezomib is normally used on the NHS as a second-line treatment in accordance with NICE guidance (TAG 129 October 2007). Although it is not commonly used as a first-line treatment, the consensus among clinicians in the UK is overwhelmingly in favour of having the option to use bortezomib in this setting for appropriate patients.

(a) Advantages

As demonstrated by the results of the international phase III VISTA trial bortezomib in combination with melphalan and prednisolone (VMP) offers an effective first-line treatment option with regard to response rates and time-to-progression, compared to melphalan and prednisolone (MP) alone[2].

Patients who respond to bortezomib have told us that they also benefit from an improvement in debilitating symptoms caused by complications of myeloma such as renal impairment and myeloma bone disease.

Myeloma bone disease is a very common complication of myeloma. It is a common cause of pain and reduced mobility for myeloma patients. Bortezomib appears to counteract the osteoclast activity which destroys bone, and stimulate osteoblast activity which leads to bone formation. Some patients tell us that they feel substantially reduced pain and improved mobility as a result of bortezomib-based treatment.

Recent data indicates that around 1 in 4 patients present with mild to moderate renal impairment at the time of diagnosis[3]. 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.

Bortezomib appears to be suitable for patients in whom renal impairment is a problem. Indeed, recent studies with both newly diagnosed and relapsed myeloma patients have shown that bortezomib has the ability to reverse or improve renal dysfunction and avoid the need for dialysis[3-7]. Bortezomib therefore appears to offer a particularly valuable treatment option for newly diagnosed patients who present with renal impairment.

(b) Disadvantages

Patients and doctors who have experience of using bortezomib (almost all in the relapsed setting) in the clinic have told us that the most common side-effect of bortezomib is peripheral neuropathy. In the most severe cases, patients have to cease bortezomib treatment, but in the majority of cases it can be managed with appropriate dose reductions. Although most UK experience of bortezomib has been in the relapsed setting, myeloma specialists consider that management issues would be similar in the newly diagnosed setting.

Bortezomib is administered intravenously in hospital twice-weekly during the treatment cycle. A recent Myeloma UK survey found that some patients find intravenous treatment problematic because, for example, of travel to and from hospital and the time spent there, having to take time off work to receive treatment or because of the invasive nature of intravenous treatment[8].

However, the same survey also identified that a similar proportion of patients prefer inpatient or intravenous treatment to oral alternatives, given the choice. Explanations given to support this preference included the feeling of security in hospital or the preference for regular contact with medical professionals. Additionally, some patients reported difficulties in committing to oral dosing schedules.

In summary

We have come a long way in developing a sensible pathway for novel drugs in the relapsed myeloma setting. NICE has approved bortezomib as a second-line treatment, and lenalidomide as a third-line or subsequent treatment. The SMC is expected to have the same pathway of approved

drugs in place by early 2010. We now have the opportunity to approve novel drugs, supported by evidence and best practice, in the first-line setting.

It is important that novel drugs are available to myeloma patients early in their disease as this is where they are most effective. Studies have proven both Thalidomide and bortezomib to be important, beneficial treatments in the first-line setting for patients not destined for a transplant. Neither is entirely benign but their side-effect profiles are manageable with dose reductions.

Thalidomide is already the standard of care for newly diagnosed patients in the UK and there is little evidence of cross-resistance to lenalidomide, despite their pharmacokinetic similarities. Given that lenalidomide is approved for later in the pathway, approving Thalidomide as a standard first-line treatment is sensible and does not rule out later treatment with lenalidomide.

Bortezomib is currently approved by NICE for use in the second-line setting and is most commonly used at that stage. However, the trial data for bortezomib in the newly diagnosed setting is also very encouraging. Its increased use on the NHS will only improve our understanding of the roles it may have to play. Clinicians in the UK have told us that they would greatly value the option to use bortezomib in this setting.

The complex and individual nature of myeloma, in addition to the various complications and side-effects patients may present with at diagnosis, means that myeloma clinicians require different treatment options at hand to ensure the best outcome for individual patients. Our evidence shows that patient preference is also a very important factor in decision-making about treatment.

We therefore consider that both Thalidomide and bortezomib are important options for the first-line treatment of myeloma. This MTA offers the chance to truly develop a responsive, practical and evidence-based approach to myeloma treatment.

References

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