Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Physicians & National Cancer Research Institute

Are you (tick all that apply):

- ✔a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation

What is the expected place of the technology in current practice?

Current treatment of multiple myeloma in the NHS

Introduction: Multiple myeloma (MM) is a plasma cell cancer that has its peak incidence in the 8th decade of life, with a higher incidence in men. The disease is preceded by a prodromal condition termed monoclonal gammopathy of uncertain significance (MGUS), that progresses (usually over years) through asymptomatic MM before symptomatic disease develops. Symptomatic MM is characterised by disease progression causing organ dysfunction, in the form of bone marrow failure, bone destruction, hypercalcaemia and renal failure, impaired immunity or symptoms related to the presence of the paraprotein. The paraprotein, or M-protein, is produced by the MM plasma cells, and, in most patients, can be used to monitor disease response to therapy, as well as subsequent relapse. Because MM is incurable, treatment is only initiated once symptomatic disease develops. Most patients are diagnosed at the stage when they develop symptoms, and the most common presentations include anaemia, recurrent infections, bone pain (especially back pain) and fractures, and renal failure.

Treatment of newly diagnosed patients: The broad aims of treatment are to achieve disease control, usually by reducing the bulk of the tumour, aiming to ameliorate symptoms (e.g. bone pain) through managing and preventing further end-organ damage, and prolonging survival whilst maintaining quality of life. A more aggressive strategy is adopted in patients who are younger and fitter at the time of diagnosis, in the expectation that prompt and maximal tumour reduction will also maximise length of first remission (termed plateau phase). This 'frontline' strategy consists of induction chemotherapy, followed by autologous stem cell transplantation (ASCT), an evidence-based strategy considered as "gold standard" (1-3). This is the approach that is recommended for patients who are considered young and fit enough (eligible) for ASCT; the age limit is generally around 65-70 years, but biological (the consideration of co-morbidity risk), rather than chronological age is considered to be key. Exploratory strategies of consolidation and/or maintenance therapy post-ASCT are only employed as part of clinical trials; these are not standard of care, nor are they licensed. This is the patient group that is relevant to the technology under consideration. In the last few years, the availability of newer, more effective anti-MM agents ("novel" or biological agents) has meant that the traditional infusional VAD (vincristine, Adriamycin and dexamethasone)–type induction regimens have been replaced, almost everywhere in the world, by induction regimens containing thalidomide, bortezomib or lenalidomide. These agents are all licensed in the relapsed setting, and thalidomide and bortezomib are licensed for the frontline therapy of patients who are *not* eligible for ASCT.

Natural history of MM: The recent inclusion of novel agents into induction regimens means that the majority of patients (80-90%) will respond (deemed to be a partial response or greater) to frontline therapy, and enter a period of disease remission, or stability (plateau phase). The natural history of the disease is repeated relapses, followed by increasingly shorter 'plateau phases', until the disease enters a refractory and aggressive end-stage, when patients die of overwhelming disease burden, or organ failure (Figure 1)(4) At each relapse, some patients will be unable to receive effective salvage, so that a decreasing proportion of patients are treated at each subsequent relapse.

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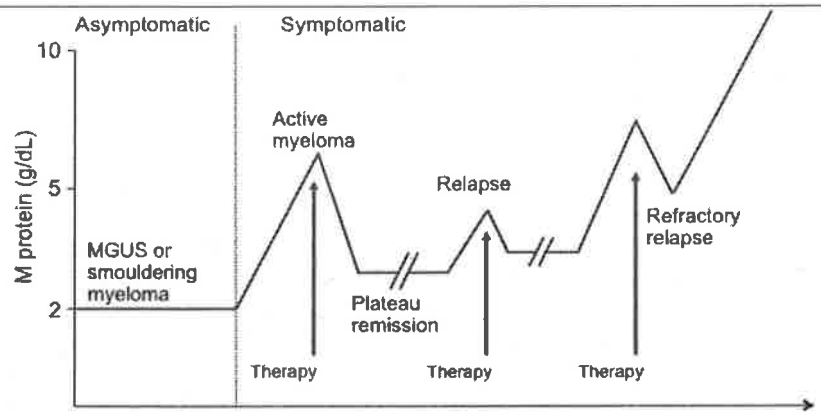

Figure 1. Disease course in multiple myeloma. Patients typically have a tri-phasic nature to their disease (MGUS, asymptomatic and symptomatic MM). Treatment is initiated when there is evidence of organ damage, usually also heralded by a rise in the paraprotein. Initial response to chemotherapy results in a period of 'remission' or plateau' followed by further relapses and subsequent disease responses that are usually less deep, and of shorter duration, until refractory end-stage disease.

Expected place of the technology in UK practice

Current UK practice in patients eligible for ASCT, including use of the technology and geographical variation in the NHS: Cyclophosphamide, thalidomide and dexamethasone (CTD) is the most widely used induction regimen in the UK, following the demonstration by the Myeloma IX study that this oral regimen can be delivered safely and effectively without the need for intra-venous therapy (5). Up to 6 cycles are administered, followed, in responding patients, by stem cell harvesting. Provided a sufficient number of stem cells are obtained, patients proceed to high dose melphalan and ASCT. There are no consolidation or maintenance strategies that are currently used in the UK, as part of standard care although these are currently being investigated in the Myeloma XI trial. Induction regimens using thalidomide produce higher response rates, but this has not resulted in longer remission periods (ie prolonged progression free survival, or PFS) (5, 6). Thus bortezomib-containing induction regimens (the technology) are used increasingly in situations where thalidomide is contra-indicated, or not tolerated by the patient. At present, under the Cancer Drugs Fund (CDF), Bortezomib as induction therapy preceding ASCT is routinely funded in 3 of the 9 CDFs including the London area (Added to the list in March 2012: http://www.nlcn.nhs.uk/interim-cancer-drugs-fund), considered but not routinely funded in 1of 9 and is not considered by 4 of 9 (in the baseline commissioning of 1 CDF: Midland & East CDF).

High risk subgroups: Considerable clinical heterogeneity in this cancer is underpinned by distinct genetic lesions, some of which impart a significantly shorter survival. Such patients are considered to have 'high risk' disease, however, other factors such as disease burden, renal failure and aggressive morphological features may also impart a worse prognosis. Thus, a proportion of patients (15-40%) are considered to have 'high risk' disease, depending upon which genetic factors are used in the definition (7, 8). Varying definitions of high risk disease are used, but in general, the following are considered by most to be high risk features: the t(4;14) and t(14;16) translocations, loss of 17p (p53 gene) and high ISS score(9-11). There are emerging data to suggest that the technology may be able, in part, to overcome the poor

prognosis of such high risk groups of patients, however, the outcome data are not sufficiently mature, and very few centres outside the major teaching hospitals have the resources to undertake routine testing for such genetic lesions. Thus, it is not clinically possible to identify a subgroup of patients who would definitely benefit from the technology, to the exclusion of the remainder.

The evidence base for the technology as induction therapy prior to ASCT

The main goal of induction therapy in patients who are fit enough to receive ASCT is to achieve maximal disease control as rapidly as possible, so as to minimise any further organ damage, whilst aiming for maximal tumour reduction and preservation of (normal haematopoietic) stem cell function. The depth of response of MM to therapy is correlated with durability of response (15, 16). The technology has been demonstrated, in 4 high quality randomised RCT, to produce superior results (higher rates of disease response, improved progression free survival) when compared with standard therapies (traditional VAD regimens, and thalidomide-containing regimens (17-20)).

Table 1. Summary of major RCTs evaluating the technology with main parameters of benefit

Study	Arm (number of patients)	Response to induction (pre-ASCT) %		Response post-ASCT %		PFS (months)	HR of PFS (95%CI)	% proceeding to ASCT
		CR	ORR	CR	ORR			
HOVON-65/GMMG-HD4	**PAD (417)**	**11**	**84.2**	**22.5**	**77.5**	**35.0**	**0.74 0.62, 0.89 p=0.001**	85
	VAD (416)	2.9**	61.3	12.3**	65.9**	28.1		84
IFM 2005-01	**Vel/Dex (240)**	**5.4**	**77.1**	**18.3**	**79.6**	**36.1**	0.88 0.7-1.11	86
	VAD (242)	1.2*	60.7	10.3*	74.4	29.7		81
PETHEMA /GEM trial	**VTD (130)**	**35.4**	**86**	**46.9**	**77.7**	**55.5**	**0.65 0.45-0.92 p=0.015**	81
	TD (127)	14.2**	62	23.6**	56.7	27.9		61
GIMEMA	**VTD (236)**	**18.6**	**93.2**	**33.7**	**93.2**	**NR**	**0.63 0.45-0.88 p=0.0061**	88
	TD (238)	4.6**	78.6	22.7*	84.5	42		82

* p<0.01** p<0.001

In each of these studies, complete response and overall response rates were higher in the bortezomib-containing arms, both post-induction, and following ASCT. This is important because increased depth of response (CR rate) is correlated with superior PFS and OS, in many reports of the outcome of upfront ASCT(16). On the other hand, some patients who never achieve a complete response enjoy a prolonged plateau phase (21). Hence clinically, the most important outcome of frontline treatment is progression free survival (PFS), because it is in the first plateau phase that QOL is highest (22). PFS was superior in 3 of the 4 studies (highlighted in bold), and in the HOVON study, a survival benefit was also seen in the

bortezomib arm. Overall survival benefit in the other studies may emerge with longer follow up, as the increasing number of new and effective salvage therapies result in longer survival for most patients with MM. Another important outcome is the percentage of patients proceeding to ASCT, as a major goal of induction therapy is to achieve sufficient disease control in order that the patient can benefit from high dose chemotherapy and ASCT. In all these studies, a higher proportion of patients were able to proceed to ASCT in the bortezomib arms.

Relevance of these RCTs to UK MM patients and clinical practice: Whilst these RCTs were on-going, the Myeloma IX study compared the intravenous induction regimen, C-VAD, with the oral regimen, CTD. Although response rates were deeper and higher in the CTD arm, there was no difference in PFS. The patient populations studied in these RCTs were broadly similar to UK patients entered into the national Myeloma IX study, except that the Myeloma IX study included a small percentage of patients older than 65 years, and a greater proportion of patients with ISS stage 3. These factors may account for a generally lower proportion of patients proceeding to ASCT in the Myeloma IX study (67%). On the other hand, a similar proportion of patients in the control (TD) arm of the PETHEMA study proceeded to ASCT (62%), with very similar PFS outcome (28.2months) compared to patients treated on the CTD arm of Myeloma IX (27 months). These figures suggest that the population of patients studied in at least the Spanish PETHEMA study, is similar to the UK population.

All 3 regimens (bortezomib/dexamethasone, PAD and VTD) are familiar to UK specialists treating patients with MM. As stated above, bortezomib is commonly used in conjunction with dexamethasone in the relapsed setting, and the addition of a third agent such as doxorubicin, cyclophosphamide or thalidomide, in order to improve disease response and response durability, is increasing. The PAD regimen has been used in the Myeloma X (n=297) study, as salvage prior to a second ASCT in suitable patients, where over 90% of patients demonstrated at least a PR (results to be presented at the EBMT Annual Scientific Conference, April 20134, London, UK).

The advantages and disadvantages of the technology

A clear clinical advantage of the technology is the ability to produce rapid disease control, with a higher proportion of patients proceeding to ASCT and hence achieving longer PFS. The benefit of improved PFS when compared with traditional and thalidomide-containing regimens has already been noted. An important benefit is the increased rate of renal recovery in patients presenting with renal failure who receive bortezomib regimens, when compared with those receiving either thalidomide or lenalidomide(23). Recovery of renal function has important implications for health resources as well as patient quality of life. Bortezomib-related toxicity has been significantly reduced with the use of careful dose adjustment schedules, and the change-over to subcutaneous mode of administration (14). Indeed with increasing experience with the technology, adverse reactions in current clinical practice are generally lower than reported in the phase 3 clinical trials, that were conducted using the intravenous route of administration (24). Disadvantages include the inconvenience of hospital attendance for the administrations, however, these attendances are brief and far shorter than with intravenous regimens. The toxicity profile of bortezomib (neuropathy, fatigue and constipation) is broadly similar to that of thalidomide, with the exception of the risk of thrombo-embolic disease with thalidomide. When used together, e.g. in the VTD regimen,

the risk and incidence of neuropathy is not increased, and the need for thrombo-prophylaxis is similar.

Any additional sources of evidence

Available guidelines: The UKMF guidelines state that "induction regimens should contain at least one novel agent… CTD, TAD, bortezomib/dexamethasone and PAD produce superior response rates to VAD. Decisions regarding the most appropriate induction regimen for individual patients will require the assessment of… renal function, thrombotic risk, pre-existing neuropathy …."(12). The IMWG Consensus statement concludes that "… recommend using one of the bortezomib-containing triplet regimens as upfront induction therapy in a transplantation-eligible MM patient." (13)

Current use of the technology in the relapse setting, variations in use, and appropriate healthcare setting: Bortezomib is approved for the treatment of patients with first relapse of their myeloma, under the VRS (velcade response scheme, Guidance TA129). Bortezomib for 2nd and subsequent relapse is routinely commissioned by 2 of 9 CDFs, considered but not routinely funded by 2 of 9 CDFs and is not considered by 5 of 9 CDFs if they are Bortezomib naïve or have previously responded well to first exposure. When used in the relapse setting, bortezomib is seldom used within its licensed indication, ie as a monotherapy. Instead, it is almost always used with dexamethasone, and often with a third agent e.g. cyclophosphamide (VCD regimen), or doxorubicin (PAD regimen. Bortezomib is usually administered as an outpatient therapy, in haematology or oncology departments with expertise in managing and preventing the most common side effects: peripheral neuropathy, low blood counts, constipation and fatigue. UK experience in managing these toxicities has grown enormously over the last 5 years, reflected in the comprehensive guidance contained in the recently published UKMF Guidelines for the management of myeloma (12). Recently, the license has been amended to allow a change from intravenous to subcutaneous route of administration, a safer mode of delivery with equivalent efficacy (14). This means that the technology is now employed safely and to maximal efficacy in the UK.

Effect of NICE guidance on the delivery of care for patients with MM

NICE guidance on the technology will permit clinical decision-making to direct treatment on an individual patient need basis rather than cohort health economic modelling. For example, when patients present with a large tumour load, on-going end-organ damage or evidence of aggressive disease tempo, the clinical need to gain rapid tumour control could be most effectively achieved with a Bortezomib-containing regimen. Additionally, the thalidomide-associated risk of venous thrombo-embolism is primarily associated with first line therapy(25), hence the need for effective thrombo-prophylaxis; however where patients are at high risk of bleeding on anti-coagulation, the use of a bortezomib-containing regimen would be clinically recommended. Thus NICE guidance would permit a different order of delivery of lines of therapy to the current status quo (Thalidomide-based, followed by Bortezomib-based followed by Lenalidomide-based), enabling clinicians to exercise clinical judgement in a patient-centred approach to therapy.

Implementation issues

Because the technology has been in use for many years in the relapsed setting, it is unlikely that any additional education or training resources will be required. It may increase the number of patients being treated on day-care units, however, home delivery schemes are

under evaluation, and, because of the greater convenience and impact on quality of life may prove to be popular. Implementation of the technology will reduce the number of patients requiring thrombo-prophylaxis, and the attendant burden of anticoagulation monitoring and bleeding complications. It will also reduce the hidden costs of health care caused by adverse events on Thalidomide eg thromboembolism, cardiac arrhythmias.

Equality

There is no particular implication for people protected by the equality legislation. We wish to point out that a negative recommendation would have an adverse impact on patents who are unable to receive thalidomide as part of their induction therapy, because they are contra-indicated to receive, or are intolerant of thalidomide. The lack of an effective induction therapy for such patients would significantly reduce their chances of receiving an ASCT. Another such group of patients are those already alluded to earlier, who present with a particularly aggressive disease and marked organ damage (e.g. Renal failure) who need rapid disease control.

Summary and conclusions

The main goal of therapy in patients with newly diagnosed MM who are fit and young enough is to achieve maximal disease control as rapidly and safely as possible, thus enabling the patient to proceed to and benefit from ASCT. The technology being appraised represents a major advance in providing an effective therapy that achieves this in >80% of such patients, and has proved to be superior in this respect, as well as in prolonging PFS (and OS), when compared to current standard therapies, including, we believe, the CTD regimen. We believe that a positive recommendation will significantly improve the outlook for this patient group with MM.

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