

NICE HEALTH TECHNOLOGY APPRAISAL

Bortezomib and Thalidomide For The First Line Treatment of Multiple Myeloma.

Submission by United Kingdom Myeloma Forum

The UK Myeloma Forum and the Royal Colleges welcome the appraisal of Bortezomib in combination with an alkylating agent and a corticosteroid, and Thalidomide in combination with an alkylating agent and a corticosteroid as initial treatment of people with previously untreated multiple myeloma for whom high dose chemotherapy with stem cell transplantation is not suitable.

Introduction: perspective on myeloma

Multiple myeloma, often just called myeloma, is a cancer of plasma cells that accumulate in the bone marrow and produce a monoclonal protein (called paraprotein, or M-protein)ⁱ. This condition affects older people with a median age at diagnosis of 65-70 years, and about 2 thirds of all new cases of myeloma will be older than 65 years. There are approximately 3500 new cases of myeloma in the UK per year, with a higher incidence in men. Myeloma causes bone marrow failure, bone destruction, kidney failure and increased infections. Common presentations are bone pain and/or fractures, anaemia, kidney failure or infections. The diagnosis of myeloma brings with it not only a reduced life expectancy but for many patients the burden of bone pain and fractures, with attendant loss of mobility and independence, and for others renal impairment which can result in the constraints imposed by dialysis. Many will also suffer frequent and serious infections, a reduction in socio-economic functioning and almost all will have a reduced quality of life.

The impact on life-style and quality can be profound because many patients are diagnosed at a time when they might have reasonably expected to start enjoying the fruits of their life long labours, for some when they are still economically active and contributing vitally to the lives of their children and grandchildren. The first treatments for myeloma were developed in the 1950's and 60's with the introduction of Melphalan and Prednisolone. This treatment led to modest improvements in survival so that instead of dying usually within a few months, patients could expect to live on average 2-2½ years. Quality of life, however, was characteristically poor and survival characterised by frequent relapses with progressive shortening of remissions frequently

associated with crippling, progressive bone disease and other complications. No real improvements were seen until the advent of high dose steroid containing regimens in the late 80's and 90's and with the introduction of bisphosphonates, which improved control of bone disease. Median survival was further improved for younger patients by the introduction of high dose melphalan and autologous stem cell transplant (ASCT), but this modality is not available for all patients, especially those who are older and who have comorbidities, the patient group relevant to this appraisal. For these patients, median survival from diagnosis has remained 2-3 years. In the past, treatment for patients who are not eligible for transplantation has been restricted to the combination of melphalan or cyclophosphamide plus prednisone (MP or CP), which leads to responses in approximately 50% of patients, however, patients rarely achieve a CR and long-term outcomes are disappointing, with a median relapse-free survival of about 18 months and a median OS of about 3 years. Importantly, the improvement in survival demonstrated for younger (<65 years) patients with myeloma is not seen in this older cohort of patientsⁱⁱ.

Thalidomide and bortezomib

Thalidomide has a number of characteristics that make it a useful treatment for myeloma. Not only does it kill malignant plasma cells directly but it also modifies the cytokine composition of the bone marrow microenvironment impairing the growth of myeloma plasma cells, suggesting that in addition to killing myeloma cells that it could also modulate the behaviour of residual tumour cells if given continuously. It also has beneficial effects acting via the immune system to modify the NK response to the myeloma clone. Following demonstrations of efficacy in the relapsed setting in the 1990s, studies investigating the use of thalidomide as front-line therapy in elderly patients have clearly shown that the use of thalidomide in combination with an alkylating agent improves response rates compared to patients treated with standard treatments. A total of 5 randomised studies (Table below) have investigated melphalan, prednisolone and thalidomide (MPT) as a therapy for untreated patients not suitable for ASCT, of these, 3 have been published as full papers^{iii, iv, v} (while early results of the other 2 are available in abstract form). All three have shown improved response rates (62-76% compared with 31-48% in the standard arm), with increased time to progression (from 14-18 months to over 2 years). Two studies (French IFM 99-06 and IFM 01-01) also demonstrated improved survival for patients receiving thalidomide, while the third (Italian GIMEMA) did not. Differences in study design, total melphalan dose, and the use of thalidomide as maintenance in the Italian study are likely to be responsible for these differences. Nevertheless, the superior outcome for patients receiving

thalidomide in combination with melphalan and prednisolone is undisputed. This is important because prolongation of first plateau phase (remission period) for this elderly group would have a major impact on quality of life. Other combinations of thalidomide, eg with cyclophosphamide and dexamethasone in the large UK Myeloma IX study have also shown high response rates compared with the standard melphalan and prednisolone arm.

Table. Summary of 5 trials of MPT vs MP in untreated patients with myeloma

Regimen	n	Median follow up	CR + PR (%)	CR (%)	PFS/EFS/TTP	OS	Reference
Thal/MP vs MP	129 126	38.1 months	76 48	16 4	21.8 14.5	45 m 47.6 m	Palumbo 2008
Thal/MP vs MP	191 124	51.5 months	76 35	13 2	27.5 m 17.8 m	51.6 m 33.2 m	Facon 2007
Thal/MP vs MP	113 116	47.5 months	62 31	7 1	24.1 m 18.5 m	44 m 29.1 m	Hulin 2009
Thal/MP* vs MP	363	36 months	42 28	6 [†] 3 [†]	20 m 18 m	29 m 33 m	Gulbrandsen 2008
Thal/MP vs MP	152 149	n/a	66 47	2 2	EFS 13 m vs 9 m PFS 13 m vs 10 m	37 m 30 m	Wijermans 2009

*Thal doses: 200-400 mg

[†]CR + nCR

Bortezomib is a first-in-class proteasome inhibitor with a novel mechanism of action that results in the death of cancer cells. Additionally it acts on the other cells in the bone marrow, to reduce the production of growth and protective factors for myeloma, thus preventing the re-growth of the cancer. Another action of bortezomib that may benefit myeloma patients is the ability of this agent to stimulate bone formation and repair^{vi}. Again, like thalidomide, bortezomib was initially used to treat relapsed disease, but several studies world wide have now produced good evidence of the efficacy of this agent as first line treatment. The VISTA study, published last year in the New England Journal of Medicine, compared the addition of bortezomib to melphalan and prednisolone (VMP) to the traditional melphalan and prednisolone (MP) combination, in untreated patients with myeloma who were >65 years^{vii}. The investigators demonstrate superior overall response rates (71% vs 35%) and complete response rate (30% vs 4%), longer time to progression (24 months vs 16.6 months) and longer duration of response (19.9 months vs 13.1 months) for patients in the VMP arm. Notably, overall survival at 3 years is 72% in the bortezomib arm, and 59% in the control MP arm, despite the fact that 43% of patients in the MP arm received bortezomib at relapse.

Thus, both thalidomide and bortezomib induce higher response rates, increase remission duration and prolong survival in this group of patients. High rates of complete response (15-

30%) are now achievable, compared with rates of less than 5% using the traditional melphalan and prednisolone regimen. Such response rates are significant, and similar to those that have been achieved in younger patients following high dose therapy and ASCT. This represents a milestone in therapy for elderly patients. Prolonged first remission and delayed relapse means that patients get the benefit of being at their best for longer. Complete responses equate not just to longer remissions but to better control of bone disease, preservation of renal function, improved functionality and quality of life.

Toxicities of thalidomide and bortezomib

Common side effects of thalidomide include somnolence, constipation, sensory neuropathy, thrombo-embolism, peripheral oedema, sinus bradycardia and rashes. Extensive experience with this drug, initially in the relapsed setting, has informed judicious dosage adjustments as well as careful monitoring. Published guidance on the prophylaxis and management of thalidomide toxicity is now available^{viii}, and physicians treating myeloma patients are aware and informed of these issues. Bortezomib also has an increasingly well characterised toxicity profile, consisting most commonly of fatigue, mild constipation and neuropathy that can be sensory or autonomic, or both. Although the incidence of neuropathy is lower than with thalidomide, painful neuropathy can be an issue because it is not predictable clinically. Significant toxicities in the VMP arm of the VISTA study compared with the MP arm were gastrointestinal and neurological. With increasing clinical experience and patient education, however, in the majority of cases these are easily managed and reversible. There is clear guidance for dose reduction and schedule modification to minimise and manage these side effects in the SPC, as well as in the newly revised UKMF guidelines soon to be published.

Balanced against these toxicities is the important consideration that neither thalidomide nor bortezomib is myelosuppressive, unlike the more traditional anti-myeloma drugs such as alkylating agents. This makes them attractive agents for the treatment of myeloma patients, especially in the older age group with their attendant co-morbidities. In addition, patients with poor-risk cytogenetics have hitherto fared badly on traditional regimens such as melphalan and prednisolone, and both thalidomide and bortezomib are effective in these subgroups of patients.

UK experience

Physicians in the UK have contributed significantly to the field by exploring another thalidomide-based combination, in an attempt to improve outcomes in the elderly patient group.

The triple regimen, cyclophosphamide, thalidomide and dexamethasone combination (CTD) was investigated in large National NCRN trial (Myeloma IX) for newly diagnosed patients. Patients who were not considered candidates for ASCT received an attenuated CTD regimen (CTDa = cyclophosphamide at 500 mg, thalidomide at 100 mg daily, dexamethasone at 20 mg), which was compared with MP. Eight hundred patients were randomised and patients treated until maximum response (6-9 cycles); randomisation to thalidomide maintenance was then permissible. CTDa resulted in significantly higher overall and complete responses than MP (ORR: 82.5% vs 48.7% [$P<0.001$], CR: 22.5% vs 6.2% [$P<0.001$]). Overall, CTDa was well tolerated; however, as with MPT, the main side effects of thalidomide therapy were DVT and peripheral neuropathy. The final analysis of Myeloma IX is underway and it is anticipated that the Myeloma IX Trial Management Group will make the results available to NICE. However most UK physicians feel that CTDa is better tolerated than MPT with fewer side effects and less myelosuppression. This regimen is increasingly used in the non-trial setting in the UK, and is associated with less myelosuppression than a melphalan-based regimen. The more widespread use of thalidomide combinations in the UK has improved our understanding of how to prevent and mitigate these side effects and have resulted in decreased side effects over the time it has been used. The most significant of the thalidomide associated side effects are peripheral neuropathy, VTE and pulmonary emboli and constipation. In collaboration with the UKMF and Myeloma IX team, physicians have developed strategies to identify patients at risk and minimise the impact of these side effects. These strategies have been incorporated into the recently updated British Committee for Standards in Haematology (BCSH)/UKMF guidelines.

Use of bortezomib has not been as widespread in the UK, but is increasing following positive recommendation by NICE 2 years ago in the relapsed setting. As a result, UK experience with bortezomib is now substantial and, as in the case for thalidomide, has resulted in the widespread introduction of practices and policies which ensure the benefits are harnessed whilst the risk of side effects are reduced. Cancer centres and local units have produced nursing proformas to guide early detection of toxicity and for patient and healthcare education. UK physicians are now well placed to use this drug effectively for front line therapy in elderly myeloma patients.

Thus UK physicians have not only noted the results of the published studies showing the benefits of Bortezomib and Thalidomide for first line treatment of Multiple Myeloma but have first hand clinical experience of patients benefiting from these treatments, and learnt to prevent

and manage the attendant side effects. Thalidomide and bortezomib not only have different mechanisms of action, but also differ in their relative benefits and drawbacks, which is important considering the disease and patient heterogeneity as explained below.

Practical considerations and special groups

Myeloma is a genetically and clinically heterogeneous disease, resulting in varied presentation, clinical course, response to therapy and organ damage. Some patients may have extensive bone disease with multiple fractures, while others have none. Some patients may have indolent disease with minimal organ damage while others have aggressive disease that requires rapid tumour reduction in order to prevent end organ damage, eg, end-stage renal failure. Both thalidomide and bortezomib regimens produce faster disease responses than melphalan and prednisolone. For example, in the VISTA study, time to first response in the VMP arm was 1.4 months, compared with 4.2 months in the MP arm. This can be crucial in particular situations such as advanced renal impairment where rapid reduction of light chains is critical to rescuing the kidney and avoiding dialysis. Avoiding dialysis improves both survival and quality of life and also has very considerable health economic consequences by avoiding annual dialysis costs of around £30,000 per patient. We have already highlighted the benefit of either thalidomide or bortezomib in hitherto poor risk genetic subgroups. In addition, the co-morbidities present in this elderly patient group also mean that particular situations may dictate whether thalidomide or bortezomib is the appropriate choice of therapy. In older and less mobile patients, an oral thalidomide regimen may be preferable. On the other hand, in a patient with a history of spontaneous and significant thromboembolic disease, it may be prudent to administer a bortezomib regimen. Patient preferences and personal predispositions may also be important, thus patients with needle phobia, or those unable to attend hospital for regular intravenous therapy may be preferentially treated with the oral thalidomide regimen.

It is vitally important that both agents are made available for UK physicians to use in treating this vulnerable patient group, with choice of regimen dictated by disease-specific as well as patient-specific factors. We believe very strongly that physicians should be able to select from the range of effective therapies the treatment which they judge, taking all the variables of co-morbidities, performance status and patient preference into account, will give an individual patient the best outcome.

Concluding remarks

The management of elderly patients with myeloma remains a challenge, and the marked heterogeneity of disease and patient means that one treatment modality cannot be optimal for every patient. Thalidomide and bortezomib represent major advances in the treatment of older patients with myeloma because prior to their availability, only one modality *was* available, namely melphalan and prednisolone, a relatively ineffective regimen. Thalidomide and bortezomib have distinct biological characteristics, and clinical profiles, however the use of either is associated with benefits in terms of PFS and OS, in comparison with melphalan and prednisolone . Because of patient and disease heterogeneity, one or other may be appropriate for front line therapy in any particular patient. We believe that clinical freedom to decide who is suitable for treatment has to be allowed because of the potential for negative impacts in poor performance status patients.

For the first time in 50 years, patients diagnosed with myeloma who are not candidates for ASCT have the opportunity to receive effective therapy that has been proven to extend survival. For these and other reasons outlined above, UK physicians are in no doubt whatsoever that both bortezomib and thalidomide, in combination with alkylators and steroids should be made available to patients.

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