Bortezomib as first line induction prior to melphalan and autologous stem cell transplantation (ASCT) in untreated symptomatic multiple myeloma patients suitable for high dose therapy

Date March 2012

Bortezomib is currently licensed as monotherapy for the treatment of patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Additionally, it is licensed in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

This review addresses the evidence to support the use of bortezomib regimens first line for induction, prior to melphalan and autologous stem cell transplantation (ASCT) in untreated symptomatic multiple myeloma patients suitable for bone marrow transplantation (BMT). Bortezomib is currently not licensed for this indication in the UK, although a variation in marketing authorisation has been submitted to the EMA, the response to which is expected in the first quarter of 2013.

According to NICE, in England and Wales, there are approximately 4300 new diagnoses of multiple myeloma recorded annually with most diagnoses recorded in people aged 75–79 years.

Multiple myeloma remains an incurable disease, with an average survival of 4–6 years, but it can be treated with a combination of supportive measures and chemotherapy. The aim of treatment is to extend the length and quality of life by alleviating symptoms, controlling disease and minimising adverse effects.

The British Committee for Standards in Haematology, in their guidance on the diagnosis and management of multiple myeloma, state that induction regimens should contain at least one novel agent - Examples of induction regimens that are superior to VAD in terms of response rates include cyclophosphamide, thalidomide and dexamethasone (CTD), thalidomide, doxorubicin and dexamethasone (TAD), bortezomib/dexamethasone and bortezomib, doxorubicin and dexamethasone (PAD).

There have been 4 phase III studies (2 fully published and 2 abstracts) that have evaluated bortezomib for induction therapy in transplant eligible untreated multiple myeloma patients (aged under 65 years):

**Harousseau J-L et al.** compared the combination of bortezomib and dexamethasone with vincristine, doxorubicin and dexamethasone (VAD) as induction before stem-cell transplantation in 482 previously untreated patients (age ≤ 65 years) with multiple myeloma.

- Overall, including responses post second transplantation, CR/nCR (39.5% vs. 22.5%; p<0.001) and at least VGPR (67.7% vs. 46.7%; p<0.001) rates, respectively, were statistically significantly higher in the bortezomib/dexamethasone group compared with VAD.
- Post-induction therapy, ORR and at least very good partial response rates were statistically significantly higher for patients in the bortezomib arm compared to the VAD arm (78.5% vs. 62.8% respectively, p<0.001, and 37.7% vs. 15.1%, p<0.001).
- The median progression-free survival (secondary outcome) was 29.7 months among patients receiving vs. 36.0 months for patients receiving bortezomib in combination with dexamethasone.
Cavo M et al. conducted a phase III study evaluating the safety and efficacy of bortezomib in combination with thalidomide and high dose dexamethasone (VTD) compared with thalidomide in combination with dexamethasone (TD) in newly diagnosed multiple myeloma patients eligible for double autologous stem cell transplantation (ASCT). The primary endpoint was the rate of complete plus near complete response to induction therapy.

- Complete response or near complete response was achieved in 73 patients (31%, 95% CI 25.0 to 36.8) in the VTD arm and 27 patients (11%, 7.3 to 15.4) in the TD arm, p<0.0001. Similarly, at least VGPR, and PR was achieved in more patients in the bortezomib arm compared to those in the thalidomide arm.

- The estimated 3-year probability of progression or relapse was 29% in the VTD group was 39% in the TD group (p=0.0061), with a HR of 0.61 (95% CI 0.48 to 0.87. p=0.0073). Progression-free survival was statistically significantly longer for patients receiving VTD than in those receiving TD (HR 0.63, 95% CI 0.45 to 0.88; p=0.0061).

Sonneveld P et al. reported results of a trial which evaluated vincristine with doxorubicin and dexamethasone (arm A) compared with bortezomib with doxorubicin and dexamethasone (arm B) at a meeting of the American Society of Hematology. They reported that nCR/CR rates were 7/9% (arm A) vs. 9/21% (arm B) at 3 months after high dose melphalan, and 12/26% (arm A) vs. 12/38% (arm B) on protocol, i.e. for patients who had undergone the first transplantation.

Rosinol L et al. presented the results of the PETHEMA/GEM phase III study comparing thalidomide/dexamethasone (TD) vs. bortezomib in combination with TD vs. combination chemotherapy plus bortezomib in symptomatic, newly diagnosed multiple myeloma patients younger than 65 years, eligible for autologous stem cell transplantation with high dose melphalan. They reported that immunofixation electrophoresis (IFE) negative (a measure of response in MM) CR rate was statistically significantly higher with VTD (35%) compared to TD (14%) and VBMCP/VBAD/B (22%) (p=0.0001 and p=0.01, respectively). Additionally, the progressive disease (PD) rate during induction was statistically significantly lower with VTD than with TD (7% vs. 23%, p=0.001). On an intention-to-treat basis, the post-ASCT CR rate was statistically significantly higher in the VTD arm compared with TD (46% vs. 24%, p=0.004) and VBMCP/VBAD/B (46% vs. 38%, p=0.1). However, the estimated overall survival (OS) at 4 years was 76% with no significant differences among the 3 arms.

The BCSH has also made recommendations on the management of adverse events associated with bortezomib.

According to Cancer Research UK, in 2009, there were approximately 4300 new diagnoses of multiple myeloma, with more than seven out of ten (72%) cases occurring in people aged 65 years or over, implying 28% of new cases are identified in patients under 65 years. Considering 4300 new diagnoses of multiple myeloma recorded annually in England and Wales, this equates to 8 new cases per 100,000 population, of which 2 cases will be patients under 65 years of age. Assuming 50% of patients under 65 years may be eligible for induction therapy and autologous stem cell transplantation, this would equate to approximately 1 person being eligible for induction therapy with bortezomib per 100,000 population.

Each bortezomib based cycle costs approximately £3800 per cycle, and patients may receive an average of 3 cycles as induction therapy. Assuming 1 patient per 100,000 population may be eligible for bortezomib induction prior to ASCT, this will equate to a cost of approximately £11,000 per 100,000 population, or an increase in approximately £6500 to £8000 compared to current treatment strategies used.
Background

According to Cancer Research UK, in 2009, there were approximately 4300 new diagnoses of multiple myeloma in England and Wales. There are currently between 10,000 and 15,000 people living with multiple myeloma in the UK.

Multiple myeloma remains an incurable disease, with an average survival of 4–6 years, but it can be treated with a combination of supportive measures and chemotherapy. The aim of treatment is to extend the length and quality of life by alleviating symptoms, controlling disease and minimising adverse effects. Factors affecting survival and outcome include burden of disease, type of cytogenetic abnormality, age and performance status, and response to treatment.

In most cases the choice of first-line treatment depends on a combination of factors. Many people with multiple myeloma are not able to withstand intensive treatment, such as high-dose chemotherapy with stem cell transplantation, because of their age, other health problems or poor performance status. These people are offered single-agent or combination chemotherapy. Typically, combination therapies include chemotherapy with an alkylating agent (such as melphalan or cyclophosphamide) and a corticosteroid. More recent treatment options include drugs such as thalidomide and bortezomib. The main objective of first-line therapy is to achieve a period of stable disease for as long as possible, thereby prolonging survival and maximising quality of life. After initial treatment, most people usually experience a period of remission, but almost all relapse eventually, and some have disease that does not respond to treatment.

This review addresses the evidence to support the use of bortezomib regimens first line for induction, prior to melphalan and autologous stem cell transplantation (ASCT) in untreated symptomatic multiple myeloma patients suitable for bone marrow transplantation (BMT). Bortezomib is currently not licensed for this indication in the UK, although a variation in marketing authorisation has been submitted to the EMA, the response to which is expected in the first quarter of 2013. The manufacturer, Janssen-Cilag, currently also has a license extension pending for the subcutaneous administration of bortezomib.

Bortezomib (Velcade) is currently licensed:

- In combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.
- As monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

NICE, in their TA on the bortezomib and thalidomide for the first-line treatment of multiple myeloma state that bortezomib in combination with an alkylating agent and a corticosteroid is only recommended as an option for the first-line treatment of multiple myeloma if high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide.

The British Committee for Standards in Haematology (BCSH) had produced guidance on the diagnosis and management of multiple myeloma. For patients where HDT is planned, or is a possible future option, the aim of induction treatment is to induce high remission rates rapidly and with minimal toxicity and to preserve haematopoietic stem cell function to ensure successful mobilisation of peripheral blood stem cells (PBSC). According to the guideline, prior to the introduction of novel therapies, the standard of care for patients in whom high dose therapy (HDT) and autologous stem cell transplantation (ASCT) was planned was the use of induction therapy based on high dose dexamethasone, such as
VAD (vincristine, doxorubicin and dexamethasone) or related infusional regimens. These combinations were associated with response rates of 55-84% and complete response (CR) rates of 8-28% although it should be noted that the current definition of CR is more rigorous. However, there was significant haematological toxicity and the need for central venous access led to an appreciable incidence of line-related infections and thrombosis, and therefore regimens containing either bortezomib, thalidomide or lenalidomide were introduced. The BCSH therefore makes the following recommendations for induction therapy prior to HDT and ASCT (taken directly from source):

- VAD or single agent dexamethasone should no longer be routinely used as induction therapy

- Induction regimens should contain at least one novel agent - Examples of induction regimens that are superior to VAD in terms of response rates include cyclophosphamide, thalidomide and dexamethasone (CTD), thalidomide, doxorubicin and dexamethasone (TAD), bortezomib/dexamethasone and bortezomib, doxorubicin and dexamethasone (PAD).

- Decisions regarding the most appropriate induction for individual patients will require the assessment of a number of factors such as renal function, thrombotic risk and pre-existing neuropathy although it is appreciated that some agents are not routinely funded as initial therapy in the UK. CTD is the combination of which there is the most clinical experience in the UK.
**Published data**

There have been 4 phase III studies (2 fully published and 2 abstracts) that have evaluated bortezomib for induction therapy in transplant eligible untreated multiple myeloma patients.

*Harousseau J-L et al* conducted a phase III study evaluating the combination of bortezomib and dexamethasone (n=240) compared with vincristine, doxorubicin and dexamethasone (VAD) as induction (n=242) before stem-cell transplantation in 482 previously untreated patients with multiple myeloma. Patients were included in the trial if they fulfilled the following criteria:

- Age ≤ 65 years
- Untreated symptomatic MM with measurable paraprotein in serum (>10g/L) or urine (>0.2g/24 hours)
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, life expectancy ≥ 2 months,
- Adequate renal, haematological and liver function

Patients were excluded if they had confirmed amyloidosis, were HIV positive, had a history of other malignancies, had uncontrolled diabetes, or suffered ≥ Grade 2 peripheral neuropathy.

The open-label phase III study was conducted at 89 sites across France, Belgium and Switzerland, and patients were randomised to one of the following four treatment options:

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Treatment allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A1; n=121</td>
<td>VAD plus no consolidation</td>
</tr>
<tr>
<td>Arm A2; n=121</td>
<td>VAD plus dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) consolidation</td>
</tr>
<tr>
<td>Arm B1; n=121</td>
<td>Bortezomib in combination with dexamethasone with no consolidation</td>
</tr>
<tr>
<td>Arm B2; n=119</td>
<td>Bortezomib with dexamethasone plus DCEP consolidation</td>
</tr>
</tbody>
</table>

- VAD comprised four 4-week cycles of vincristine 0.4 mg/day and doxorubicin 9mg/m²/day by continuous infusion days 1 to 4 plus dexamethasone 40mg orally days 1 to 4 (all cycles) and days 9 to 12 and days 17 to 20 (cycles 1 and 2).
- Bortezomib plus dexamethasone comprised four 3-week cycles of bortezomib 1.3mg/m² intravenously days 1, 4, 8, and 11 plus dexamethasone 40mg days 1 to 4 (all cycles) and days 9 to 12 (cycles 1 and 2).
- DCEP comprised two 4-week cycles of dexamethasone 40mg on days 1 to 4 plus cyclophosphamide 400mg/m², etoposide 40 mg/m², and cisplatin 15 mg/m²/day by continuous infusion days 1 to 4.

Recommended concomitant medications included bisphosphonates (pamidronate 90 mg, or zoledronate 4 mg) monthly until first transplantation, plus antibiotics, antifungal agents, and antiviral prophylaxis in accordance with local practice. Stem-cell mobilisation was undertaken with granulocyte colony-stimulating factor (G-CSF) 10mcg/kg/day from day 15 of induction cycle 3. If collection was inadequate, a second mobilisation was undertaken with cyclophosphamide 3g/m² plus G-CSF 5mcg/kg/day after induction cycle 4. The primary end point was post-induction complete response/near complete response (CR/nCR) rate. Secondary end points included post-induction overall response rate, CR/nCR rate with and without DCEP consolidation, CR/nCR and at least very good partial response (VGPR) rates post first transplantation, proportions of patients requiring a second transplantation, and safety and toxicity of induction. The response was evaluated by investigators, according to the modified European Group for Blood and Marrow.
Transplantation (EBMT) criteria, including additional categories of nCR (i.e. immunofixation-positive CR), and VGPR (serum M-protein reduction $\geq 90\%$; urine light chain $< 100$mg/24 hours). Responses were determined post-induction, post-DCEP (consolidation), and after first and second transplantation. Blood and urine samples were taken at baseline, before each induction/consolidation cycle, 4 weeks after the last induction/consolidation cycle, at transplantation, and 1 to 3 months post-transplantation.

The evaluable population included 441 patients, 218 who received VAD (110, A1, and 108, A2), and 223 who received bortezomib with dexamethasone. A total of 41 patients were excluded from the efficacy analysis due to: non-measurable disease on central review, patients had liver dysfunction, high-dose dexamethasone was contra-indicated, patients had received previous therapy, concomitant cancer, poor performance status and other. The following results were reported:

<table>
<thead>
<tr>
<th>Induction Therapy</th>
<th>Parameter</th>
<th>ORR (CR+PR)</th>
<th>CR</th>
<th>CR/nCR</th>
<th>$\geq \text{VGPR}$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAD (n=218)</td>
<td>62.8%</td>
<td>1.4%</td>
<td>6.4%</td>
<td>15.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib/DEX (n=223)</td>
<td>78.5%</td>
<td>5.8%</td>
<td>14.8%</td>
<td>37.7%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p value</td>
<td>$&lt;0.001$</td>
<td>0.012</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post first ASCT</th>
<th>Parameter</th>
<th>ORR (CR+PR)</th>
<th>CR</th>
<th>CR/nCR</th>
<th>$\geq \text{VGPR}$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAD + HDMSCT (n=184)</td>
<td>91.3%</td>
<td>10.3%</td>
<td>21.7%</td>
<td>44.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib/DEX + HDMSCT (n=197)</td>
<td>90.9%</td>
<td>18.3%</td>
<td>39.6%</td>
<td>61.4%</td>
<td></td>
<td>0.921</td>
</tr>
<tr>
<td>p value</td>
<td>0.921</td>
<td>0.020</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response to induction with or without consolidation:
- Following induction with or without consolidation, CR/nCR (14.0% vs. 15.1%; $p=0.720$), and at least VGPR (28.4% vs. 32.0%; $p=0.371$) rates were similar in patients who were to receive consolidation therapy (A2 and B2; n=219). Among patients who actually received DCEP, 91 in A2 and 96 in B2), CR/nCR and at least VGPR rates were 8.0% and 22.2% in A2 (vs. 8.2% and 15.4% in A1), and 26.0% and 50.0% in B2 (vs. 19.6% and 41.1% in B1).

Response post second transplantation:
- Overall, including responses post second transplantation, CR/nCR (39.5% vs. 22.5%; $p<0.001$) and at least VGPR (67.7% vs. 46.7%; $p<0.001$) rates, respectively, were statistically significantly higher in the bortezomib/dexamethasone group compared with VAD.

Overall secondary outcomes and safety outcomes:
- The median progression-free survival (PFS) was 29.7 months among patients who received VAD versus 36.0 months among patients who received bortezomib plus dexamethasone induction, with 128 (52.9%) of 242, and 110 (45.8%) of 240 patients respectively, having progressed after a median follow-up of 31.2 months.
- At the time of writing median overall survival (OS) has not been reached in either group after a median follow-up of 32.2 months – with 45 (18.6%) patients in the VAD group and 40 patients (16.7%) in the bortezomib/dexamethasone group having died – respective 3-year OS rates were 77.4% in the VAD group, and 81.4% in the bortezomib/dexamethasone group.
- Overall, the incidence of adverse effects was higher in the
bortezomib/dexamethasone group (96.7%) compared to the VAD group (91.6%), p<0.05
- Grade 3 to 4 anaemia, neutropenia, and thrombosis were more frequent in the VAD group compared to the bortezomib group
- Seven deaths (2.9%) related to toxicity were noted in the VAD group compared to none in the bortezomib/dexamethasone group (p=0.02)

The researchers concluded that the results of this randomised phase III study demonstrate that among previously untreated MM patients age ≤ 65 years, induction therapy with bortezomib plus dexamethasone significantly improved both post-induction and post-transplantation rates of CR/nCR and at least VGPR compared with VAD, previously the standard of care in this setting.

Cavo et al conducted a phase III study to evaluate the safety and efficacy of bortezomib in combination with thalidomide and high dose dexamethasone (VTD) compared with thalidomide in combination with dexamethasone (TD) in newly diagnosed multiple myeloma patients eligible for double autologous stem cell transplantation (ASCT)\textsuperscript{5}. In this open-label study, patients were enrolled at 73 hospitals of the GIMEMA (Gruppo Italiano Malattie EMatologiche dell’Adulto) Myeloma Network in Italy between the period May 2006 and April 2008. Patients were included in the trial if they fulfilled the following criteria:
- Age 18 to 65 years
- Previously untreated symptomatic and measurable MM
- Karnofsky performance status ≥ 60%
- Adequate renal, haematological, cardiovascular and liver function

Patients were excluded if they had had a myocardial infarction within the last 6 months of enrollment, NYHA class II-IV heart failure, uncontrolled angina, liver dysfunction confirmed amyloidosis, previously suffered ≥ Grade 2 peripheral neuropathy, or a history of venous thromboembolism or a diagnosis of thrombophylic alterations.

Patients were randomised to receive three 21-day cycles of induction therapy with VTD (n=236) or TD (n=238).
- VTD comprised of 1.3mg/m\textsuperscript{2} of bortezomib on days 1, 4, 8 and 11, 100mg thalidomide for the first 14 days and 200mg thereafter, and 40mg dexamethasone on days 1, 2, 4, 5, 8, 9, 11 and 12
- TD comprised of 100mg thalidomide for the first 14 days and 200mg thereafter, and 40mg dexamethasone on days 1 to 4, and days 9 to 12

After mobilisation of autologous peripheral blood stem cells, all patients received double ASCT, done 3-6 months apart, to support two sequential courses of 200mg/m\textsuperscript{2} melphalan. Once patients had recovered haemopoiesis after the first transplant, they were given TD until the day before the second transplant. Two 5-week cycles of consolidation therapy were started 3 months after the second transplant, and maintenance therapy was then given until relapse or progression.

Treatment was discontinued in cases of disease progression, unacceptable adverse events, failure to achieve a minimum threshold of stem cells to support at least one transplantation, or if the patient withdrew consent. In cases of specific pre-defined haematological and non-haematological adverse events, doses of bortezomib and thalidomide were reduced.

The primary endpoint was the rate of complete plus near complete response to induction therapy. Secondary outcomes included the rate of complete plus near complete response to double transplantation, and subsequent consolidation therapy, time to progression or relapse, progression-free survival overall survival and safety. Median follow up was 36 months (range 22 to 42 months) from the start of study treatment.
The following results were obtained:

<table>
<thead>
<tr>
<th></th>
<th>VTD (n=236)</th>
<th>TD (n=238)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>After Induction therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>44 (19%, 13.7-23.6)</td>
<td>11 (5%, 2.0-7.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR/nCR</td>
<td>73 (31%, 25.0-36.8)</td>
<td>27 (11%, 7.3-15.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>146 (62%, 55.7-68.1)</td>
<td>66 (28%, 22.0-33.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>220 (93%, 90.0-96.4)</td>
<td>187 (79%, 73.4-83.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minimal response or stable disease</td>
<td>16 (7%, 3.6-10.0)</td>
<td>39 (16%, 11.7-21.1)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>12 (5%, 2.3-7.8)</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Best response to overall treatment protocol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>136 (58%, 51.3-63.9)</td>
<td>97 (41%, 34.5-47.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR/nCR</td>
<td>168 (71%, 65.4-77.0)</td>
<td>128 (54%, 47.4-60.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>210 (89%, 85.0-93.0)</td>
<td>175 (74%, 67.9-79.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>227 (96%, 93.7-98.6)</td>
<td>212 (89%, 85.1-93.0)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Minimal response, stable disease or progressive disease</td>
<td>9 (4%, 1.4-6.3)</td>
<td>26 (11%, 7.0-14.9)</td>
<td>0.0031</td>
</tr>
</tbody>
</table>

Additionally, the following results were reported:

- Overall, median time to best complete response or near complete response was statistically significantly shorter for patients receiving VTD (9 months, range 3.1 months to not reached) compared to those receiving TD (14 months, range 8.4 months to no reached), \( p<0.0001 \)
- The estimated 3-year probability of progression or relapse was 29% in the VTD group versus 39% in the TD group (\( p=0.0061 \))
- Progression-free survival was statistically significantly longer for patients receiving VTD compared to those receiving TD (HR 0.63, 95% CI 0.45 to 0.88, \( p=0.0061 \)).
- The estimated 3-year rate of progression-free survival was 68% in the VTD group and 56% in the TD group (\( p=0.0057 \))
- The estimated 3-year rate of overall survival was 86% in the VTD group and 84% in the TD group (\( p=0.30 \))
- With respect to adverse events, grade 3 or 4 adverse events were reported in a statistically significantly higher number of patients on VTD (n=132, 56%), than in those on TD (n=79; 33%, \( p<0.0001 \))
- Peripheral neuropathy was reported in a greater number of patients on VTD than in those on TD (n=23 [10%] vs. n=5 [2%]; \( p=0.0004 \)).
- More patients on treatment with TD discontinued treatment during or after induction therapy compared with those on VTD (26 [11%] vs. 13 [6%], respectively, \( p=0.0319 \))

The researchers concluded that induction therapy with VTD was associated with a higher rate of complete or near complete response than was induction therapy with TD, although VTD was also associated with a higher incidence of adverse events.
Sonneveld P et al. The results of the HOVON-65/GMMG-HD4 study at the American Society of Hematology conference in 2010 (abstract only available) which evaluated the efficacy of bortezomib (B) during induction and maintenance on progression-free survival (PFS) in patients with newly diagnosed symptomatic MM, who were candidates for high-dose therapy\(^6\). Patients were randomly assigned to three 28-day cycles of standard vincristine with doxorubicin and dexamethasone (VAD) (arm A, n=305) or PAD (Arm B, n=308); PAD was dosed as bortezomib 1.3 mg/m\(^2\), days 1,4,8,11, doxorubicin 9 mg/m\(^2\), days 1-4, and dexamethasone 40 mg, days 1-4, 9-12, 17-20) Patients received one (HOVON) or two (GMMG) high-dose melphalan (HDM) 200 mg/m\(^2\) with ASCT. Maintenance consisted of thalidomide (T) 50 mg daily (for arm A) or bortezomib 1.3 mg/m\(^2\), 2-weekly (arm B) for 2 years. Primary endpoint was PFS, and other endpoints were complete response (CR) (EBMT), immunofixation positive CR (nCR), VGPR pre-and post HDM and overall survival (OS). The protocol specified analysis was intention-to-treat and censored for patients who received allo-SCT after HDM (n=46). An initial analysis of the first 626 randomised patients was presented in the abstract. Median follow up was 40 months, with 89% of patients completing induction and HDM. In the GMMG group, after HDM, 80% of patients received the second course of HDM.

Some of the following results were reported:

- PFS at 36 months was 42% in arm A vs. 46% in arm B.
- nCR/CR rates were 7/9% (arm A) vs. 9/21% (arm B) at 3 months after high dose melphalan, and 12/26% (arm A) vs. 12/38% (arm B) on protocol, i.e. for patients who had undergone the first transplantation.
- Patients treated with bortezomib had a better OS compared with those on arm A (HR 0.74, p=0.048) – absolute data not available from the abstract.
- WHO grade 3 and 4 polyneuropathy occurred in 7% of patients in arm A and 16% of patients in arm B.

The researchers conclude that the bortezomib regimen achieves high nCR/CR during induction, and achieved a better overall survival (although complete data were not available from the available abstract).

Finally, Rosiñol L et al presented the results of the PETHEMA/GEM phase III study comparing thalidomide/dexamethasone (TD) vs. bortezomib in combination with TD vs. combination chemotherapy plus bortezomib in symptomatic, newly diagnosed multiple myeloma patients younger than 65 years, eligible for autologous stem cell transplantation with high dose melphalan\(^9\).

- TD consisted of thalidomide 200 mg daily (escalating doses in the first cycle) and dexamethasone 40 mg on days 1-4 and 9-12 at 4-week intervals for 6 cycles (n=127).  
- The VTD regimen was identical to TD plus bortezomib 1.3 mg/m\(^2\) on days 1,4,8,11 of each cycle (n=130).
- Combination chemotherapy plus bortezomib consisted of 4 cycles of VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, prednisone)/VBAD (vincristine, bischloroethylnitrosourea, Adriamycin, and dexamethasone on an alternating basis followed by 2 cycles of bortezomib (1.3 mg/m\(^2\) on days 1,4,8, and 11 every 3 weeks) (n=129).

The duration of induction therapy was 24 weeks for both groups. The primary endpoints were response rates after induction, and after ASCT, and time to progression. The following results were reported:

- The immunofixation electrophoresis (IFE) negative (a measure of response in MM) CR rate was statistically significantly higher with VTD (35%) compared to TD (14%) and VBMCP/VBAD/B (22%) (p=0.0001 and p=0.01, respectively).
- The progressive disease (PD) rate during induction was statistically significantly lower with VTD than with TD (7% vs. 23%, p=0.001).
Nine patients (3 in each arm) died during induction therapy.

On an intention-to-treat basis, the post-ASCT CR rate was statistically significantly higher in the VTD arm compared with TD (46% vs. 24%, p=0.004) and VBMCP/VBAD/B (46% vs. 38%, p=0.1).

The estimated overall survival (OS) at 4 years was 76% with no significant differences among the 3 arms.

After a median follow-up of 27 months, the progression-free survival (PFS) was not reached with VTD while it was 27 and 38 months with TD and VBMCP/VBAD/B, respectively (p=0.006).

The frequency of grade ≥3 peripheral neuropathy was 12% with VTD compared to 1% in both the TD and the VBMCP/VBAD/B arms (p= 0.0002).

Treatment was discontinued due to toxicity in 16 patients (VTD:9, TD:4, VBMCP/VBAD/B:3).

The incidence of thrombotic events was 2%, 6% and 5% for VTD, TD and VBMCP/VBAD/B, respectively (p=not significant).

The researchers conclude that induction with VTD resulted in a statistically significantly higher CR rate during induction and post ASCT. Additionally, whilst treatment with VTD resulted in a longer PFS, overall survival did not differ between the three groups.

Safety

The BCSH guideline makes the following statements with respect to important toxicities to be considered with the use of bortezomib (taken directly from source)³:

- **Peripheral neuropathy:** predominantly sensory and painful, usually progressive and variably reversible. A summary of key recommendations from the supportive care guideline regarding treatment emergent peripheral neuropathy is described. It is managed by early detection, dose-reduction and analgesia.
- **Gastrointestinal toxicity:** constipation, diarrhoea, abdominal bloating or pain. Patients should be warned of possible symptoms. Severe diarrhoea is relatively rare but occasional patients with severe diarrhoea, unresponsive to loperamide may require admission for hydration as these patients are at risk of developing pre-renal acute renal failure.
- **Postural hypotension and pre-syncope secondary to autonomic neuropathy:** pre-hydration with saline infusion prior to each dose of bortezomib is a useful prophylactic measure. Screen for pre-syncope and syncope and assess for a postural drop at the start of each treatment cycle. The administration of 500 mL of normal saline prior to each dose of bortezomib may improve tolerance of the drug.
- **Many patients require dose adjustment of their usual anti-hypertensives for the duration of bortezomib therapy**
- **Thrombocytopenia:** usually progressive over 21-day cycle with recovery prior to next cycle. Check FBC on days 1 and 8; consider dose reduction if platelets <30 x 10⁹ on day 1 and transfuse platelets if <30 x 10⁹ on any other treatment day
- **Fatigue**
**Cost**

According to the BCSH guidance on the management of myeloma, the majority of patients achieve maximum response to induction therapy after 4 to 6 cycles, although response should be assessed after each cycle. However, CR prior to HDT is a good prognostic factor, and there is currently no evidence that prolongation of induction treatment to achieve a CR improves outcome. It is currently therefore recommended to treat to at least PR which usually occurs within 4 to 6 cycles and to switch to an alternative regimen if there is evidence of progressive disease after 2 cycles or less than PR after 4. The following induction regimens have been recommended in the BCSH guidelines:

- cyclophosphamide, thalidomide and dexamethasone (CTD)
- thalidomide, doxorubicin and dexamethasone (TAD)
- bortezomib/dexamethasone and
- bortezomib, doxorubicin and dexamethasone (PAD)

The costs of each regimen are listed per monthly cycle (inclusive of VAT):

<table>
<thead>
<tr>
<th>28-day cycles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubophosphamide 500mg weekly</td>
<td>£6.80</td>
</tr>
<tr>
<td>Thalidomide 100-200mg daily</td>
<td>£716.35 to £1432.70</td>
</tr>
<tr>
<td>Dexamethasone 40mg daily on days 1 to 4, and days 15 to 18</td>
<td>£25.20</td>
</tr>
<tr>
<td>Total</td>
<td>£1464.70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>21-day cycles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide 100mg daily on days 1 to 14, then 200mg thereafter</td>
<td>£1074.53</td>
</tr>
<tr>
<td>Doxorubicin 9mg/m²/day by continuous infusion days 1 to 4</td>
<td>£180.00</td>
</tr>
<tr>
<td>Dexamethasone 40mg on days 1 to 4, and days 9 to 12 21 day cycles</td>
<td>£25.20</td>
</tr>
<tr>
<td>Total</td>
<td>£1066.44</td>
</tr>
</tbody>
</table>

According to Cancer Research UK, more than seven out of ten (72%) multiple myeloma cases occur in people aged 65 years or over, implying 28% of new cases are identified in patients under 65 years. Considering 4300 new diagnoses of multiple myeloma were
recorded in 2009 in England and Wales, this equates to 8 new cases per 100,000 population, of which 2 cases will be patients under 65 years of age. Assuming 50% of patients under 65 years may be eligible for induction therapy and autologous stem cell transplantation, this would equate to approximately 1 person being eligible for induction therapy with bortezomib per year per 100,000 population.

Each bortezomib based cycle costs, on average, approximately £3800 per cycle, and patients may receive an average of 3 cycles as induction therapy. Assuming 1 patient per 100,000 population may be eligible for bortezomib induction prior to ASCT, this will equate to a cost of approximately £11,000 per 100,000 population. If an alternate regimen without bortezomib was used, this would cost approximately £3000 to £4500 for 3 cycles. Therefore, using a bortezomib containing regimen instead of an alternative would lead to an incremental cost of approximately £6500 to £8000 per 100,000 population.

At present, changing from a non-bortezomib regimen to a regimen containing bortezomib will not increase the number of days of hospital admission per cycle.

References

2. Velcade (bortezomib) 3.5 mg powder for solution for injection SPC (Date of revision = Aug 2011)
6. Sonneveld P et al. HOVON-65/GMMG-HD4 Randomized Phase III Trial Comparing Bortezomib, Doxorubicin, Dexamethasone (PAD) Vs VAD Followed by High-Dose Melphalan (HDM) and Maintenance with Bortezomib or Thalidomide In Patients with Newly Diagnosed Multiple Myeloma (MM). American Society of Hematology oral presentation 5 December 2010

Details of search strategy:

1. Velcade (bortezomib) SPC Aug 2011
2. MICROMEDEX (accessed 2 March 2012)
3. NICE (accessed 2 March 2012)
4. Cochrane Library (accessed 2 March 2012)
6. EMBASE
7. PubMed
8. British National Formulary