Bortezomib for Relapsed or Refractory Mantle Cell Lymphoma

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Bortezomib for Relapsed or Refractory Mantle Cell Lymphoma

1.0 Summary for Patients

- Bortezomib (brandname Velcade) is an injection. It has been used to treat a cancer called mantle cell lymphoma (MCL) when it either gets worse again after successful treatment (“relapsed”), or when it does not respond to treatment (“refractory”). Successful treatment with bortezomib does not cure MCL but it may prolong life.

- There is no UK guidance on treating relapsed or refractory MCL, and a large number of different treatments are used. One medicine called temsirolimus is licensed for MCL but it has been rejected by NICE because the manufacturer did not provide them with evidence that it worked.

- It is not possible to measure the benefits or risks of bortezomib against other treatments for relapsed or refractory MCL because no one has studied this.

- In the largest study published, the average patient with MCL lived for just over 23 months after bortezomib treatment, but one-third of patients showed a response to treatment which lasted 9 months. These “responders” lived longer and survived for around 35 months. Two other smaller studies showed similar results.

- One in five patients treated with bortezomib in the largest study had a side effect that was life-threatening, required admission to hospital, or resulted in significant disability or death. Bortezomib contributed to the deaths of 5 out of the 155 patients treated.

- More than 1 out of every 10 patients treated with bortezomib for a different cancer (multiple myeloma) suffers each of the following side effects: shingles, higher risk of infection, anaemia, decreased appetite, nerve problems, fever, vomiting, rash and muscle pain.

1.1 Summary for Healthcare Professionals

- There is no robust evidence available to support the use of bortezomib in the treatment of relapsed or refractory mantle cell lymphoma (MCL) in that there are no randomised controlled trials that quantify the benefits and risks compared to other treatments or best supportive care.

- Three uncontrolled phase II studies indicate that around one third of patients treated with bortezomib achieve a response to treatment and in those patients this response typically lasts for around 9 months, and increases median overall survival by around 12 months. However, it is not possible to quantify this in terms of patient-orientated outcomes like overall survival or impact on quality of life.

- Conversely temsirolimus, which has recently been rejected by NICE, does have data from a single randomised trial showing benefit in terms of progression free survival over investigator-chosen treatments (which did not include bortezomib).

- There are significant safety concerns. The largest study showed 21% of patients experienced an adverse effect that resulted in death or persistent/significant disability or incapacity, was life-threatening or required hospitalisation. The SPC for bortezomib cites a greater than 10% incidence of reactions such as Herpes zoster infections, thrombocytopenia and neuropathy.

- An average bortezomib course costs up to £12,198 (excluding VAT). No health economic studies of bortezomib for this indication have been identified.
The figure below highlights the balance of risks, benefits, evidence, costs and regulatory position for this intervention:

The data in the diagram above is taken from assessment against the standard options below:

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<tbody>
<tr>
<td><strong>Health benefits expected</strong></td>
<td>Minor symptom control, or potential but unproven patient benefit</td>
<td>Symptom control, improved health related quality of life (HRQoL)</td>
<td>Major HRQoL gain e.g. months of life gained</td>
<td>Transforming HRQoL e.g. years of life gained</td>
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<td><strong>Safety</strong></td>
<td>Early death or substantial morbidity</td>
<td>Severe side effects affecting HRQoL</td>
<td>Moderate side effects</td>
<td>Minor side effects</td>
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<tr>
<td><strong>Strength of evidence</strong></td>
<td>Speculative approach</td>
<td>Single case or small case series, uncontrolled studies</td>
<td>Small controlled studies</td>
<td>At least one large RCT</td>
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<tr>
<td><strong>Regulatory status</strong></td>
<td>No UK licensed product. No licence globally</td>
<td>No UK licensed product. Licensed products exist in USA/Europe but not necessarily for this intervention</td>
<td>UK licensed product. Intervention off-label in UK, and in USA/Europe</td>
<td>UK licensed product. Intervention off-label in UK but licensed in USA/Europe</td>
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<tr>
<td><strong>Affordability</strong></td>
<td>Very significant costs above current best care option</td>
<td>Increased costs above current best care option</td>
<td>Modest increased costs or cost neutral</td>
<td>Cost saving compared with current best option</td>
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2.0 Intervention

Mantle cell lymphoma (MCL) is a well-recognised distinct subtype of B-cell non-Hodgkin's lymphoma (NHL) that usually occurs in older adults. It is estimated to have an incidence of approximately 500 cases per year in the UK and median overall survival (OS) of patients is 3 to 5 years after diagnosis and 1 to 2 years after relapse [1]. Although some patients with MCL may follow an indolent clinical evolution, most patients experience aggressive disease. The majority of patients present with advanced-stage disease, which necessitates systemic treatment. MCL usually responds to initial chemotherapy, but only a small minority of patients achieve sustained remission, generally the duration of response (DR), time to progression (TTP), and OS for MCL are much shorter than seen for other types of NHL. Recent studies have shown that the early use of stem cell transplantation (SCT) can lead to long-term survival in MCL, the treatment approach for newly diagnosed patients therefore generally depends on whether they are transplant-eligible [2].

The clinical management of non-transplant eligible patients with MCL is complex and in practice there is a great variation in treatment approach. A number of combination chemotherapies (with or without rituximab) are available for first line treatment and these may be given in combination with radiotherapy, interferon-alfa and corticosteroids for aggressive disease. Second line treatment may depend upon patient co-morbidities, side effect profiles and prior chemotherapies. For some patients, the sequential use of standard chemotherapy regimens or aggressive combination chemotherapy regimens with rituximab may be treatment options. People experiencing multi-relapsed disease often become intolerant to combination chemotherapies, however presently there is no consensus on standard care for this group.

The aim of treatment of relapsed or refractory disease, as with other forms of incurable cancer is to increase overall and progression free survival (PFS) and improve health-related quality of life. To achieve these outcomes a range of single agents may be tried. These include bortezomib, fludarabine, chlorambucil, gemcitabine, etoposide, cladribine, thalidomide, vinblastine, alemtuzumab, temsirolimus and lenalidomide [1]. With the exception of temsirolimus, none of these are specifically licensed for use in MCL and NICE recently announced that they could not support the use of temsirolimus in the NHS as they had not received a submission from the manufacturer [3]. Therefore there are currently no licensed, NICE-approved agents available in the NHS for the treatment of relapsed or refractory MCL.

In a randomised study, temsirolimus was compared with investigator's choice of single-agent therapy in relapsed or refractory disease [n = 53, predominately gemcitabine (n= 22), fludarabine IV (n=12), 8 other agents (n=19)] [4]. Temsirolimus was associated with a significant increase in median PFS compared with investigator’s choice of treatment (4.8 months vs. 1.9 months, respectively) but the study was not adequately powered to assess impact on OS and no significant effect was shown (11.1 months vs. 9.5 months, respectively). It is also important to note that 22% of patients discontinued temsirolimus during the trial because of adverse effects and 89% of patients experienced grade 3 or 4 adverse events compared with 11% and 68% of patients that received investigator’s choice of treatment, respectively. These data indicate that there is currently an unmet need for new approaches to treating relapsed or refractory disease that prolong disease-free survival and are well-tolerated.

Bortezomib (Velcade®) is an injectable proteasome inhibitor that is licensed for the treatment of multiple myeloma in the UK, but it is also licensed in the US for use in patients with MCL that have received at least one prior therapy [5,6]. It is thought to have several different mechanisms of action including inhibition of cell-cycle progression, induction of apoptosis, inhibition of Nuclear factor–kB and inhibition of angiogenesis which suggests it should be active in MCL [7].
3.0 Review of Data Available

No randomised controlled studies assessing the role of bortezomib as a single-agent in the treatment of relapsed or refractory MCL were identified. Reports that described the use of bortezomib as part of a combination regimen or as a first line treatment have not been included in this review. There are three published phase II uncontrolled trials of bortezomib in the treatment of MCL that meet the inclusion criteria for this review (see section 6.2 for reasons for excluding studies). These studies are the principal means of assessing benefits and risks, and are discussed below.

3.1 Benefits

The largest relevant phase II study identified is the PINNACLE study and this formed the basis for approval of the MCL indication in the US [6]. This prospective, single-arm study was conducted at 35 centres in the US, UK and Germany from June 2003. It included 155 adults (median age 65 years) with pathologically confirmed MCL that had relapsed or progressed after one to two prior lines of chemotherapy (including an anthracycline or mitoxantrone, and rituximab, each in one line). Patients had a Karnofsky performance status (KPS) of 50% or higher. They received an IV bolus injection of bortezomib at a dose of 1.3mg/m$^2$ twice weekly for 2 weeks (days 1, 4, 8 and 11) followed by a 10-day rest period for a maximum of 17 treatment cycles. The bortezomib dose was modified based on emergent toxicities during the study. Disease response parameters of complete response (CR), unconfirmed CR (CRu), and partial response (PR) were evaluated using the International Workshop Response Criteria (IWRC). Additional response parameters included DR, TTP and OS. Due to lack of ability to identify a control cohort of sufficient size, the intended primary endpoint of a formal comparison of TTP with historical controls was not accomplished [7].

The evaluable patients ($n=141/155$) were subject to independent radiological review, and the main findings were as follows:

- The overall response rate (CR, CRu or PR) was 33% (95% confidence interval [CI] 26 to 42).
- Of the 47 responders, CR plus CRu occurred in 11 (8%; 95% CI 4 to 14, a CR in 9 (6%; 95% CI 3 to 12), and a PR in 36 (26%; 95% CI 19 to 34).
- While the median number of treatment cycles was 4 for all patients, the median number of cycles was 8 among responders, with a median time to response of 1.3 months.
- The median DR was 9.2 months among responders (95% CI 4.9 to 13.5), with a median DR of 13.5 months in patients with CR plus CRu.
- Median TTP was 6.2 months for all patients (95% CI 4.0 to 6.9) and 10.6 months for responders (95% CI 7.3 to 15.2).
- The median OS was not reached by the median follow-up of 13.4 months.

Updated results after a median follow-up period of 26.4 months were reported more recently [8]. Although the response results were very similar to those presented above, further data on OS were available (previously the median had not been reached).

- The overall response rate (ORR) was 32% (95% CI 24 to 40), including 8% (95% CI 4 to 14) with CR or CRu (i.e. similar to that previously reported).
- Median time to response was 1.4 months.
- Median DR was 9.2 months in all responders (95% CI 5.9 to 13.8). For those achieving a CR/Cru it was not reached; for those with a PR it was 6.7 months (95% CI 4.9 to 9.7).
- The median TTP was 6.7 months (12.4 months in responding patients) and the median time to next therapy was 7.4 months (14.3 months in responding patients).
- The median PFS was 6.5 months overall and was 12.4 months in responders. Median OS was 23.5 months overall and 35.4 months in responding patients. The 1-year OS rates were 69% and 91%, respectively.
There is a clinical view that the increased overall median PFS (6.5 months) seen in this study compares favourably with the median PFS seen in the control arm of the temsirolimus trial discussed above [4]. In this trial patients received the clinician’s choice of treatment and a median PFS of 1.9 months was reported – thus strengthening the case for using bortezomib in this indication. Although the patient population involved in each trial appears similar it is not valid to draw conclusions from the comparison of outcomes across different trials in this way.

A further phase II trial investigated the safety and efficacy of bortezomib monotherapy in 29 adults with MCL; almost half of whom had not received any prior therapy [9]. The 16 patients with relapsed MCL had received a maximum of two courses of previous treatment (five patients had received two courses and 11 had received one course). The median age of the group was 67 years (range 48 to 79) and 72% were male; the majority (25/29) had an Eastern Cooperative Oncology Group (ECOG) performance status of either 0 or 1. The dose of bortezomib administered was the same as that used in the PINNACLE study and the response was assessed in the same way, with 28/29 patients assessable for response. With a median of four cycles administered per patient, the main findings reported were as follows:

- The ORR was 46.4% (95% CI 27.5 to 66.1), including one CRu and 12 PRs. Response rates were similar in previously untreated (46.2%) and treated (46.7%) patients.
- The median response duration was 10 months (range 2.1 to 25.1).
- The median TTP in all patients was 12.5 months.

O'Connor et al report the results of another phase II study, which included 40 patients with heavily pre-treated MCL (median of 2 prior therapies; range 0 to 4) [10]. The majority were white, non-Hispanic (95%) and the median age was 67 years (range 45 to 83 years). Bortezomib was administered at a dose of 1.5mg/m² on days 1, 4, 8 and 11, every 21 days. This dose is higher than in the PINNACLE study. The main findings were as follows:

- The ORR was 47%, including 6 CR/CRu, and 12 PRs. There was no statistically significant difference in response between patients who had relapsed disease (50%) and those who had refractory disease (42%).
- The median PFS was 5.3 months; in those who responded it was 7.8 months. Again there was no statistically significant difference in response duration between patients who had relapsed disease (5.6 months) and those who had refractory disease (3.9 months; P=0.81).

**Summary**

In a series of 3 uncontrolled studies it has been shown that bortezomib treatment is associated with at least some degree of clinical response in between one third and one half of patients treated. Typically the response lasts for between 6 and 9 months in those patients that do respond and there does not appear to be a difference in level of response between patients with relapsed and refractory disease.

In the largest case series (the PINNACLE study) it was shown that patients that responded to bortezomib lived for about 11 months longer than the average patient treated with the drug. However given the lack of control groups it is not possible to set these response rates into clinical context in terms of comparing these data to what would normally be expected to happen when alternative approaches to care are employed.
3.2 Strength of Evidence

The published evidence available to support the use of bortezomib is limited to a series of uncontrolled phase II studies involving a total of 224 patients with relapsed or refractory disease. The studies have been published in high profile medical journals and provide appropriate detail of the risks and benefits of treatment. However, as discussed above it is not possible to set these data into context without any RCTs comparing bortezomib to standard care – although it is accepted that that would be difficult, given the lack of consensus on what would constitute an appropriate control group. Randomised trials adequately powered to assess impact on patient-orientated outcomes, especially OS, are also required.

3.3 Risks

In the phase II trials reported there is clear evidence that bortezomib is associated with serious and fatal adverse events in up to 20% of patients treated. In the largest study, at least 1 drug-related adverse event (AE) occurred in 145 patients (94%), with the most common AEs being fatigue, peripheral neuropathy and gastrointestinal events. The most common grade 3 or higher AEs were peripheral neuropathy (13%), fatigue (12%) and thrombocytopenia (11%). Grade 4 or higher AEs occurred in 26 patients (17%), with the most common grade 4 AEs being thrombocytopenia (4%), sepsis and disease progression (3% each) and neutropenia (2%). 21% of patients were deemed to have experienced an adverse effect that resulted in death, was life-threatening, required hospitalisation or resulted in persistent or significant disability or incapacity. Among 12 deaths that occurred within 28 days after the last bortezomib dose, 5 were considered to be bortezomib-related (3 due to sepsis, 1 due to respiratory failure, and 1 unwitnessed death due to disease progression where relation to bortezomib could not be ruled out) [6,7].

In a second study, neurological toxicity and myalgia led to treatment discontinuation in 10 patients (34%). Five serious adverse events including 2 deaths in the first 12 patients treated were noted. All these patients had oedema or effusion at baseline and following protocol amendment to exclude patients with baseline effusions, dyspnoea and oedema no further occurrences were noted.

Careful patient selection is required to minimise these risks and in particular to ensure that the risks of treating patients with effusions, dyspnoea or oedema are taken into account. According to the SPC for bortezomib, the following adverse events occur in over 10% of patients with multiple myeloma treated with the drug: herpes zoster infections, thrombocytopenia, neutropenia, rash, anaemia, decreased appetite, peripheral neuropathy, peripheral sensory neuropathy, myalgia, paraesthesia, headache, dyspnoea, vomiting, nausea, diarrhoea, constipation, fatigue and pyrexia [5]. Many of these events were also seen in the phase II studies in patients with MCL and therefore it is assumed that the complete adverse event profile described in the SPC is also relevant in this population.

Within the SPC it is also recommended that patients with diabetes receiving oral hypoglycaemic drugs require close monitoring of their blood glucose and if necessary adjustment of their antidiabetic regimen [5]

3.4 Regulatory Status

Bortezomib is licensed in the UK and approved by NICE for the treatment of multiple myeloma, however it is not licensed for the treatment of MCL. In the US bortezomib is licensed for use in patients with MCL who have received at least one prior treatment.
3.5 Affordability

Bortezomib costs £762.38 for a 3.5mg vial (excluding VAT) [11]. Therefore to treat a patient with a body surface area of 1.7m$^2$ with 4 cycles of a regimen of 1.3mg/m$^2$ given twice weekly for 2 weeks would require 2mg of bortezomib per dose given. Assuming vial sharing is not possible, an average treatment course would therefore cost up to £12,198 (excluding VAT). No health economic studies of bortezomib for this indication have been identified.
4.0 References

6. FDA. FDA approves bortezomib (Velcade) for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Accessed via http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm094929.htm on 24/12/10
11. Haymarket Medical Media. MIMS. February 2011

5.0 Quality Assurance

5.1 Author
David Erskine, Director, London & South East Medicines Information Service.

5.2 Checker
Nicola Pocock, Senior Medicines Information Pharmacist, London & South East Medicines Information Service.

5.3 Expert Comment
6.0 Appendix

6.1 Search strategy
The following strategy was used to find the evidence contained in this report:

- Embase (1980 to December 2010): “bortezomib” and “mantle cell lymphoma with drug therapy”.
- Medline (1950 to December 2010): “bortezomib” in the title or abstract combined with “lymphoma, mantle-cell”.
- Micromedix monograph for bortezomib was scanned for relevant references on 20 December 2010.
- The Cochrane Library: “bortezomib” (20 December 2010).
- The Dynamed database was searched for relevant references on 20 December 2010.
- Citation review from all relevant studies identified.
- The ASCO website was searched for relevant abstracts and presentations.

6.2 Data selection

Reasons for excluding papers

<table>
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<th>Studies identified through Medline</th>
<th>Studies identified through Embase</th>
<th>Studies identified through other sources</th>
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<tr>
<td>n=7</td>
<td>n=8</td>
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Studies identified through more than one source removed from count n=6

Studies screened n=9

Studies excluded n=6 because:

- assessed bortezomib as part of a combination regimen (n=3)
- assessed bortezomib as a first line treatment (n=1)
- assessed bortezomib as a first line treatment and as part of a combination regimen (n=2)

Studies included n=3
6.3 Acknowledgements
Janssen-Cilag Ltd.

6.4 Declarations of Interest
None declared from all those participating in the creation of this review.

6.5 Disclaimer
This review relates solely to the medicine and clinical intervention described within the text and reflects UK practice. Should you have any doubts about whether it is relevant to a specific patient, or are unsure whether you understand it, seek appropriate professional assistance.

The contents were believed to be an accurate reflection of the medical literature at the time of preparation. However, you should always consult the literature and take account of new developments.

The authors are not responsible for the content of external websites and any links are made available solely to indicate their potential usefulness. You must use your judgement to determine the accuracy and relevance of the information they contain.