

Bortezomib for the treatment of multiple myeloma (Protocol)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	5
REFERENCES	5
APPENDICES	6
CONTRIBUTIONS OF AUTHORS	10
DECLARATIONS OF INTEREST	10
SOURCES OF SUPPORT	11

Bortezomib for the treatment of multiple myeloma

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

We will assess the effects of bortezomib treatment in comparison to other therapies, different doses, treatment administration and schedules of bortezomib, on overall survival (OS), progression-free survival (PFS), response rate (RR), health-related quality of life (HRQoL), adverse events (AE) and treatment-related death.

BACKGROUND

Description of the condition

Multiple myeloma is a bone marrow malignancy characterised by clonal proliferation of neoplastic plasma cells, monoclonal protein in the blood or urine and organ dysfunction (Palumbo 2011). An estimated 102,000 people were diagnosed with myeloma globally in 2008, accounting for approximately 1% of all cancers diagnosed and 12% of all haematological malignancies (Ferlay 2010). The median age at diagnosis is approximately 70 years (Palumbo 2011). Recent advances in treatment have led to significant improvements in relative survival rates of five and ten years, improving from 32.8% and 15% in 1998 to 2002, to 40.3% and 20.8%, respectively in 2003 and 2007 (Pulte 2011). Myeloma remains an incurable condition, however, and therefore the primary goal of treatment is to control the disease, attain sustainable remissions and optimise quality of life.

Description of the intervention

Until relatively recently, treatment for multiple myeloma consisted of either single agent or combination regimens of chemotherapy drugs such as melphalan, doxorubicin and vincristine, and the glucocorticosteroids prednisone and dexamethasone (Raab 2009). The introduction of stem cell transplantation for certain subgroups also led to further improvements in disease-free and overall survival (Raab 2009). More recently, the clinical development of targeted agents such as the immunomodulatory drugs thalidomide and lenalidomide and proteasome inhibitor treatment has considerably expanded therapeutic options for myeloma patients (Raab 2009). The first-in-class proteasome inhibitor, bortezomib, is considered a major drug treatment for multiple myeloma. A novel agent, bortezomib was approved for clinical use based on an overall response rate of 35% and a median time to progression of seven months observed in a phase II trial of patients with relapsed and refractory disease who were treated with single agent bortezomib (Richardson 2003). Subsequently, an international randomised phase III trial evaluating bortezomib versus high dose dexametha-

sone demonstrated superior response rates, improved time to progression and median overall survival of 29.8 months versus 23.7 months (Richardson 2005; Richardson 2007).

A number of trials evaluating bortezomib in combination treatment with other drugs have also been reported (Moreau 2012). Preclinical and clinical data of various combination treatments are believed to support the hypothesis that bortezomib sensitises myeloma cells to other therapies, resulting in additive or synergistic activity (Shah 2009).

While clinically effective, some myeloma patients are unable to complete bortezomib treatment due to adverse events, such as nausea, fatigue, diarrhoea, peripheral neuropathy and thrombocytopenia (Kyle 2009). Most of these conditions are predictable and manageable, but in some cases they may be life threatening and may also worsen quality of life (Bertolotti 2008). Ongoing trials investigating bortezomib in combination treatment aim to define regimens that will provide a more favourable risk-benefit profile (Palumbo 2011).

A number of new 'second generation' proteasome inhibitor agents (carfilzomib, marizomib and MLN9708), each with distinct chemical properties, have also been developed and are undergoing evaluation in clinical trials (Moreau 2012). The most clinically advanced of these agents is carfilzomib, which was approved for patients with multiple myeloma progression while on or after treatment with bortezomib and an immunomodulatory agent based on a phase II trial of patients with relapsed/refractory multiple myeloma treated with single agent carfilzomib. An overall response rate of 23.7% (95% confidence interval (CI): 18.7 to 29.4%), median response duration of 7.8 months and median overall survival of 15.6 months was observed (Siegel 2012). It is anticipated, that in addition to clinical benefits, these agents will also have a more acceptable adverse event profile compared to bortezomib, and will be clinically useful in patients with myeloma resistant to bortezomib (Chen 2011).

As these newer proteasome inhibitor agents are still being clinically evaluated, this review will focus only on bortezomib for the treatment of multiple myeloma.

How the intervention might work

Bortezomib belongs to a new generation of anti-cancer drugs that work by targeting specific cell receptors, proteins and signalling pathways, or both. Proteasomes are 26S ATP-dependent protein complexes within the ubiquitin-proteasome pathway present in all cells and responsible for regulating the majority of intracellular proteins (Moreau 2012). Cancer cells generally have higher levels of proteasome activity compared with normal cells, and are therefore more sensitive to proteasome inhibition (Moreau 2012) leading to disruption of cellular growth and survival, de-regulating signalling pathways within the myeloma cell and its interaction with the bone marrow microenvironment (Chen 2011).

Bortezomib is a dipeptidyl boronic acid, reversible proteasome inhibitor that primarily targets the chymotrypsin-like and caspase-like active sites of the proteasome, with minimal effect on trypsin-like activity (Lawasut 2012). Through proteasome inhibition, bortezomib acts via multiple mechanisms to suppress tumour survival pathways and to arrest tumour growth, tumour spread, and angiogenesis (Moreau 2012).

Why it is important to do this review

Bortezomib is commonly used for the treatment of multiple myeloma at all stages of the disease and in all major myeloma treatment settings. A systematic review is important to evaluate the accumulated clinical evidence and effects of bortezomib treatment.

Randomised controlled trials (RCTs) investigating bortezomib treatment have demonstrated statistically significant improvements in response rates and event-free survival, however these are primarily surrogate outcome measures for overall survival. A systematic review and meta-analysis of relevant and similar trials will therefore analyse overall survival (OS), while analysis of combined data from similar RCTs will also enable greater precision in making an unbiased estimation of the effects of treatment.

OBJECTIVES

We will assess the effects of bortezomib treatment in comparison to other therapies, different doses, treatment administration and schedules of bortezomib, on overall survival (OS), progression-free survival (PFS), response rate (RR), health-related quality of life (HRQoL), adverse events (AE) and treatment-related death.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients of any age, gender or ethnic origin and with any diagnosis of multiple myeloma (according to either the Durie-Salmon staging system or International Staging System (ISS) (Kyle 2009). Newly diagnosed patients and relapsed/refractory patients will be analysed separately as subgroups.

Types of interventions

RCTs that investigate the following comparisons will be included:

- Bortezomib versus no bortezomib (with same background therapy in each arm);
- Bortezomib versus no bortezomib (with different background therapy in each arm);
- Bortezomib versus other agent(s);
- Bortezomib dose comparisons and comparisons of different treatment administrations and schedules.

Types of outcome measures

Primary outcomes

The primary outcomes for this review are:

1. Overall survival (OS): time from date of randomisation to date of death (from any cause).
2. Progression-free survival (PFS): time from date of randomisation to date of progression or death (from any cause).

Secondary outcomes

The secondary outcomes for this review are:

1. Overall response rate (ORR), complete response rate (CRR) and partial response rate (PRR): the proportion of patients with overall, complete or partial response.
2. Time to progression (TTP): time from randomisation to date of progression. TTP may also be referred to as PFS. Where defined differently, TTP will be analysed separately.
3. Treatment-free interval (TFI): time from randomisation to date of initiation of next treatment regimen or similar (we will allow for different definitions across trials as long as the trial-defined outcome measures the described construct).
4. Treatment-related death: death due to treatment-related toxicity and not disease progression.
5. Adverse events (AE): as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).
6. Health-related quality of life (HRQoL): as defined by the validated quality of life measures or instruments used in each trial.

Search methods for identification of studies

Electronic searches

We will perform a systematic search of the following electronic databases, using comprehensive search strategies incorporating key search terms, from the year 2000 (when clinical studies of bortezomib in multiple myeloma commenced) to present:

- MEDLINE (Ovid) ([Appendix 1](#))
- The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*) ([Appendix 2](#))
- EMBASE (Elsevier) ([Appendix 3](#))

Ongoing and recently completed trials will be identified by searching national and international clinical trials registries. We will search the International Standard Randomised Controlled Trial Number (ISRCTN) register and the National Institute of Health (NIH) Register for ongoing trials: <http://www.controlled-trials.com> and also <http://clinicaltrials.gov>.

Language restrictions will not be imposed. Searches will be updated every two years.

The search strategy will include the following terms:

- Disease specific terms: Myelom*, Multiple Myeloma (using free text and/or MeSH terms where appropriate).
- Intervention specific terms: proteasome inhibitors, bortezomib, velcade (trade name for bortezomib), (using free text and/or MeSH terms where appropriate). Future updates to the review will include searches for new proteasome inhibitors.
- The Cochrane Highly Sensitive Search Strategy ([Lefebvre 2011](#)) will be used for identifying randomised trials in MEDLINE to identify RCTs. Search strategies will be tailored to the other databases.

Searching other resources

Using the terms 'myeloma', 'proteasome inhibitor' 'bortezomib', 'velcade' (all words anywhere in abstract), we will search the following conference proceedings both electronically and manually:

- American Society of Hematology
- American Society of Clinical Oncology
- European Hematology Association
- European Society of Medical Oncology

We will search conference proceedings in the last five years (from 2008 to present). Other appropriate restrictions such as publication status (published or unpublished) will also be considered.

We will manually search reference lists of included studies and also national and international myeloma treatment guidelines.

We will contact principal investigators if relevant data have not yet been published.

All references will be managed using the reference manager software Endnote X6 ([EndNote 2012](#)).

Data collection and analysis

Selection of studies

Two review authors will independently screen the abstracts of retrieved articles for eligibility according to pre-determined criteria (Criteria for considering studies for this review) and will resolve

any inconsistencies through discussion with a third review author. If a decision cannot be made on the basis of the abstract, a full-text article of the study in question will be retrieved and assessed independently by two authors to make the final decision regarding study eligibility. The number of studies identified, included and excluded studies and reasons for inclusion/exclusion will be documented according to PRISMA guidelines (Moher 2009).

Data extraction and management

For each eligible trial, two review authors will independently extract data using a data extraction form, which will include the following:

- Trial identification: title, authors, journal name, publication date, countries, sponsor, funding
- Trial design: type of trial design, treatment setting, number of arms, number of centres, sample size and rationale, randomisation method, allocation concealment, blinding, stratification factors, analysis methods, pre-specified alpha error, beta error, effect size, analysis types (e.g. intention-to-treat (ITT), per protocol)
 - Trial comparisons: Experimental and control arms, number of courses of treatment, doses, timing and route of administration, other treatments received
 - Trial participants: age (median/mean and age range), sex, stage (Durie-Salmon, International or both), inclusion criteria, exclusion criteria
 - Trial progress and follow up: duration of accrual and follow-up periods, number of participants per arm, number of participants lost to follow up, and excluded from analysis
- Outcomes:
 - i) Overall survival
 - ii) Progression-free survival
 - iii) Overall response rate; complete response rate; partial response rate
 - iv) Time to progression
 - v) Treatment-free interval
 - vi) Treatment-related death
 - vii) Adverse events
 - viii) Health-related quality of life

We will extract data manually using a standardised data extraction form and then enter the data into RevMan for analysis. A second review author will check the entered data for accuracy.

For studies with more than one publication, we will extract data from all publications as per recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), however we will consider the final or updated version of each trial as the primary source. If there are two or more detailed publications relating to the same study e.g. reporting different periods of follow-up, data extraction will be performed separately for each article and data collated afterwards.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of included studies according to guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Types of bias to be considered include: selection bias, performance bias, detection bias, attrition bias and reporting bias. If adequate information is missing or not clear, additional information will be sought from the principal investigator of the trial. A summary of the risk of bias for each included trial will be presented using the Cochrane 'Risk of bias' tool.

Measures of treatment effect

We will extract hazard ratios (HR) and 95% confidence intervals (CI) for overall survival and progression-free survival from included studies and calculate the overall odds ratio (OR) and 95% CIs for combined studies using methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). In the case of continuous data such as health-related quality of life data, a variety of quality of life instruments may be reported. To allow meta-analysis of these together, we shall convert all results into standardised mean differences (SMDs) prior to meta-analysis.

Unit of analysis issues

Unit of analysis issues are not anticipated.

Dealing with missing data

We will deal with missing data according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will classify data as either 'missing at random' or 'not missing at random'. In the case of data considered to be missing at random we will analyse the available data. For data considered to be not missing at random, we will contact the trial authors for further information. If data are still not available, we will state the assumptions made for the analysis. Logrank statistics that are not available from the published articles will be estimated. Where possible we will use previously reported methods (Parmar 1998; Tierney 2007).

Assessment of heterogeneity

The presence of statistical heterogeneity of included studies will be assessed using the Chi² test at a significance level of $P < 0.10$ (Deeks 2011). The I² statistic will be used to quantify heterogeneity according to the following thresholds described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011):

- 0% to 40% (heterogeneity possibly not important)
- 30% to 60% (may represent moderate heterogeneity)
- 50% to 90% (may represent substantial heterogeneity)

- 75% to 100% (considerable heterogeneity).

If heterogeneity is identified, we will conduct subgroup analyses as outlined in the section Subgroup analysis and investigation of heterogeneity.

Assessment of reporting biases

To assess the likelihood of reporting bias, funnel plots will be produced according to methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). A minimum of ten trials in the meta-analysis will be required.

Data synthesis

We will use the latest version of the software package RevMan 5 (RevMan 5.2) to enter data and combine results from included studies.

Standard statistical methods for the meta-analysis of dichotomous, time-to-event and continuous variables will be used. If time-to-event outcomes are not available, we will calculate summary estimates. Fixed-effect methods for meta-analysis will be utilised. We will produce a 'Summary of findings' table using GRADE software (Schünemann 2011) and we will summarise the results for OS, PFS, RR, TTP, Treatment-related death and AEs. We will pool results where the data are sufficiently similar to be combined. We will perform a meta-analysis for each comparison.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be considered for the following variables:

Age

- 18 to 65 years
- ≥ 65 years

Disease setting

- Newly diagnosed:

- Transplant eligible
 - Transplant ineligible
- Relapsed disease and/or relapsed/refractory disease

Therapy setting

- Front-line therapy (transplant ineligible)
- Induction therapy (pre-transplant)
- Consolidation therapy (post-transplant)
- Maintenance therapy (post-transplant and consolidation)
- Relapse therapy and/or relapse/refractory therapy

Tests for heterogeneity will be used to investigate whether the treatment effect is greater in some subgroups than in others.

Sensitivity analysis

We will use the 'Risk of bias' assessment tool as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), and classify trials at low, medium or high risk of bias.

We will conduct a sensitivity analysis excluding trials considered to be medium or high risk of bias.

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* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE search strategy

ID	Search
1	exp MULTIPLE MYELOMA/
2	myelom\$.tw,kf,ot.
3	exp PLASMACYTOMA/
4	plasm?cytom\$.tw,kf,ot.
5	plasmozytom\$.tw,kf,ot.
6	plasm\$ cell myelom\$.tw,kf,ot.
7	myelomatosis.tw,kf,ot.
8	LEUKEMIA, PLASMA CELL/
9	(plasma\$ adj3 neoplas\$).tw,kf,ot.
10	kahler.tw,kf,ot.
11	or/1-10
12	(proteasom\$ adj2 inhibitor\$).tw,kf,ot.
13	bortezomib\$.tw,kf,ot,nm.
14	proscript\$.tw,kf,nm,ot.
15	(PS-341 or PS341).tw,kf,nm,ot.
16	(LDP-341 or LDP341 or MLN-341 or MLN341 or MG-341 or MG341).tw,kf,nm,ot
17	velcad\$.tw,kf,ot.
18	or/12-17
19	11 and 18
20	randomized controlled trial.pt.
21	controlled clinical trial.pt.

(Continued)

22	randomi?ed.ab.
23	placebo.ab.
24	clinical trials as topic.sh.
25	randomly.ab.
26	trial.ti.
27	or/20-26
28	humans.sh.
29	27 and 28
30	19 and 29

Appendix 2. Cochrane Central Register of Controlled Trials search strategy

ID	Search
1	MeSH descriptor: [Multiple Myeloma] explode all trees
2	myelom*
3	MeSH descriptor: [Plasmacytoma] explode all trees
4	plasm*cytom*
5	plasmozytom*
6	plasm* cell myelom*
7	myelomatosis
8	MeSH descriptor: [Leukemia, Plasma Cell] explode all trees
9	(plasma* near/3 neoplas*)
10	kahler*
11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

(Continued)

12	(proteasom* near/2 inhibitor*)
13	bortezomib*
14	proscript*
15	(PS-341* or PS341*)
16	(LDP-341* or LDP341* or MLN-341* or MLN341* or MG-341* or MG341*)
17	velcad*
18	#12 or #13 or #14 or #15 or #16 or #17
19	#11 and #18

Appendix 3. EMBASE search strategy

ID	Search
1	randomization/exp
2	(factorial AND design)
3	(crossover AND procedure/exp)
4	placebo/exp
5	(double AND blind/exp AND procedure/exp)
6	(single AND blind/exp AND procedure/exp)
7	assign*
8	allocat*
9	volunteer*
10	(randomized AND controlled AND trial)
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	(multiple AND myeloma/exp)
13	myelom*

(Continued)

14	plasmacytoma/exp
15	(plasm* AND cell/exp AND myelom*)
16	(plasma/exp AND cell/exp AND leukemia/exp)
17	(plasma* NEAR/3 neoplas*)
18	12 or 13 or 14 or 15 or 16 or 17
19	(proteasome/exp AND inhibitor)
20	bortezomib/exp
21	velcade/exp
22	velcad*
23	PS 341/exp OR PS341/exp
24	LDP 341/exp OR LDP341/exp or MLN 341/exp OR MLN341/exp OR MG 341/exp OR MG341/exp
25	19 or 20 or 21 or 22 or 23 or 24
26	11 and 18 and 25

CONTRIBUTIONS OF AUTHORS

Kathleen Scott: drafting the protocol, searching for trials, trial selection, data extraction, statistical analysis, data presentation and drafting the review.

Patrick J Hayden: provision of clinical expertise and interpretation of trial data, input to drafting the protocol and review.

Keith Wheatley: advice and expertise on statistical methods and Cochrane review methodology, statistical analysis and data presentation, input to drafting the protocol and review.

Andrew Howman: advice and expertise on statistical methods and Cochrane review methodology, searching for trials, selection of studies, data extraction, statistical analysis and data presentation, input to drafting the protocol and review.

Imelda Coyne: Cochrane fellowship supervisor to Kathleen Scott, advice and guidance on Cochrane review methodology, input to drafting the protocol and review.

DECLARATIONS OF INTEREST

None known.

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