

National Horizon Scanning Centre

Bortezomib for relapsed and/or refractory follicular non-Hodgkins lymphoma

August 2008



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Bortezomib for relapsed and/or refractory follicular non-Hodgkins lymphoma

Target group

Follicular non-Hodgkin's lymphoma (NHL)-relapse of and/or refractory in combination with rituximab.

Technology description

Bortezomib (Velcade) is a first-in-class proteasome inhibitor that inhibits the growth and metastasis of tumours by reducing the activity of the chymotrypsin-like 26S proteasome. It is believed that one of the major effects of this inhibition leads to alterations in regulatory proteins. This in turn leads to cell cycle arrest and cell death.

In the current phase III clinical trial bortezomib is administered intravenously (IV) at a dose of 1.6mg/m² on days 1, 8, 15, and 22 of a 35 day cycle for 5 cycles. It is given in combination with 4 doses of rituximab at 375mg/m² once a week on days 1, 8, 15, and 22 for cycle 1 and on day 1 of cycles 2-5.

Bortezomib has EU marketing authorisation for relapsed or refractory multiple myeloma and license application has been submitted for bortezomib for first line treatment of multiple myeloma.

Innovation and/or advantages

The bortezomib and rituximab combination may be more efficacious than rituximab alone.

Developer

Janssen-Cilag Ltd.

Availability, launch or marketing dates, and licensing plans:

In phase III clinical trials

NHS or Government priority area:

This topic relates to the National Service Framework for Cancer (2000).

Relevant guidance

- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma. 2007¹.
- NICE technology appraisal. Rituximab for the treatment of follicular lymphoma. 2006².
- NICE technology appraisal. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non Hodgkin's lymphoma (review of technology appraisal guidance 37). 2008³.
- NICE technology appraisal. Non Hodgkin's lymphoma rituximab. 2003⁴.
- NICE cancer service guideline. Haemato-oncology. 2003⁵.
- European Society for Medical Oncology. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow up. 2008.⁶

Clinical need and burden of disease

In 2005 there were 9,106 new cases of NHL in England and Wales, and in 2006 there were 3,982 deaths attributed to NHL in England and Wales⁷. About 1 in 5 patients diagnosed with NHL have follicular NHL, approximately 1,768⁸ people in England and Wales. Disease remissions characteristically become shorter with each successive treatment.

Existing comparators and treatments

There are several management options that are used in sequence:

- Watching and waiting whilst the disease remains stable and the patient symptom free.
- Single agent chemotherapy such as, chlorambucil with or without steroids, or fludarabine or rituximab.
- Combination chemotherapy such as, CHOP with or without additional agents such as fludarabine or rituximab (R-CHOP).
- Other therapies such as, cladribine and interferon.

Efficacy and safety

Trial code, name, phase	Phase 2 study of bortezomib weekly or twice weekly plus rituximab in patients with follicular (FL) or marginal zone (MZL) lymphoma.	NCT00312845: bortezomib plus rituximab or rituximab; phase III ⁹ .
Sponsor	Millennium Pharmaceuticals	Millennium Pharmaceuticals
Status	Abstract ¹⁰	Ongoing
Location	USA	Europe (inc. UK), Asia, North America, South America, Australia, India, Israel, New Zealand, Russia, South Africa, Ukraine.
Design	Randomised, open-label, dose comparison.	Randomised, open-label, active control.
Participants in trial	n=81; adults; relapsed/refractory follicular NHL. Randomised to bortezomib 1.3mg/m ² on days 1, 4, 8, 11 of a 21 day cycle (5 cycles) plus 375mg/m ² rituximab weekly for 4 weeks from day 1 of cycle 1; <u>or</u> bortezomib 1.6 mg/m ² on days 1, 4, 8, 11 of a 21 day cycle (5 cycles) plus 375 mg/m ² rituximab weekly for 4 weeks from day 1 of cycle 1.	n=670; adults; relapsed/refractory follicular NHL. Randomized to 1.6mg/m ² bortezomib for on days 1, 8, 15, and 22 of a 35 day cycle (5 cycles) plus 375mg/m ² rituximab on days 1, 8, 15, and 22 of cycle 1, day 1 of cycles 2-5; <u>or</u> 375 mg/m ² rituximab on days 1, 8, 15, and 22 of cycle 1 and day 1 of cycles 2-5.
Follow-up	4-7 months	47 months
Primary outcome	Response	Progression free survival.
Secondary outcomes	Time to progression; time to first response; duration of response.	Overall response rate, complete response; duration of response; time to progression; overall survival and 1 year survival rate.
Key results	A similar response and time to progression was found between the two treatment regimens. The 1.6mg/m ² regimen had fewer grade 3 or greater adverse events 35% vs 54% for	N/A

	1.3mg/m ² regimen.	
Expected reporting date	N/A	Expected completion date March 2010.
Adverse effects	Fatigue, GI events, and peripheral neuropathy, most common grade 3> adverse effects included neutropenia, thrombocytopenia and peripheral neuropathy along with GI events.	N/A

Estimated cost and cost impact

The cost of Bortezomib at the regimen used in the phase III clinical trial is £15,249 for 20 doses over 35 day cycle (5 cycles). The rituximab treatment will cost £9,779 for 8 doses over the 35 day cycles (5 cycles). This gives a combined cost of £25,276 assuming some wastage^a.

Potential or intended impact – speculative

Patients

- Reduced morbidity
- Quicker, earlier or more accurate diagnosis or identification of disease
- Reduced mortality or increased survival
- Other:
- Improved quality of life for patients and/or carers
- None identified

Services

- Increased use: intravenous administration and monitoring.
- Decreased use
- Service reorganisation required
- Other:
- Staff or training required
- None identified

Costs

- Increased unit cost compared to alternative
- New costs: combination drug regimen.
- Increased costs: more patients coming for treatment
- Savings:
- Increased costs: capital investment needed
- Other:

References

- ¹ National Institute for Health and Clinical Excellence. Bortezomib monotherapy for relapsed multiple myeloma. October 2007.
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- ⁷ Cancer Research UK. Non-Hodgkin Lymphoma: Cancer stats information. Available at: <http://info.cancerresearchuk.org/cancerstats/types/nhl/> (Accessed August 2008).
- ⁸ Cancer Research UK. Statistics and outlook for non-Hodgkin's lymphoma. Available at:

^a Average surface area 1.7 m², Costs from BNF 55March 2008.

- <http://www.cancerhelp.org.uk/help/default.asp?page=3961> (Accessed August 2008).
- ⁹ Clinical Trials. Study of VELCADE and rituximab in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. Available at:
<http://www.clinicaltrials.gov/ct2/show/NCT00312845?term=NCT00312845&rank=1> (Accessed August 2008).
- ¹⁰ De Vos S, Dakhil S R, McLaughlin P, et al. Phase 2 study of bortezomib weekly or twice weekly plus rituximab in patients with follicular (FL) or marginal (MZL) lymphoma: Final results. Blood (ASH Annual Meeting) 2006. 108: abstract 694.

The National Institute for Health Research National Horizon Scanning Centre Research Programme is funded by the Department of Health.
The views expressed in this publication are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health

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