NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplantation

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation for the treatment of multiple myeloma.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells produce large quantities of an abnormal antibody that is not able to fight infection. Myeloma cells build up in the bone marrow and interfere with the production of normal blood cells, which are responsible for blood clotting, carrying oxygen around the body and fighting infections. They also have the ability to spread throughout the bone marrow and into the hard outer casing of the bone. The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

About 4300 people were diagnosed with multiple myeloma in England and Wales in 2009. It is most frequently diagnosed in people over 60 years and it is slightly more common in men than in women. Average survival for people with multiple myeloma is between 4 and 6 years, but can be up to 20 years. In 2008, approximately 820 autologous stem cell transplants were conducted in the UK for people with multiple myeloma.

The aim of multiple myleomoa therapy is to achieve stable disease for as long as possible, thereby prolonging survival and maximising quality of life. First-line treatment with high-dose chemotherapy (usually melphalan) followed by stem cell transplantation may be considered for people in good general health. Induction therapy is given before high-dose chemotherapy with an aim to induce high remission rates rapidly and to preserve haemopoietic stem cell function to ensure successful mobilisation of peripheral blood stem cells. After induction therapy, haematopoietic stem cells are harvested and these stem cells are reintroduced to the patient's blood (autologous stem cell transplants) following chemotherapy. This enables the bone marrow to recover quickly, so it can produce healthy blood cells again.

The most commonly used induction regimen in UK clinical practice is thalidomide in combination with cyclophosphamide and dexamethasone (CTD), however other regimens such as thalidomide in combination with dexamethasone and doxorubicin (TAD), bortezomib in combination with dexamethasone, and bortezomib in combination with doxorubicin and dexamethasone (PAD) are also used. Vincristine, doxorubicin and dexamethasone (VAD) is not used in UK clinical practice. Decisions regarding the most appropriate induction treatment for individual patients will require the assessment of a number of factors such as renal function, thrombotic risk and pre-existing neuropathy. NICE has not made any recommendations for induction therapies for in the treatment of multiple myeloma. However for people with multiple myeloma for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate, NICE has recommended thalidomide in combination with an alkylating agent and a corticosteroid and if the person is unable to tolerate or has contraindications to thalidomide, bortezomib in combination with an alkylating agent (Technology Appraisal No. 228).

The technology

Bortezomib (Velcade, Janssen) is an anticancer drug that works by reversible proteasome inhibition. By inhibiting proteasomes (multi-enzyme complexes present in all cells), bortezomib interferes with the cell cycle leading to cell death. It is administered by intravenous infusion.

Bortezomib does not currently have a UK marketing authorisation for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation in people with multiple myeloma. It has been studied in clinical trials as induction therapy in combination with thalidomide and dexamethasone compared with thalidomide and dexamethasone and compared with a combination of alternating cycles of vincristine, carmustine melphalan, cyclophosphamide and prednisone (VBMCP), and vincristine, doxorubicin and dexamethasone (VAD) and bortezomib. Bortezomib has also been studied as induction therapy in combination with doxorubicin and dexamethasone, compared with combination therapy of vincristine, doxorubicin and dexamethasone (VAN). It has also been studied in combination with dexamethasone compared with combination therapy of vincristine, doxorubicin and dexamethasone (VAD). In all trials, participants receive high dose chemotherapy (namely melphalan) and autologous stem cell transplantation after induction therapy.

Bortezomib has a UK marketing authorisation for use in combination with chemotherapy (melphalan and prednisone) for the treatment of people with multiple myeloma who have not received prior therapy and who are not eligible for high-dose chemotherapy with bone marrow transplantation. It also has a UK marketing authorisation as monotherapy for the treatment of multiple myeloma that has progressed despite the use of at least one prior therapy and where the individual has already undergone or is unsuitable for bone marrow transplantation.

Interventions	Bortezomib in combination with other chemotherapy regimens for induction therapy.
Populations	Adults with newly diagnosed multiple myeloma for whom induction therapy is considered appropriate prior to high dose chemotherapy and autologous stem cell transplantation
Comparators	Chemotherapy regimens containing thalidomide.
Outcomes	The outcome measures to be considered include: • progression-free survival • response rate • proportion of people undergoing high dose chemotherapy and autologous stem cell transplantation • overall survival • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, a subgroup of people with myeloma cell genetic abnormalities should be considered. Guidance will only be issued in accordance with the marketing authorisation
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 228, July 2011, 'Bortezomib and thalidomide for the first line treatment of multiple myeloma'. Expected review date July 2014. Suspended Technology Appraisal, 'Lenalidomide for the

	treatment of newly diagnosed multiple myeloma'. Suspended Technology Appraisal, 'Lenalidomide for the maintenance treatment of multiple myeloma after autologous stem cell transplantation'. Related Guidelines: Cancer Service Guidance, October 2003, Improving Outcomes in Haematological Cancer.