

Statement from the Regional HTA Centre of the Region Västra Götaland in Sweden

Treatment in relapsed multiple myeloma; bortezomib, lenalidomide, thalidomide

The Regional Health Technology Assessment Centre (HTA-centrum) of the Western Region in Sweden (Region Västra Götaland, VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

The Council of Internal Medicine in the Western region of Sweden requested the present HTA.

A working group under the chairmanship of associate professor Per-Ola Andersson, MD, PhD, Department of Haematology, Sahlgrenska University Hospital, Göteborg, Sweden, produced the HTA report. The other members of the working group were Cecilie Blimark, MD, and Ljupco Veskovski, MD, both at the Department of Haematology, Sahlgrenska University Hospital, Göteborg, Sweden

The participants from the HTA centre were Annika Strandell, MD, PhD, Ola Samuelsson MD, PhD, Therese Svanberg, HTA-librarian, and Ann Liljegren, librarian.

Anders Larsson, MD, PhD, Department of Neurology, Southern Älvsborg Hospital, Borås, Sweden, and Karin Manhem, MD, PhD, Department of Internal Medicine Sahlgrenska University Hospital, Göteborg, Sweden have critically appraised the report .

The project lasted during the time period 2010-02-10-- 2010-10-13.
The literature search covered publications up to March 2010.

Question at issue:

Does treatment with bortezomib (Velcade®), lenalidomide (Revlimid®) or thalidomide (Thalidomide Celegene®) prolong survival in comparison with conventional chemotherapy in patients with relapsed multiple myeloma?

PICO: (Patient, Intervention, Comparison, Outcome)

P= Adult patients with multiple myeloma that have relapsed after successful induction therapy (stem cell transplantation; chemotherapy; chemotherapy + thalidomide)

I = Bortezomib (Velcade®), lenalidomide (Revlimid®), thalidomide (Thalidomide Celegene®) with or without corticosteroids

C= Monotherapy or combined therapy with chemotherapy, corticosteroids, or stem cell transplantation

O= Primary outcome variable: Overall survival; OS
Secondary outcome variables: Progression-free survival; PFS
Time to progression; TTP
Complete response; CR
Partial response; PR
Quality of life
Adverse effects/complications

SUMMARY OF THE HEALTH TECHNOLOGY ASSESSMENT

Multiple myeloma is an incurable plasma cells malignancy. The choice of initial therapy depends on the biological age of the patient and includes chemotherapy, corticosteroids and immunomodulating agents. Most patients below 65 years of age are thereafter treated with stem cell transplantation. However, almost all patients relapse and become refractory to conventional therapy. Presently, there are no consensus guidelines how to treat relapsed or refractory multiple myeloma. New types of immunomodulatory drugs, such as bortezomib, lenalidomide and thalidomide, are nowadays frequently being used to treat these patients. Thalidomide and lenalidomide inhibit the growth of the myeloma cells by immunomodulatory anti-inflammatory and anti-neoplastic activities. Both drugs can be administered orally. Bortezomib inhibit many proteins (known as proteasomes) that cancer cells need to survive and multiply. It has been shown to have anti-tumor activity in B cell malignancies. It is administered intravenously.

Level of evidence

The systematic literature search identified ten publications of controlled studies of which three randomised, controlled trials (RCTs) and one non-randomised, controlled cohort study were included for grading of evidence. In two of the RCTs lenalidomide was compared with conventional therapy, and in a third RCT bortezomib was compared with conventional treatment in patients with relapsed myeloma. The non-randomised cohort study compared thalidomide with conventional therapy. These studies were of moderate scientific quality. Two small cohort studies of low quality did not contribute to the overall estimation of effect and grading of evidence.

Adverse effects and complications have been reported in 18 case series.

Primary outcome variable**Overall survival:**

Bortezomib. The median overall survival was prolonged by 6 months in bortezomib-treated patients in comparison with dexamethasone-treated patients. The 1-year survival rate increased with 14 % (95 % CI 7-21), (80% vs. 66%). The level of evidence is low according to the GRADE system (GRADE ⊕⊕).

Lenalidomide prolonged the median overall survival by 9 months (GRADE ⊕⊕).

Thalidomid. The 3-year survival rate increased with 34% (95% CI 19-49), in thalidomide-treated patients in comparison to dexamethasone-treated patients (60% vs. 26%).

The level of evidence is very low according to the GRADE system (GRADE ⊕).

Lenalidomide and thalidomide are drugs with similar type of actions. When viewed together they have a positive effect on overall survival (GRADE ⊕⊕).

Secondary outcome variables

Time to progression (TTP) and progression-free survival (PFS): The median TTP was prolonged by 3 months in the bortezomib-treated patients and by 6 months in the lenalidomide-treated patients (GRADE ⊕⊕⊕). The median PFS was prolonged by 6 months in the thalidomide-treated patients in the subgroup of myeloma patients which was treated for their first relapse (GRADE ⊕), while no significant effect was observed in the patients with more than one relapse of the disease.

Complete and partial response: The response rates, measured as M protein in serum and urine, were higher in both the bortezomib and the lenalidomide treated patients than in those treated with dexamethasone (GRADE ⊕⊕⊕).

Quality of life: Only one of the RCTs evaluated the effects on quality of life. Positive effects were reported in bortezomib-treated compared to the dexamethasone-treated patients. However, the level of evidence is very low according to the GRADE system (GRADE ⊕).

Risks

Adverse effects are common for all three drugs and can be serious. The treatment-related mortality has been reported to be about 2 % for both lenalidomide and bortezomib. Bortezomib can cause neuropathy and thrombocytopenia. Lenalidomide can be toxic to the bone marrow and increase the risk of infection. Thalidomide can cause peripheral neuropathy and thrombotic complications.

Ethical aspects

The time to relapse and the overall survival may be prolonged by treatment with these immunomodulatory drugs. However, these effects should be considered in the light of high costs (see below) and possibly negatively affected quality of life due to serious adverse effects. The high cost of treatment may lead to reduced treatment possibilities for other patient categories.

Economical aspects

The direct cost of drugs for conventional chemotherapy is estimated to be 160 - 555 Euros per patient and relapse. The same kind of calculations for bortezomib, lenalidomide and thalidomide resulted in an estimated cost of 31 000 Euros, 45 000 – 55 000 Euros, and 10 000 – 19 000 Euros, respectively. These estimations are associated with a relatively high degree of uncertainty.

Concluding remarks

The treatment of patients with relapsed multiple myeloma with bortezomib, lenalidomid or talidomide can prolong overall survival (6-9 months) and the time to progression to some extent, and result in a better tumour cell response in comparison to conventional corticosteroid therapy. The level of evidence is low with regard to survival (GRADE ⊕⊕) and moderate with regard to tumour cell response (GRADE ⊕⊕⊕).

Adverse effects are common and can be serious.

The cost of treatment is high.

On behalf of HTA-centrum Göteborg, Sweden 2011-01-26

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