

Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Brentuximab for Hodgkin lymphoma

Product: Brentuximab (Adcetris[®])

Class of Drugs: anti-CD30 monoclonal antibody-drug conjugate

Reason for Use: Hodgkin lymphoma

Manufacturer: Seattle Genetics

Date of Review: September 11, 2013

CED Recommendation

The CED recommended brentuximab (Adcetris[®]) not be funded for the treatment of Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior chemotherapy regimens in patients who are not ASCT candidates. The CED noted that the clinical benefit of this therapy was uncertain based on the submitted evidence and the drug was not cost-effective. The CED acknowledged that patients in this clinical setting are very ill and have few treatment options.

Executive Officer Decision*

Taking into consideration the CED's recommendation and based on an agreement with manufacturer to help address concerns raised by the CED, the Executive Officer decided to fund brentuximab (Adcetris[®]) for the treatment of Hodgkin lymphoma (HL) according to specific criteria.

Funding Status*

Funded through Cancer Care Ontario's New Drug Funding Program according to specific criteria.

* This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.

Highlights of Recommendation:

- The SG035-0003 study enrolled patients with Hodgkin lymphoma (HL) who had relapsed after, or did not respond to, high-dose chemotherapy and autologous stem cell transplant (ASCT). The study showed that brentuximab was associated with a 75% objective response rate and a 34% complete response rate. (*Complete response means disappearance of all evidence of disease and objective response means either a partial or complete response.*)
- The study results appeared very favourable considering that these patients had previously received other treatments and had limited options remaining. Since study SG0035-0003 was a non-comparative single-arm trial, it provided no evidence on the efficacy or safety of brentuximab compared to alternative treatments.
- Study SG035-0003 did not include patients who were not candidates for ASCT and who had failed at least two prior therapies. Therefore, there was insufficient evidence to determine whether brentuximab provided clinical benefit in this particular patient population.
- Quality of life (QOL) data were not measured in the study, so it was not clear whether treatment with brentuximab improved or maintained QOL.
- The safety profile of brentuximab appeared reasonable and manageable for patients in this treatment setting.
- Brentuximab costs \$4,840 per 50mg vial. At the recommended dose of 1.8mg/kg, the average cost per 28-day course is \$16,262. Based on economic analyses conducted by the manufacturer and pCODR, brentuximab was not considered cost-effective.
- Overall, the CED noted that patients with HL who relapse after, or do not respond to ASCT or chemotherapy, or who are not candidates for ASCT, are very ill and have few treatment options. Since study SG035-0003 did not include patients who were not candidates for ASCT and who had failed at least two prior therapies, there was insufficient clinical evidence to determine whether brentuximab treatment would provide a clinical benefit in this patient group. Although the study showed that a substantial proportion of patients experienced a complete and lasting response, the lack of any comparative data made it difficult to assess the clinical benefit and safety of brentuximab. Brentuximab was not cost-effective.

Background:

Hodgkin lymphoma (HL) is an uncommon disease typically seen in young adults and those over the age of 60 years. HL accounts for approximately 8-10% of all diagnoses of lymphoma. There are approximately 900 new cases of HL in Canada each year and approximately 160 Canadians will die annually from this disease.

Approximately two thirds of patients with HL have localized disease (stage I and II), and are generally treated with combination chemotherapy and radiation. Those who present with advanced disease (stage III and IV) and those who present with constitutional (“B”) symptoms are usually managed with combination chemotherapy alone. Despite the excellent complete remission rates with modern chemotherapy approaches, 10-15% of patients with early disease and 30% of those with advanced disease experience relapse.

Patients who fail initial treatment are usually candidates for second-line chemotherapy followed by autologous stem cell transplantation (ASCT). Approximately 50% of those undergoing ASCT

will be alive and relapse-free five years after treatment and are generally considered cured. However, some people are not suitable candidates for ASCT, and some receiving ASCT still experience disease progression. For these patients, options for additional treatment are very limited and prognosis is poor. The median survival following relapse after ASCT is approximately 2 years or less.

Detailed Discussions:

- For this evaluation, the CED took into consideration:
 - Findings from the pan-Canadian Oncology Drug Review (pCODR) and the recommendation of the pCODR Expert Review Committee.
 - Information in the manufacturer's submission.
 - A patient group submission to pCODR.
 - Feedback from Cancer Care Ontario's Hematology Disease Site Group.
- The CED evaluated one non-randomized, single arm, phase II clinical trial, the SG035-0003 study.
- The primary endpoint of this study was objective response rate (ORR), with complete response rates (CRR) and duration of response evaluated as secondary outcomes.
- ORR was 75% (95% CI: 64.9%-82.6%), while the CRR was 34% (95% CI: 25.2%-44.4%). The median duration of ORR was 6.7 months (95% CI: 3.6-14.8 months) and the median duration of CRR was 20.5 months (95% CI: 10.8 to not estimable). These results were considered impressive for this group of heavily pre-treated patients with no effective alternative treatment options.
- Although the results of Study SG035-0003 demonstrated that there was a clinical benefit associated with brentuximab, the CED was concerned with the design of the study. As Study SG035-0003 was a non-comparative single arm trial, it provided no comparative evidence regarding the efficacy or safety of brentuximab in relation to any other treatments that may be used in this clinical setting. In addition, the level of evidence provided by this study was not considered to be as robust as the type of evidence typically seen and evaluated by the CED.
- Although the manufacturer's funding request for brentuximab was for HL patients after failure of ASCT and after failure of at least two prior therapies in patients who are not candidates for ASCT, the SG035-0003 study did not include patients who were not candidates for ASCT and who had failed at least two prior therapies. Therefore, there was insufficient evidence to determine whether brentuximab would provide a clinical benefit in this particular patient population.
- Quality of life (QOL) data were not measured in study SG035-0003.
- The most common grade 3 or 4 adverse events associated with brentuximab included neutropenia, peripheral sensory neuropathy, fatigue, pyrexia, diarrhea, and peripheral motor neuropathy. It was challenging to assess the toxicity profile of brentuximab in the absence of randomized comparative data. Considering that patients in this clinical setting do not have

other effective therapeutic options and would otherwise be exposed to toxic chemotherapies, the toxicity profile of brentuximab appears reasonable and manageable.

- At the list price, brentuximab costs \$4,840 per 50mg vial. At the recommended dose of 1.8mg/kg, the average cost per 28-day course is \$16,262. Based on economic analyses conducted by the manufacturer and pCODR, brentuximab was not considered cost-effective.
- The CED reviewed the patient submission provided to pCODR. The patient submission highlighted the burden of illness, the lack of effective treatment options, and patients' wishes for therapies that extend survival.
- Overall, the CED noted that patients with HL who relapse after, or do not respond to ASCT or chemotherapy, or who are not candidates for ASCT, are very ill and have few treatment options. Since study SG035-0003 did not include patients who were not candidates for ASCT and who had failed at least two prior therapies, there was insufficient clinical evidence to determine whether brentuximab treatment would provide a clinical benefit in this patient group. Although the study showed that a substantial proportion of patients experienced a complete and lasting response, the lack of any comparative data made it difficult to assess the clinical benefit and safety of brentuximab. Brentuximab was not cost-effective.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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