Brentuximab vedotin (Adcetris) for Hodgkin lymphoma

SUMMARY

Brentuximab vedotin (Adcetris) is intended to be used for the treatment of adult patients at high risk of residual CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT). If licensed it would offer an additional treatment option that may reduce the chance of relapse following ASCT. Brentuximab is an anti-CD30 antibody conjugated to the anti-tubulin agent, monomethyl auristatin E (MMAE) by a plasma-stable, enzyme-cleavable linker that selectively induces apoptosis in CD30+ cells.

HL accounts for approximately 0.6% of all cancers diagnosed in the UK each year, and around 20% of all diagnosed lymphomas. In 2010, there were 1,866 people diagnosed with HL, and 319 registered deaths from HL in the UK. The age-specific incidence of HL shows two peaks, one in people aged 20-25 years, and the second from age 70 years onwards, with approximately 75% of patients with HL under the age of 65. More than 80% of people diagnosed with HL now survive for at least 5 years, however 15-30% of patients with HL do not achieve long-term remission with conventional therapy and may be offered an ASCT. For those who relapse following ASCT, overall survival falls to around 32% at 5 years.

Chemotherapy is usually used for the first line treatment of HL. Patients who are refractory to, or relapse following conventional chemotherapy may be offered a potentially curative ASCT. However there is no standard of care for those that relapse following ASCT.

Brentuximab is currently in one phase III clinical trial comparing its effect on progression-free survival against treatment with placebo. This trial is expected to complete in 2014.
TARGET GROUP

- Hodgkin lymphoma (HL): adults at high risk of residual CD30+ HL following autologous stem cell transplant (ASCT).

TECHNOLOGY

DESCRIPTION

Brentuximab vedotin (Adcetris; SGN-35, cAc10-vcMMAE) is an anti-CD30 antibody conjugated to the anti-tubulin agent, monomethyl auristatin E (MMAE) by a plasma-stable, enzyme-cleavable linker. Brentuximab vedotin selectively induces apoptosis in CD30+ cells by binding, internalising, and releasing MMAE. It is intended for the treatment of adult patients at high risk of residual CD30+ HL following ASCT and is administered by intravenous (IV) infusion at 1.8mg/kg every 21 days.

Brentuximab vedotin is currently licensed for the treatment of patients with relapsed or refractory CD30+ HL following ASCT or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and for the treatment of adults with relapsed or refractory systemic anaplastic large cell lymphoma. Common recognised adverse effects (>10%) of brentuximab include infection, neutropenia, peripheral sensory neuropathy, diarrhoea, nausea, vomiting, alopecia, pruritus, myalgia, pyrexia and fatigue.

Brentuximab vedotin is currently also in phase III clinical trials for the treatment of advanced classical HL (combination therapy), CD30+ mature T-cell lymphoma (first line, combination therapy), CD30+ cutaneous T-cell lymphoma and newly diagnosed anaplastic large cell lymphoma (first line, combination therapy). It is also in phase II clinical trials for elderly patients with newly diagnosed HL, CD30+ non-Hodgkins lymphoma, multiple myeloma and leukaemia.

INNOVATION and/or ADVANTAGES

If licensed, brentuximab vedotin will offer an additional treatment option that may reduce the chance of relapse following ASCT.

DEVELOPER

Takeda UK Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

HL is a cancer of the lymphatic system, which arises from mutated B lymphocyte cells. HL is characterised by the presence of these cancerous B cells, known as Reed-Sternberg (RS)
cells, which express the integral membrane antigen CD30\(^3\). RS cells uncontrollably multiply in the lymph nodes in a particular area of the body\(^2\). Patients usually present with a painless lump in the neck or other parts of the body such as the groin. Other symptoms include recurring fevers and night sweats, weight loss and itchy skin\(^4\).

HL is divided into two main groups: classical and nodular lymphocyte-predominate types. There are four sub-divisions of classical type: nodular sclerosis, mixed cellularity, lymphocyte-depleted and lymphocyte-rich\(^5\). No major risk factors for the development of HL have been identified, but age, previous infection with the Epstein-Barr virus and reduced immunity are associated with an increased incidence\(^6\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to: Improving Outcomes: A Strategy for Cancer (2011).

**CLINICAL NEED and BURDEN OF DISEASE**

HL accounts for approximately 0.6% of all cancers diagnosed in the UK each year\(^7\), and around 20% of all diagnosed lymphomas\(^4\). In 2010, there were 1,866 people diagnosed with HL, and 319 registered deaths from HL in the UK\(^7\). The age-specific incidence of HL shows two peaks, one in people aged 20-25 years, and the second from age 70 years onwards\(^9\). Approximately 75% of patients with HL are under the age of 65\(^9\). Men have a higher incidence rate than women; the lifetime risk of developing HL is 1 in 440 for men, and 1 in 500 for women\(^9\).

More than 80% of people diagnosed with HL now survive for at least 5 years\(^10\). However, approximately 15-30% of patients with HL do not achieve long-term remission with conventional therapy\(^11\). For these patients with progressive or relapsed HL, ASCT is a potentially curative treatment. However, this is only effective in approximately 50% of such patients and among those who relapse following ASCT, overall survival falls to around 32% at 5 years\(^11\). In 2012, there were 17,895 admissions for HL (ICD10 C81) in England, resulting in 17,330 bed days and 18,461 finished consultant episodes\(^12\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

<table>
<thead>
<tr>
<th><strong>NICE Guidance</strong></th>
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<tr>
<td>NICE cancer service guidance. Improving outcomes in haematological cancers - the manual (CSGHO). 2003(^4).</td>
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<tr>
<th><strong>Other Guidance</strong></th>
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<tbody>
<tr>
<td>European Society for Medical Oncology. Hodgkin’s lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow up. September 2011(^13).</td>
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</tbody>
</table>

\(^a\) Expert personal communication.
EXISTING COMPARATORS and TREATMENTS

The treatment of HL depends upon the disease type, stage and location; the size of affected lymph nodes and disease spread; the patient’s age and general health; and the presence of systemic symptoms (high temperature, night sweats and weight loss)\(^{14}\).

Treatment options include combinations of\(^{13,14,15}\):

- **Radiotherapy.**
- **Short duration chemotherapy**
  - ABVD – doxorubicin, bleomycin, vinblastine and dacarbazine - standard therapy.
  - CHVPP – chlorambucil, vinblastine, procarbazine and prednisolone - rarely used, except for older, frail patients.
  - BEACOPP – bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone - rarely used as first line therapy in the UK.
  - Stanford V – mustine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide and corticosteroids.
  - GemP – gemcitabine and cisplatin.
  - VEPEMB – vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone and bleomycin – regimen for the elderly (\(>65\) years)\(^{b}\).
- **High-dose chemotherapy with autologous haematopoietic stem cell transfusion (ASCT) for unresponsive or relapsed HL.**
- BEAM – carmustine, etoposide, cytarabine, melphalan.
- Younger patients who are refractory to or fail conventional therapy early, or who have received multiple treatments but have relapsed following ASCT may also receive an allogeneic bone marrow transplantation\(^{13,6}\).

For patients whose disease proves refractory or has relapsed after high dose chemotherapy and ASCT, then chemotherapy with gemcitabine, vinblastine, or vinorelbine, alone or in combination may be used (off-licence)\(^{16}\). There is no standard care for patients that fail these therapies\(^{13}\).

Efficacy and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>AETHERA, NCT01100502, SGN35-005; brentuximab vedotin vs placebo, both in combination with best supportive care; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Seattle Genetics, Inc.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Clinical trial registry(^{17}), manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (incl UK), USA and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>(n=329) (planned); aged (\geq 18) years; HL; received ASCT in the previous 30-45 days; at high risk of residual HL post ASCT.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to brentuximab vedotin 1.8mg/kg IV as a 30 minute infusion every 21 days or placebo IV every 21 days, both in combination with best supportive care (infection prophylaxis).</td>
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<td>Follow-up</td>
<td>Active treatment for 16 cycles (or 12 months), follow-up for 2 years with clinical lymphoma assessments performed every 6 months thereafter until disease progression or study closure.</td>
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<td>Primary</td>
<td>Progression free survival.</td>
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\(^{b}\) Expert personal communication.
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<th>outcome</th>
<th>Secondary outcomes</th>
<th>Expected reporting date</th>
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<td>Overall survival; safety; anti-therapeutic antibodies to SGN-35; no quality of life measurement included in trial outcomes.</td>
<td>Primary completion date reported as Jan 2014.</td>
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**ESTIMATED COST and IMPACT**

**COST**

Brentuximab vedotin is already marketed in the UK; a 50mg vial costs £2,500, and treatment with 1.8mg/kg for one cycle would cost £7,500\(^{18,c}\).

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Other: Reduced symptoms or disability
- No impact identified

**Impact on Services**

- Increased use of existing services
- Re-organisation of existing services
- Other: Decreased use of existing services
- Need for new services
- None identified

**Impact on Costs**

- Increased drug treatment costs
- Other: Reduced drug treatment costs
- Other reduction in costs:
- None identified

**Other Issues**

- Clinical uncertainty or other research question identified: Expert opinion suggests that identifying patients at high risk of failure following ASCT is not easy. The most reliable indicator is time of relapse in relation to initial therapy; the longer the remission the higher the cure rate following ASCT. Other indicators include a higher relapse risk in those who do not achieve metabolic remission, and lung involvement at relapse also indicates a higher cure rate. Based on average adult body weight of 77.9kg.
- None identified

\(^{c}\) Based on average adult body weight of 77.9kg.

\(^{d}\) Expert personal communication.
relapse risk following ASCT. Expert opinion also suggests that rare fatal side effects of biological agents, such as progressive multifocal leucoencephalopathy must be considered carefully. In addition, expert opinion suggested more research is required for the use of Brentuximab to improve the curability of the elderly, the curability of allogeneic stem cell transplantation and to determine if combination treatment can reduce the number of patients who need a stem cell transplant to effect a cure6.

REFERENCES