Brentuximab vedotin

INDICATION

Relapsed / refractory CD30-positive Hodgkin's lymphoma
- following autologous stem cell transplant (ASCT) (NICE TA524 - BLUETEQ required)
- following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option (NICE TA524 - BLUETEQ required)
- re-use after ASCT as bridge to allogenic stem cell transplant or donor lymphocyte infusion after a previous partial/ complete response to brentuximab vedotin (Cancer Drug Fund-BLUETEQ required)

Relapsed / refractory systemic anaplastic large cell lymphoma (NICE TA478- BLUETEQ required)

CD30-positive Hodgkin’s lymphoma at increased risk of relapse or progression following ASCT (Licensed but not funded by NHS England)

TREATMENT INTENT

Disease modification or curative when used as a bridge to transplant.

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - PET-CT (preferably with contrast) scan, presence or absence of B symptoms, clinical extent of disease.
3. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent.
4. Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions. Ensure irradiation card is attached to the patient's notes and copy given to the patient. See 'Guidelines for the use of blood components in adult haematology'.
5. If raised glucose or previously diagnosed diabetes: ensure blood glucose monitored frequently during treatment and oral hypoglycaemic agents / subcutaneous insulin administered as appropriate.
6. If symptoms of peripheral neuropathy pre-treatment, perform nerve conduction studies. If clinical or electrophysiological evidence of neuropathy, discuss with consultant as to whether treatment should commence.
7. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or have undergone a hysterectomy.
8. ECG +/- Echo - if clinically indicated.
10. Record height and weight.
11. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
12. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice (by referring to the Oxford Fertility Unit).
13. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Patients at high risk of tumour lysis, refer to the tumour lysis protocol.
14. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
15. Treatment should be agreed in the relevant MDT.

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**DRUG REGIMEN**

**Day 1**  **BRENTUXIMAB VEDOTIN** 1.8 mg/kg in 150 mL sodium chloride 0.9% (final concentration 0.4-1.2 mg/mL) IV infusion over 30 minutes (maximum dose: 180 mg)

NB: The routine use of steroids as pre-medication is NOT indicated. In patients who sustain mild infusional reactions, pre-medication with paracetamol 1 g PO and chlorphenamine 10 mg IV 30 min before infusion for subsequent infusions should be tried.

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**CYCLE FREQUENCY**

Repeat every 3 weeks.
Patients should be re-staged after every 3-4 cycles (or earlier if clinically indicated) usually with PET-CT scan.
Discontinue if:
- patient has no response after 4 courses
- patient has progressive disease
- maximum number of cycles:

<table>
<thead>
<tr>
<th>Relapsed / refractory CD30-positive Hodgkin’s lymphoma</th>
<th>16 cycles</th>
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<tbody>
<tr>
<td>following autologous stem cell transplant</td>
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<tr>
<td>following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option</td>
<td>16 cycles (up to 10 cycles commissioned by NHS England, additional 6 cycles may be available from manufacturer under compassionate use supply)</td>
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<tr>
<td>re-use after ASCT as bridge to allogenic stem cell transplant or donor lymphocyte infusion</td>
<td>Maximum 16 cycles in combination with previous cycles of brentuximab vedotin</td>
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This treatment alone is not considered curative. Patients responding to treatment should be considered for a possible curative treatment as consolidation, e.g. allogeneic or autologous stem cell transplantation.

No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or in the case of intercurrent co-morbidities) for patients treated under cancer drug fund without a re-application for new funding.
RESTAGING
After every 3-4 cycles (or earlier if clinically indicated) usually with PET-CT (preferably with contrast).

DOSE MODIFICATIONS
Please note: Maximum dose 180 mg.

Haematological dysfunction

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<td>Grade 1 or 2 ( &gt; 1x10^9/L)</td>
<td>Continue with same dose</td>
</tr>
<tr>
<td>Grade 3 or 4 ( ≤ 1x10^9/L)</td>
<td>Withhold until neutropenia grade 2 or less then resume at previous dose and schedule; consider adding in GCSF to subsequent cycles</td>
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Renal impairment

The recommended starting dose in patients with severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with renal impairment should be closely monitored for adverse events.

Hepatic impairment

The recommended starting dose in patients with hepatic impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with hepatic impairment should be closely monitored for adverse events.

Neuropathy

New / worsening grade 2/3 neuropathy: withhold dose until improved to grade 1 or baseline, then re-start at 1.2 mg/kg. Grade 4: discontinue.

INVESTIGATIONS
FBC, U&Es, Creatinine, LFTs, glucose, Mg^{2+}, Ca^{2+} and PO_4 at clinic attendance.

CONCURRENT MEDICATION

| Ranitidine (or PPI if specifically indicated - discuss with consultant) | Daily for the duration of treatment |
| Aciclovir | 200 mg three times a day for duration of treatment and for 3 months after completion |

EMETIC RISK
Low risk.
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

1. Myelosuppression including neutropenia. Advice should be given to all patients that neutropenia is likely and advice given as per local institution policy
2. Infusional reactions: Can be given subsequently with suitable pre-medication. NB routine premedication is not advised
3. Peripheral neuropathy – this occurs in up to 30% of patients but usually does resolve to an extent in most patients once the treatment is stopped.
4. Hyperglycaemia
5. Rash / Stevens-Johnson syndrome (rare)
6. Should be assumed to be teratogenic although no data is available
7. Diarrhoea
8. Nausea
9. Pyrexia
10. Fatigue

TREATMENT RELATED MORTALITY

<1%

REFERENCES