INOTUZUMAB OZOGAMICIN

INDICATION

Inotuzumab Ozogamicin (IO) is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL).

Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI).

TREATMENT INTENT

- Haematological remission
- Proceed to stem cell transplantation
- Prolong survival

PRE-ASSESSMENT

1. IO should only be used by physicians familiar with administering IO. Medical and nursing teams must be aware of the side effects and how to treat promptly and appropriately.
2. Baseline CD22 positivity of > 0% using a validated and sensitive assay is required prior to initiating treatment.
3. For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxycarbamide, steroids, and/or vincristine to a peripheral blast count ≤ 10,000/mm³ is recommended prior to the first dose.
4. ECOG Performance status ≤2
5. Hepatotoxicity, including severe, life-threatening, and sometimes fatal hepatic veno-occlusive liver disease (VOD)/sinusoidal obstructive syndrome (SOS), was reported in patients with relapsed or refractory ALL receiving IO. IO significantly increased the risk of VOD/SOS above that of standard chemotherapy regimens in this patient population. This risk was most marked in patients who underwent subsequent haematopoietic stem cell transplant (HSCT).
6. In the following subgroups, the reported frequency of VOD/SOS post-HSCT was ≥ 50%:
   - Patients who received a HSCT conditioning regimen containing 2 alkylating agents;
   - Patients aged ≥ 65 years; and
   - Patients with a serum bilirubin ≥ ULN prior to HSCT
7. Patients who received a HSCT conditioning regimen containing 2 alkylating agents;
8. Patients aged ≥ 65 years; and
9. Patients with a serum bilirubin ≥ ULN prior to HSCT
10. Obtain written consent.
11. Fertility - potential risk of infertility; all patients should be offered fertility advice.

INVESTIGATIONS

To confirm diagnosis of relapsed or refractory CD22 positive B cell precursor acute ALL

- Full blood count
- ≥5% bone marrow blasts on local morphological analysis
- CD22-positive
- Philadelphia chromosome (Ph)-positive or Ph-negative

Assessment prior to commencing Inotuzumab Ozogamicin

- 18 years of age or older
- Adequate liver and renal function
  - total serum bilirubin ≤1.5 × ULN, except for documented Gilbert syndrome
  - ≤2 × ULN for hepatic abnormalities considered tumour-related
  - alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN
  - serum creatinine ≤1.5 × ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥40 mL/min
- IO should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available.
- For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles. For patients not proceeding to HSCT, a maximum of 6 cycles may be administered. Any patients who do not achieve a CR/CRi within 3 cycles should discontinue treatment.
### Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-medication</strong> (30 minutes prior to Inotuzumab infusion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone IV 100mg * * * * * * * * * * * * * *</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To reduce reaction to Inotuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracetamol po 1g * * * * * * * * * * * * * * * * * * * *</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To reduce reaction to Inotuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorphenamine IV 10mg * * * * * * * * * * * * * * * * * * * *</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To reduce reaction to Inotuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INOTUZUMAB</strong> * * * * * * * * * * * * * * * * * * * * * * *</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Allopurinol 300mg od * * * * * * * * * * * * * * * * * * * *</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>
DRUG REGIMEN

For the first cycle, the recommended total dose of IO for all patients is 1.8 mg/m² per cycle, given as 3 divided doses on Days 1 (0.8 mg/m²), 8 (0.5 mg/m²), and 15 (0.5 mg/m²). Cycle 1 is 3 weeks in duration but may be extended to 4 weeks if the patient achieves a CR or CRi, and/or to allow recovery from toxicity.

For subsequent cycles, the recommended total dose of IO is 1.5 mg/m² per cycle given as 3 divided doses on Days 1 (0.5 mg/m²), 8 (0.5 mg/m²), and 15 (0.5 mg/m²) for patients who achieve a CR/CRi or 1.8 mg/m² per cycle given as 3 divided doses on Days 1 (0.8 mg/m²), 8 (0.5 mg/m²), and 15 (0.5 mg/m²) for patients who do not achieve a CR/CRi. Subsequent cycles are 4 weeks in duration.

ADMINISTRATION

- Patients must be admitted as an inpatient for most of the first two weeks of Cycle 1. This is primarily because of the risk of tumour lysis or cytokine release type symptoms with the first dose. If patient is well and stable for the first 3 days post Day 1 or for 2 days post Day 8 then discharge home may be considered.
- IO is for intravenous use. The infusion must be administered over 1 hour.
- IO should not be administered as an intravenous push or bolus.
- IO must be reconstituted and diluted before administration, using appropriate aseptic technique. For instructions on reconstitution and dilution of IO see the product SmPC.
- IO is light sensitive and should be protected from ultraviolet light during reconstitution, dilution, and administration. Protect the intravenous bag from light using an ultraviolet light-blocking cover (i.e., amber, dark brown or green bags or aluminium foil) during infusion. The infusion line does not need to be protected from light.

- The maximum time from reconstitution through to the end of administration should be ≤ 8 hours, with ≤ 4 hours between reconstitution and dilution.
- If the diluted solution is stored in a refrigerator (2-8 °C), it must be allowed to equilibrate at room temperature (20-25 °C) for approximately 1 hour prior to administration.
- Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulphone (PES)-, polyvinylidene fluoride (PVDF)-, or hydrophilic polysulphone (HPS)-based filters are recommended. Do not use filters made of nylon or mixed cellulose ester (MCE).
- Infuse the diluted solution for 1 hour at a rate of 50 mL/h at room temperature (20-25 °C). Protect from light. Infusion lines made of PVC (DEHP or non-DEHP-containing), polyolefin (polypropylene and/or polyethylene), or polybutadiene are recommended.
- Do not mix IO or administer as an infusion with other medicinal products.

- Precede each dose of IO with:
  - Hydrocortisone 100mg IV
  - Chlorphenamine 10 mg IV
  - Paracetamol 1g po
MONITORING

Patients should be observed during, and for at least 1 hour after, the infusion for signs of infusion related reactions.

Carefully monitor patient clinically for evidence of veno-occlusive disease: hyperbilirubinemia (>34 μmol/L or >2 mg/dL), ascites or sudden weight gain (>2.5% of baseline body weight), and painful hepatomegaly.

- Weigh patient daily
- Keep strict fluid balance chart daily
- Four-hourly temperature, pulse, BP, oxygen saturations, respiratory rate
- Daily urine test for glucose
- Daily FBC, U&Es and LFTs

CONCURRENT MEDICATIONS

- Pre-medication with a corticosteroid, antipyrretic, and antihistamine is recommended prior to dosing, to minimise the risk of infusion-related reactions.
- Allopurinol 300mg po od.
  - For patients with a high tumour burden, pre-medication to reduce uric acid levels and hydration is recommended prior to dosing.
- Prophylaxis medications
  - Posaconazole 300mg bd for 2 doses then od thereafter OR Liposomal Amphotericin (Ambisome©) 2mg/kg on Monday/Wednesday/ Friday
  - Aciclovir po 200mg 8 hourly
  - Continue prophylaxis for a minimum of 4 weeks
- GCSF is NOT recommended

EMETIC RISK

- Low emetogenic risk

CONTRA-INDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Prior confirmed severe or ongoing veno-occlusive liver disease/sinusoidal obstruction syndrome (VOD/SOS).
- Serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis).
WARNINGS AND SPECIAL PRECAUTIONS / ADVERSE REACTIONS / REGIMEN SPECIFIC COMPLICATIONS

- Hepatotoxicity, including venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS)
  - See Pre-assessment section above
- Myelosuppression/cytopenias
  - Complete blood counts should be monitored prior to each dose and signs and symptoms of infection during treatment and after HSCT, bleeding/haemorrhage, and other effects of myelosuppression should be monitored during treatment. As appropriate, prophylactic anti-infectives should be administered and surveillance testing should be employed during and after treatment.
- Management of severe infection, bleeding/haemorrhage and other effects of myelosuppression, including severe neutropenia or thrombocytopenia, may require a dosing interruption, dose reduction, or discontinuation of treatment.
- Infusion related reactions
  - Patients should be monitored closely during and for at least 1 hour after the end of infusion for the potential onset of infusion related reactions, including symptoms such as hypotension, hot flush, or breathing problems. If an infusion related reaction occurs, the infusion should be interrupted and appropriate medical management should be instituted. Depending on the severity of the infusion related reaction, discontinuation of the infusion or administration of steroids and antihistamines should be considered. For severe or life-threatening infusion reactions, treatment should be permanently discontinued.
- Tumour lysis syndrome (TLS)
  - Pre-medication to reduce uric acid levels and hydration is recommended prior to dosing for patients with a high tumour burden.
- QT interval prolongation
  - IO should be administered with caution in patients who have a history of, or predisposition to QT interval prolongation, who are taking medicinal products that are known to prolong QT interval and in patients with electrolyte disturbances. ECG and electrolytes should be obtained prior to the start of treatment and periodically monitored during treatment.
- Increased amylase and lipase
  - Patients should be monitored for increases in amylase and lipase.

EXTRAVASATION RISK

Inotuzumab: Non-vesicant

REFERENCES

1. Inotuzumab Ozogamicin SmPC https://www.medicines.org.uk/

REVIEW

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jon Barrett</td>
<td>Annual Protocol meeting</td>
<td>October 2019</td>
<td>1.0</td>
<td>October 2021</td>
</tr>
</tbody>
</table>