Inotuzumab Ozogamicin

Indication

Monotherapy for relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL) (under expert supervision). Patients with relapsed or refractory Philadelphia-chromosome-positive disease should have had at least 1 tyrosine kinase inhibitor.

(NICE TA514)

ICD-10 codes

Codes with a pre-fix C91.0

Regimen details

Day	Drug	Dose	Route
1*	Inotuzumab Ozogamicin	*0.8mg/m^2	IV infusion
8 and 15	Inotuzumab Ozogamicin	0.5mg/m^2	IV infusion

*Day 1 dose reduced to 0.5mg/m^2 for subsequent cycles once complete remission obtained.

Cycle frequency

Cycle 1: 21 days (or until count recovery)
Subsequent cycles: 28 days

Number of cycles

Maximum of 6 cycles. Patients should be assessed after 3 cycles and treatment should be discontinued if complete remission not achieved.

For patients proceeding to haematopoietic stem cell transplant, the recommended duration of treatment is 2 cycles. A third cycle should only be given to achieve minimal residual disease (MRD) negativity or if there is a delay with transplant.

Administration

Inotuzumab Ozogamicin is administered in 50mL sodium chloride 0.9% over 60 minutes. The infusion bag should be protected from light during administration.

The infusion should be allowed to equilibrate to room temperature for approximately 1 hour prior to administration.

Consider administering the first dose as an in-patient to allow close monitoring for tumour lysis syndrome and infusion related toxicity.

Patients should be observed during, and for at least 1 hour after the end of infusion for symptoms of infusion related reactions, including hypotension, hot flushes, or dyspnoea. If an infusion related reaction occurs, the infusion should be interrupted and appropriate supportive medical management commenced. 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.

Pre-medication

30-60 minutes prior to Inotuzumab Ozogamicin:
Dexamethasone 8mg PO or Hydrocortisone 100mg IV
Chlorphenamine 10mg IV
Paracetamol 500mg-1g PO

For patients with a high tumour burden premedication to reduce uric acid levels (with allopurinol or rasburicase) and pre hydration is recommended.

For patients with circulating lymphoblasts, cytoreduction with a combination of hydroxyurea, steroids, and/or vincristine to a peripheral blast count ≤10 000/mm^3 is recommended before the first dose.

Emetogenicity

This regimen has moderate emetic potential.

Additional supportive medication

Allopurinol or rasburicase
Prophylactic anti-infectives as per local policy
Antiemetics as required.

Extravasation

Inotuzumab is a potential irritant.

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days and on day 8 and 15*
U+Es (including creatinine)	7 days and on day 8 and 15*
LFTs	7 days and on day 8 and 15 and post each dose*
ECG	Baseline
Weight	Baseline

* results must be reviewed before dose is given

All patients should be assessed for hepatocellular toxicity risk prior to commencing treatment. FBC, U+Es and LFTs must be checked prior to each dose during cycle 1. LFTs must also be checked following each dose.

Investigations – pre each subsequent dose

Investigation	Validity period
FBC	24 hours prior to each dose*
U+Es (including creatinine)	24 hours prior to each dose*
LFTs	24 hours prior to each dose*
ECG	As clinically indicated
Weight	Prior to each dose

* results must be reviewed before dose is given

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
CrCl	> 15mL/min
Bilirubin	≤ 1.5 x ULN
ALT/AST	≤ 2.5 x ULN

Dose modifications

Management of toxicity may require dose reduction or treatment delay, or permanent discontinuation of treatment. If the dose is reduced due to toxicity it should not be re-escalated.

Doses should be modified based on the length of dose interruption as per table below:

Duration of dose interruption due to toxicity	Dose modification
< 7 days (within a cycle)	Delay next dose (maintain minimum of 6 days between doses)
≥ 7 days	Omit next dose in the cycle
≥ 14 days	On recovery reduce dose by 25% for subsequent cycles. If further dose modification required reduce to 2 doses per 28 day cycle for subsequent cycles. If still not tolerated permanently discontinue treatment.
> 28 days	Consider permanently discontinuing treatment.

- **Haematological toxicity**

Day 1:

Prior to Inotuzumab treatment	Toxicity and management
Neutrophils ≥ 1.0 x 10^9/L	If decreases: withhold until ≥ 1.0 x 10^9/L. Consider GCSF support as per local policy.
Platelets ≥ 50 x 10^9/L	If decreases: withhold until ≥ 50 x 10^9/L
If neutrophils < 1.0 x 10^9/L and/or platelets < 50 x 10^9/L	If either decreases: withhold until: - neutrophils and platelets recover to at least baseline for the previous cycle or - neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L or - stable or improved disease (based on most recent bone marrow assessment) and the neutrophil and platelet count decrease is considered to be due to the underlying disease (not considered inotuzumab toxicity)

Dose interruption within a treatment cycle (on days 8 and/or 15) due to neutropenia or thrombocytopenia is not required.

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.

- **Renal impairment**

No dose adjustment is required in mild- severe renal impairment (CrCl >15mL/min). No studies have been carried out in patients with end stage renal disease.

- **Hepatic impairment**

No adjustment to the starting dose is required if bilirubin ≤ 1.5 × ULN and AST/ALT ≤ 2.5 × ULN. There is limited data in patients with total bilirubin > 1.5 × ULN and AST/ALT > 2.5 × ULN prior to dosing so treatment is not recommended. See below for management of liver toxicity during treatment.

Permanently discontinue treatment if bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN .

Inotuzumab is contraindicated in patients who have experienced prior confirmed severe or ongoing veno-occlusive liver disease/sinusoidal obstruction syndrome (VOD/SOS) and patients with serious ongoing hepatic disease (e.g. cirrhosis, nodular regenerative hyperplasia, active hepatitis).

- **Other toxicities**

Hepatotoxicity and veno-occlusive disease (VOD):
Monitor closely for signs and symptoms of VOD, including elevations in total bilirubin, hepatomegaly (which may be painful), rapid weight gain and ascites. LFTs should be monitored prior to and after each dose. Elevation of LFTs may require dose interruption, dose reduction or permanent discontinuation of treatment.

During treatment if bilirubin > 1.5 × ULN and AST/ALT > 2.5 × ULN interrupt dosing until recovery (bilirubin to ≤ 1.5 × ULN and AST/ALT to ≤ 2.5 × ULN) unless due to Gilbert's syndrome or haemolysis.

Permanently discontinue treatment if bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN.

If VOD occurs treat according to standard medical practice and permanently discontinue treatment. Moderate to severe VOD should be managed with defibrotide as per local VOD policy. This drug should be accessible in centres administering inotuzumab.

The use of HSCT conditioning regimens containing 2 alkylating agents should be avoided. The benefit/risk should be carefully considered before administering inotuzumab to patients in whom the future use of HSCT conditioning regimens containing 2 alkylating agents is likely unavoidable.

In patients in with serum bilirubin ≥ ULN prior to haematopoietic stem cell transplantation (HSCT), HSCT post inotuzumab should only be commenced after careful consideration of the benefit/risk. If these patients do proceed to HSCT, signs and symptoms of VOD should be monitored closely.

Infusion related reactions:
Interrupt the infusion and treat as per standard medical management. Depending on the severity of the infusion related reaction, consider discontinuation of the infusion or administration of steroids and antihistamines. For severe or life-threatening infusion reactions, permanently discontinue treatment.

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. Patients should be monitored for signs and symptoms of TLS and treated according to standard medical practice.

QT interval prolongation:
Use 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.

For any other toxicity ≥ grade 2, withhold treatment until recovery to grade 1 or baseline.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Hepatotoxicity, including veno-occlusive disease
Myelosuppression
Infections
Infusion related reactions
Haemorrhage

- **Frequently occurring side effects**

Myelosuppression
Tumour lysis syndrome
GI symptoms – abdominal pain, diarrhoea, constipation, nausea, vomiting
Reduced appetite
Stomatitis
QT interval prolongation
Increased amylase and lipase
Increased LFTs
Headache

Significant drug interactions – for full details consult product literature/ reference texts

No formal drug interaction studies have been carried out.

Medicinal products known to **prolong QT interval or to induce Torsades de Pointes**: avoid concomitant administration. If considered essential the QT interval should be monitored closely. Common medications known to cause QT prolongation include antiarrhythmic drugs (e.g., quinidine, procainamide, amiodarone), antibiotics (e.g., macrolides, ketoconazole), antihistamines (e.g., terfenadine, astemizole), antidepressants (e.g., tricyclic antidepressants), and antipsychotics (e.g., haloperidol).

Hepatotoxic medications: (e.g. azoles) avoid concomitant administration due to increased risk of hepatotoxicity. Alternative antifungal prophylaxis with less hepatotoxic drugs should be considered.

Additional comments

The name and the batch number and expiry of the administered product should be clearly recorded in the patients notes.

Women should use effective contraception during treatment and for at least 8 months after the last dose. Men with female partners of childbearing potential should use effective contraception during treatment and for at least 5 months after the last dose.

References

- National Institute for Health and Clinical Excellence. NICE TA514. Accessed 21 November 2018 via www.nice.org.uk
- Summary of Product Characteristics Inotuzumab Ozogamicin (Pfizer) accessed 21 November 2018 via www.medicines.org.uk
- Kantarjian HM. et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med 2016; 375:740-753.
- Kebriaei, P. et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplantation 2018; 53,449–456.

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Date: November 2018