SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

INOTUZUMAB OZOGAMYCIN
Relapsed/refractory Acute Lymphoblastic Leukaemia

PROTOCOL REF: MPHAINOHA
(Version No. 2.0)

Approved for use in:

- 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 2nd or 3rd generation tyrosine kinase inhibitor (TKI)

Blueteq required

Dosage:

Cycle 1 ONLY (21 day duration, can be extended to 28 days if needed)

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

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.

Cycle 2+ (28 day duration)

Drug	Dose	Route	Frequency
Inotuzumab ozogamicin	**0.8mg/m^2** if NOT in CR/CRi or **0.5mg/m^2** if in CR/CRi	IV infusion	Day 1
Inotuzumab ozogamicin	**0.5mg/m^2**	IV infusion	Day 8
Inotuzumab ozogamicin	**0.5mg/m^2**	IV infusion	Day 15

Maximum of 6 cycles.

Administration (+/- Counselling Points):

- 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.
- Inotuzumab ozogamicin is for intravenous use. The infusion must be administered over 1 hour.
- Inotuzumab ozogamicin should not be administered as an intravenous push or bolus.
- Inotuzumab ozogamicin had the potential to cause infertility, all patients should be offered fertility advice.
- Inotuzumab ozogamicin 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 inotuzumab ozogamicin or administer as an infusion with other medicinal products.
- Precede each dose of inotuzumab ozogamicin with the required pre-medications.
- 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), 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

Emetogenic risk:

Low emetogenic risk

Supportive treatments:

Inotuzumab ozogamicin pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Dexamethasone 16.5mg IV

Supportive medicines:

- Allopurinol PO 100mg or 300mg OD (depending on renal function) for first cycle
- Aciclovir 400mg PO twice daily
- Posaconazole 300mg BD for 2 doses and then once daily thereafter
- Ursodeoxycholic acid 500mg twice daily
- GCSF is not recommended

Extravasation risk:

Inotuzumab ozogamicin: Non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	Inotuzumab ozogamicin	No adjustment to the starting dose is required in renal impairment. The safety and efficacy has not been studied in patients with end-stage renal disease CrCl <30mL/min

		Parameter	**Action**
Hepatic	Inotuzumab ozogamicin	Total bilirubin > 1.5 ×ULN and AST/ALT > 2.5 ×ULN	Interrupt the dosing until recovery of total bilirubin to ≤ 1.5 × ULN and AST/ALT to ≤ 2.5 × ULN prior to each dose unless due to Gilbert's disease or haemolysis. There is limited safety data in hepatic function outside of these parameters. Permanently discontinue treatment if total bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN
		VODS/SOS	Permanently discontinue

In all patients, liver tests should be monitored, including, ALT, AST, total bilirubin, and alkaline phosphatase, prior to and following each dose. For patients who develop abnormal liver tests, liver tests and clinical signs and symptoms of hepatotoxicity should be monitored more frequently.

Interactions:

In patients receiving inotuzumab ozogamicin, prolonged QT interval was observed. Therefore, the concomitant use of inotuzumab ozogamicin with medicinal products known to prolong QT

interval or to induce Torsades de Pointes should be carefully considered. The QT interval should be monitored in case of combinations of such medicinal products.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Dexamethasone	**16.5mg**	**IV**	Bolus dose over 3-5 minutes
	Inotuzumab ozogamicin	**0.8mg/m^2 Or 0.5mg/m^2**	**IV**	In 50mL Sodium Chloride 0.9% over 1 hour
8	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Dexamethasone	**16.5mg**	**IV**	Bolus dose over 3-5 minutes
	Inotuzumab ozogamicin	**0.5mg/m^2**	**IV**	In 50mL Sodium Chloride 0.9% over 1 hour
15	**Paracetamol**	**1g**	**PO**	
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes
	Dexamethasone	**16.5mg**	**IV**	Bolus dose over 3-5 minutes
	Inotuzumab ozogamicin	**0.5mg/m^2**	**IV**	In 50mL Sodium Chloride 0.9% over 1 hour

Main toxicities:

Inotuzumab ozogamicin

The most common (≥ 20%) adverse reactions were thrombocytopenia (51%), neutropenia (49%), infection (48%), anaemia (36%), leukopenia (35%), fatigue (35%), haemorrhage (33%), pyrexia (32%), nausea (31%), headache (28%), febrile neutropenia (26%), increased transaminases (26%), abdominal pain (23%), increased gamma-glutamyltransferase (21%), and hyperbilirubinaemia (21%).

The most common (≥ 2%) serious adverse reactions were infection (23%), febrile neutropenia (11%), haemorrhage (5%), abdominal pain (3%), pyrexia (3%), VOD/SOS (2%), and fatigue (2%).

Hepatotoxicity, including venoocclusive liver disease/sinusoidal obstruction syndrome (VOD/SOS)

Inotuzumab ozogamicin significantly increased the risk of VOD/SOS above that of standard chemotherapy regimens. This risk was most marked in patients who underwent subsequent HSCT.

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.

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

In patients in whom the serum bilirubin is ≥ ULN prior to HSCT, HSCT post inotuzumab ozogamicin treatment should only be undertaken after careful consideration of the benefit/risk. Monitor closely for signs and symptoms of VOD/SOS.

Careful consideration is required before administering to patients who have had a prior HSCT. No patients with relapsed or refractory ALL who were treated in clinical trials had undergone HSCT within the previous 4 months.

Patients with a history of liver disease should be carefully evaluated (e.g., ultrasound scan, viral hepatitis testing) prior to treatment with inotuzumab ozogamicin to exclude serious ongoing hepatic disease.

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

QT interval prolongation

Inotuzumab ozogamicin 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.

Investigations and treatment plan:

	Pre	Cycle 1 day 1	Daily during cycle 1	Cycle 2+ day 1	Daily during cycle 2+	Ongoing
Informed Consent	x					
Clinical Assessment	x			X		As clinically indicated or at the end of treatment
SACT Assessment (including PS and toxicity assessment)	x	X		X		Every cycle
FBC	x	X	X	X	X	Every cycle once outpatient
U&E & LFTs & Magnesium	x	X	X	X	X	LFTs should be monitored prior to and following each dose
CrCl	x	X	X	X	X	Every cycle once outpatient
Temperature, respiratory rate, pulse, blood pressure		X	X	X	X	Four hourly monitoring on days of treatment and as required
Fluid balance		X	X	X	X	Continue daily at clinician discretion
Weight	x	X	X	X	X	Continue daily at clinician discretion
Urine test for glucose	x	X	x	X	x	Repeat if clinically indicated
CT scan	x					At the end of treatment and if clinically indicated
CSF analysis	x					
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	x					
Height	x					
Pregnancy test	x					If clinically indicated
ECG						If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle can proceed if-

ANC ≥ 1.0 x 10^9/L	Platelet ≥ 50 x 10^9/L

Note day 8 and day 15 doses do not need interrupting for haematological toxicity (neutropenia / thrombocytopenia), however should be interrupted for non-haematological toxicity.

Parameter	Action
ANC < 1 × 10^9/L and/or Platelet count < 50 × 10^9/L	Interrupt the next cycle of treatment until at least one of the following occurs: • ANC and platelet count recover to at least baseline levels for the prior cycle, or • ANC recovers to ≥ 1 × 10^9/L and platelet count recovers to ≥ 50 × 10^9/L, or • Stable or improved disease (based on most recent bone marrow assessment) and the ANC and platelet count decrease is considered to be due to the underlying disease (not considered to be inotuzumab-related toxicity).

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

See section entitled ‘Dosing in Renal and Hepatic Impairment’

References:

1. Inotuzumab Ozogamicin SmPC https://www.medicines.org.uk/ Myeloid group This is a controlled document and therefore must not be changed ML.82 Inotuzumab Ozogamicin Authorised by Myeloid lead Prof Adam Mead October 2019 V. 1.0 7 of 2. Inotuzumab
2. Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukaemia. Hagop M. et al. N Engl J Med 2016;375:740-53.DOI: 10.1056/NEJMoa1509277

Circulation/Dissemination

Date added into Q-Pulse	9th June 2023
Date document posted on the Intranet	N/A

Version History

Date	Vesion	Author name and designation	Summary of main changes
	1.0	**Kelly Crampton**	New protocol
April 2023	2.0	**Jennifer Gibson**	**Transferred to new CCC template. Indications and dosing tables re-formatted / simplified. Additional information added re VODS. Ursodeoxycholic acid added as supportive medication.**