**Chemotherapy Protocol**

## Relapsed or refractory CD22-positive B-Cell acute lymphoblastic leukaemia

INOTUZUMAB OZOGAMICIN

### Regimen

- ALL – Inotuzumab ozogamicin

### Indication

- Inotuzumab Ozogamicin (IO) is indicated as monotherapy for the treatment of adults with acute lymphoblastic leukaemia (ALL) provided the following criteria are met;

  - relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL).
  - Philadelphia chromosome negative ALL
  - Philadelphia chromosome positive ALL in which case treatment with at least one second or third generation TKI must have also failed
  - the patient has been previously treated with intensive combination chemotherapy as initial treatment with or without subsequent salvage chemotherapy or blinatumomab
  - inotuzumab ozogamicin will only be requested by and administered in either bone marrow transplant centres or in major haematological centres that regularly treat patients with relapsed/refractory ALL and who have regular ALL multi-disciplinary team meetings and close links with bone marrow transplant centres
  - the following treatment duration policy will apply to the use of inotuzumab ozogamicin: for those patients proceeding to a stem cell transplant (SCT), the recommended duration of treatment is 2 cycles. A 3rd cycle may be considered for those patients who do not achieve a complete remission (CR) or a CR with incomplete haematological recovery (CRi) and minimal residual disease negativity after 2 cycles. For patients not proceeding to a SCT, a maximum of 6 cycles of treatment may be administered. Patients who do not achieve a CR or CRi within 3 cycles should discontinue treatment
  - inotuzumab ozogamicin will be used as monotherapy
  - that the patient has an ECOG performance status of 0 - 2

### Toxicity

| Drug | Adverse Effect |
|---|---|
| Inotuzumab Ozogamicin | Hepatotoxicity including veno-occlusive disease and sinusoidal obstruction syndrome (risk increases with increasing number of cycles), myelosuppression, severe infection, bleeding, infusion related reactions, tumour lysis syndrome, QT prolongation, raised amylase and lipase. |

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Contra-Indications include patients who have experienced prior confirmed severe or ongoing veno-occlusive liver disease/sinusoidal obstruction syndrome (VOD/SOS).

## 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

## Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

### *Haematological*

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 80g/L.

| Haematological toxicity | Toxicity and dose modification(s) |
|---|---|
| Levels prior to Inotuzumab ozogamicin treatment: | |
| ANC was ≥ 1 × $10^9$/L | If ANC decreases, interrupt the next cycle of treatment until recovery of ANC to ≥ 1 × $10^9$/L. |
| Platelet count was ≥ 50 × $10^9$/L | If platelet count decreases, interrupt the next cycle of treatment until platelet count recovers to ≥ 50 × $10^9$/L |
| ANC was < 1 × $10^9$/L and/or platelet count was < 50 × $10^9$/L | If ANC and/or platelet count decreases, interrupt the next cycle of treatment until at least one of the following occurs:<br>- ANC and platelet count recover to at least baseline levels for the prior cycle, or<br>- ANC recovers to ≥ 1 × $10^9$/L and platelet count recovers to ≥ 50 × $10^9$/L, or<br>- 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 Ozogamicin -related toxicity). |

*Hepatic Impairment*

Inotuzumab is contra-indicated in patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis)

The following criteria should be met prior to commencing inotuzumab ozogamicin and be used under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available

- Adequate liver and renal function with 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

| Toxicity | Dose Modification |
|---|---|
| VOD/SOS or other severe liver toxicity | Permanently discontinue treatment |
| 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. Permanently discontinue treatment if total bilirubin does not recover to ≤ 1.5 × ULN or AST/ALT does not recover to ≤ 2.5 × ULN |

*Renal Impairment*

No adjustment to the starting dose is required in patients with mild, moderate, or severe renal impairment (creatinine clearance [$CL_{cr}$] 60-89 mL/min, 30-59 mL/min, or 15-29 mL/min, respectively)

| Toxicity | Dose Modification |
|---|---|
| Infusion related reaction | Interrupt the infusion and institute appropriate 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 |
| Grade ≥ 2 non-haematological toxicity (Inotuzumab Ozogamicin-related) | Interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose. |

| **Dose modifications depending on duration of dosing interruption due to toxicity** | |
|---|---|
| **Duration of dosing interruption due to toxicity** | **Dose modification(s)** |
| < 7 days (within a cycle) | Interrupt the next dose (maintain a minimum of 6 days between doses). |
| ≥ 7 days | Omit the next dose within the cycle. |
| ≥ 14 days | Once adequate recovery is achieved, decrease the total dose by 25% for the subsequent cycle. If further dose modification is required, then reduce the number of doses to 2 per cycle for subsequent cycles. If a 25% decrease in the total dose followed by a decrease to 2 doses per cycle is not tolerated, then permanently discontinue treatment |
| > 28 days | Consider permanent discontinuation of Inotuzumab ozogamicin. |

Regimen

The cycle length between cycle one and two varies. This cannot be easily accommodated on ARIA (unless day 1 of cycle two becomes day 22 of cycle one). For ease two regimens will be set up on ARIA.

**Cycle 1**

21 day cycle (can be increased to 28 days if patient achieves a Cr or CRi and/or to allow recovery from toxicity)

| Drug | Dose | Days | Administration |
|---|---|---|---|
| Inotuzumab ozogamicin | 0.8mg/$m^2$ | 1 | Intravenous infusion over 60 minutes in 50mL sodium chloride 0.9% |
| Inotuzumab ozogamicin | 0.5mg/$m^2$ | 8 and 15 | Intravenous infusion over 60 minutes in 50mL sodium chloride 0.9% |

**Cycle 2-6**

If patient achieves a CR/Cri prescribe 0.5mg/m$^2$. If patient does not achieve a CR/CRi then dose as per cycle 1 at 0.8mg/m$^2$ on day 1 and 0.5mg/m$^2$ on days 8 and 15.

Cycles 2-6 are 28 day cycles

| Drug | Dose | Days | Administration |
|---|---|---|---|
| Inotuzumab ozogamicin | 0.5mg/m$^2$ | 1, 8 and 15 | Intravenous infusion over 60 minutes in 50mL sodium chloride 0.9% |

## Dose Information

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.

Inotuzumab ozogamicin will be dose banded in accordance with national dose bands.

## Administration Information

- Patients can 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 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.

- 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.

### *Extravasation*

- Inotuzumab ozogamicin – Non Vesicant

## Additional Therapy

- Antiemetics
    - ondansetron 8mg oral or intravenous
    - metoclopramide 10mg three times a day when required oral
- Inotuzumab ozogamicin pre-medication
    - hydrocortisone 100mg intravenous
    - chlorphenamine 10 mg intravenous
    - paracetamol 1g oral
- Anti-infective prophylaxis
    - aciclovir 400mg twice a day oral
    - co-trimoxazole 960mg once a day on Monday/Wednesday and Friday only (pentamidine 300mg nebulised once a month can be considered)
    - antifungal prophylaxis if neutropenic; consider posaconazole or liposomal amphotericin (Ambisome)
- For tumour lysis prevention consider allopurinol 300mg daily oral for 7 days or in high risk disease rasburicase 200mcg/kg intravenous for a maximum of 5 days

## References


1. Inotuzumab Ozogamicin SmPC https://www.medicines.org.uk/
2. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukaemia. Hagop M. et al. N Engl J Med 2016;375:740-53.DOI: 10.1056/NEJMoa1509277

## REGIMEN SUMMARY

## Inotuzumab Ozogamicin (Cycle One)

### Cycle 1

### Day 1

1. Sodium Chloride 0.9% 500mL intravenous infusion over 60 minutes
   Admin instructions
   To be administered 30 minutes prior to inotuzumab ozogamicin

2. Hydrocortisone sodium succinate 100mg intravenous injection
   Admin instructions
   To be administered 30 minutes prior to inotuzumab ozogamicin

3. Paracetamol 1000mg oral
   Admin instructions
   To be administered 30 minutes prior to inotuzumab ozogamicin. The maximum dose is 4000mg / 24 hours. Please check if the patient has taken paracetamol before administering.

4. Chlorphenamine 10mg intravenous injection
   Admin instructions
   To be administered 30 minutes prior to inotuzumab ozogamicin

5. Ondansetron 8mg oral or intravenous injection

6. Rasburicase 7.5mg intravenous infusion over 30 minutes in 50mL sodium chloride 0.9%

7. Inotuzumab ozogamicin 0.8mg/$m^2$ intravenous infusion in 50mL sodium chloride 0.9% over 60 minutes.
   Administration Instructions
   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.

8. Hydrocortisone 100mg intravenous once only when required for the relief of inotuzumab ozogamicin infusion related reactions

9. Salbutamol 2.5mg nebule once only when required for the relief of inotuzumab ozogamicin related bronchospasm

10. Chlorphenamine 10mg intravenous injection once only when required for the relief of inotuzumab ozogamicin related reactions

### Day 8 and 15

11. Hydrocortisone sodium succinate 100mg Intravenous Injection
    Admin instructions
    To be administered 30 minutes prior to inotuzumab ozogamicin

12. Paracetamol 1000mg Oral
    Admin instructions
    To be administered 30 minutes prior to inotuzumab ozogamicin. The maximum dose is 4000mg / 24 hours. Please check if the patient has taken paracetamol before administering.

13. Chlorphenamine 10mg Intravenous Injection
    Admin instructions
    To be administered 30 minutes prior to inotuzumab ozogamicin

14. Ondansetron 8mg Intravenous Injection

15. Inotuzumab ozogamicin 0.5mg/$m^2$ intravenous infusion in 50mL sodium chloride 0.9% over 60 minutes.
    Administration Instructions
    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.

16. Hydrocortisone 100mg intravenous once only when required for the relief of inotuzumab ozogamicin infusion related reactions

17. Salbutamol 2.5mg nebule once only when required for the relief of inotuzumab ozogamicin related bronchospasm

18. Chlorphenamine 10mg intravenous injection once only when required for the relief of inotuzumab ozogamicin related reactions

**Take Home medicines**

19. Aciclovir 400mg twice a day for 21 days oral

20. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 21 days oral

21. Allopurinol 300mg once a day oral for 7 days

22. Metoclopramide 10mg three times a day when required oral

## Inotuzumab Ozogamicin (Cycle Two Onwards)

### Cycle 1

1. Warning – Cycle simply to keep cycle number correct
   Administration Instructions
   This regimen should be preceded by inotuzumab ozogamicin (cycle one). This cycle is simply to keep the cycle number correct due to a change in cycle length.

### Cycle 2 - 6 Day 1, 8 and 15

23. Warning – Please confirm dose and number of cycles.
    Administration Instructions

    The dose to be prescribed on cycle two will depend on the response to cycle one. If patient achieves a CR/Cri prescribe 0.5mg/$m^2$. If patient does not achieve a CR/CRi then dose as per cycle 1 at 0.8mg/$m^2$ on day 1 and 0.5mg/$m^2$ on days 8 and 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.

    The regimen changes to 28 days from cycle 2 onwards.

24. Hydrocortisone sodium succinate 100mg intravenous injection
    Admin instructions
    To be administered 30 minutes prior to inotuzumab ozogamicin

25. Paracetamol 1000mg Oral
    Admin instructions
    To be administered 30 minutes prior to inotuzumab ozogamicin

26. Chlorphenamine 10mg Intravenous Injection
    Admin instructions
    To be administered 30 minutes prior to inotuzumab ozogamicin

27. Ondansetron 8mg oral or intravenous

28. Inotuzumab ozogamicin 0.5mg/$m^2$ intravenous infusion in 50mL sodium chloride 0.9% over 60 minutes.
    Administration Instructions
    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.

29. Hydrocortisone 100mg intravenous once only when required for the relief of inotuzumab ozogamicin infusion related reactions

30. Salbutamol 2.5mg nebule once only when required for the relief of inotuzumab ozogamicin related bronchospasm

31. Chlorphenamine 10mg Intravenous Injection once only when required for the relief of inotuzumab ozogamicin related reactions

### Take home medicines Cycles 2-6

32. Aciclovir 400mg twice a day for 28 days oral

33. Co-trimoxazole 960mg once a day on Monday, Wednesday, Friday for 28 days oral

34. Metoclopramide 10mg three times a day when required oral

## DOCUMENT CONTROL

| Version | Date | Amendment | Written By | Approved By |
|---|---|---|---|---|
| 1 | March 2022 | None | Nanda Basker Haematology Pharmacist | Dr Matthew Jenner<br><br>Dr Edward Belsham<br><br>Consultant Haematologists |

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.