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PHARMACOCLINICAL PROTOCOL FOR THE USE OF INOTUZUMAB OZOGAMYCIN IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN THE NATIONAL HEALTH SYSTEM

Developed by the group of experts on the use of CAR medications from the "Plan for Implementation of Advanced Therapies in the NHS: CAR Drugs"

Approved by the Permanent Pharmacy Commission

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All the experts have made a conflict of interest declaration

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1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous haematologic disease characterised by the proliferation of immature lymphoid cells (lymphoblasts) in the bone marrow and/or other organs.

ALL accounts for approximately 20% of leukemias in adults and 80% of acute leukemias in children (1). In Europe it has a gross incidence of 1.3 cases per 100,000
100.00 inhabitants and year (2). The median age at diagnosis for ALL is 14 years. Approximately 58% of cases are diagnosed before age 20. In contrast, 26% of cases are diagnosed after the age of 45 and about 11% are diagnosed in the over 65s.

Due to their therapeutic implications, it is important to differentiate between Philadelphia chromosome positive (Ph+) ALL, precursor B-ALL (B-ALL) and precursor T-ALL (T-ALL). The B-cell subtype occurs in approximately 75% of cases in adults and in approximately 88% of cases in children. Most B-cell ALL express the CD19 antigen, 20-40% CD20, and 70% CD22 (4). Overall, between 20% and 30% of adults with ALL have Ph+ chromosomes, with an incidence exceeding 50% in people over 65 years of age. Initial diagnosis of ALL requires the demonstration of
≥ 20% lymphoblasts in the bone marrow. Patients diagnosed with B-cell ALL are tested for the presence of the CD22 protein in tumour cells.

Cure and survival rates for B-ALL have improved in recent decades, especially in children and young adults. As noted above, approximately 20-30% of B-ALL is the Ph+ form and the development of BCR-ABL tyrosine kinase inhibitors has substantially improved prognosis. There is general agreement that in patients with Ph+ ALL in first complete remission, allogeneic haematopoietic stem cell transplantation (allo-HCT) is the best treatment option for both children and adults who are physically well and have a suitable haematopoietic stem cell donor.

From a prognostic point of view, older patients have a significantly worse outcome than younger patients. The prognosis for adult patients with ALL who recur or are refractory is very poor. There is no standard treatment for these patients with R/R ALL and the results are generally unsatisfactory. Approximately 5-10% of patients are refractory to current chemotherapy regimens. In adults with first recurrence, current

chemotherapy treatments have a median overall survival (OS) of 4.5 to 6 months, with a 5-year survival of 7-10%.

Inotuzumab ozogamicin is a conjugate formed of a humanised IgG4 antibody against CD22 (inotuzumab) with a calicheamycin-class cytotoxic agent called ozogamicin. This is the treatment product discussed in this protocol.

In adult patients with relapsed or refractory ALL, the goal of treatment is to induce complete remission (CR) in order to proceed to allogeneic haematopoietic stem cell transplantation, the only potentially curative therapeutic option.

2. TREATMENT OBJECTIVE

Achieve complete remission to subsequently undergo allo-HCT.

3. PATIENT SELECTION CRITERIA

Inotuzumab ozogamicin is authorised as monotherapy in 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).

Patients who meet all of the following criteria are considered candidates for initiation of inotuzumab ozogamicin therapy:

- Confirmed presence of CD22-positive refractory disease in ≥ 20% of blasts
- Patients who are candidates for allo-HCT.
- Relapsed or refractory ALL patients who had received 1 or 2 previous lines of induction chemotherapy for ALL
- Patients with Ph+ ALL must have failed at least one TKI treatment.
- Age ≥ 18 years.
- ECOG ≤2
- Adequate liver function (total serum bilirubin ≤1.5 x upper limit of normal (ULN) unless the patient has documented Gilbert's syndrome, and aspartate and alanine aminotransferase ≤2.5 x ULN

- No history of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS)
- No Burkitt lymphoma
- No active CNS leukemia
- No history of cardiac abnormalities (QTcF<470 msec)

Treatment with inotuzumab ozogamicin **should not be started** in the following cases:

- Hypersensitivity to inotuzumab ozogamicin or any of the excipients.
- Patients who have previously experienced VOD/SOS
- Patients with severe liver disease
- Isolated testicular or CNS relapse
- Active leukemia in the CNS
- Patients with active or latent hepatitis B, active hepatitis C or positive for human immunodeficiency virus.

- Prior allogeneic haematopoietic transplantation or other anti-CD22 immunotherapy ≤ within 4 months prior to initiation of treatment.
- Peripheral lymphoblasts >10,000/mm^3
- QTcF>470 msec
- Subjects of childbearing age who are not using contraception or pregnant women.

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH INOTUZUMAB OZOGAMICIN

All patients or their legal representatives must be informed of the benefits and risks and must sign an informed consent.

Conditions for administration

When considering the use of inotuzumab as a treatment for relapsed or refractory B-ALL, **baseline CD22>0% positivity** determined by a validated and sensitive test is required prior to initiating treatment.

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

Premedication with a corticosteroid, antipyretic and antihistamine is recommended prior to administration.
Premedication to reduce uric acid and hydration levels is recommended prior to administration in patients with a high tumour burden.

Patients should be observed for at least one hour after the end of the medicinal product infusion for symptoms of drug-related reactions.

- **Dose:**

Inotuzumab ozogamicin should be administered in cycles of 3 to 4 weeks. For patients who are going to undergo allo-HCT, the recommended duration of the treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve complete remission (CR) or who achieve complete remission with incomplete haematologic recovery (CRi) and who are minimal residual disease (MRD) negative after 2 cycles. Treatment should be discontinued in patients who do not achieve CR/CRi after all three cycles.

For the first cycle, the recommended dose of inotuzumab ozogamicin is 1.8 mg/m^2 administered in 3 doses divided over day 1 (0.8 mg/m^2), 8 (0.5 mg/m^2) and 15 (0.5 mg/m^2). The first cycle lasts 3 weeks, which can be extended to 4 weeks if the patient reaches CR or CRi and/or to allow recovery from toxicity.

For the subsequent cycles, the total recommended dose of inotuzumab ozogamicin is 1.5 mg/m^2 per cycle, administered in 3 doses on day 1 (0.5 mg/m^2), 8 (0.5 mg/m^2) and 15 (0.5 mg/m^2) for patients achieving CR/CRi, or 1.8 mg/m^2 per cycle, administered in 3 doses divided between days 1 (0.8 mg/m^2), 8 (0.5 mg/m^2) and 15 (0.5 mg/m^2) for patients who do not achieve CR/CRi. These cycles last for 4 weeks.

Dose modifications

The dose of inotuzumab ozogamicin may need to be modified based on individual safety and tolerability. The treatment of some adverse reactions

may require discontinuation and/or dose reduction, or permanent discontinuation of inotuzumab ozogamicin. If the dose is reduced due to toxicity related to inotuzumab ozogamicin, the dose should not be increased again.

Discontinuation of inotuzumab ozogamicin within a treatment cycle (i.e. days 8 and/or 15) is not necessary due to neutropenia or thrombocytopenia, but discontinuation within a cycle is recommended for non-haematological toxicities.

- **Precautions for use**

Hepatotoxicity, including hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD / SOS)

In the following subgroups, the frequency of VOD/SOS reported after allo-HCT was ≥ 50%:

- patients who received an allo-HCT conditioning regimen with 2 alkylating agents;
- patients ≥ 65 years of age; and
- patients with serum bilirubin ≥ ULN before allo-HCT.

The use of conditioning guidelines for allo-HCT with 2 alkylating agents should be avoided. The benefit/risk should be carefully considered before administering inotuzumab ozogamicin to patients in whom future use of allo-HCT conditioning regimens with 2 alkylating agents is likely to be unavoidable.

In patients in whom serum bilirubin is ≥ ULN before allo-HCT, allo-HCT should only be performed after treatment with inotuzumab ozogamicin after careful benefit/risk assessment.

If these patients undergo allo-HCT, signs and symptoms of VOD/SOS should be closely monitored. Other patient factors that appear to be associated with an increased risk of VOD/SOS after allo-HCT include a previous allo-HCT, age ≥55 years, a history of pre-treatment liver disease and/or hepatitis, subsequent salvage treatments, and a higher number of treatment cycles.

Careful evaluation is required before inotuzumab ozogamicin is administered to patients who have undergone prior HCT. There were no patients with relapsed or refractory ALL treated with inotuzumab ozogamycin in clinical trials who had undergone HCT in the previous 4 months.

Patients with a history of liver disease should be carefully evaluated (e.g., ultrasound, viral hepatitis testing) prior to treatment with inotuzumab ozogamicin to exclude ongoing severe liver disease. Due to the risk of VOD/SOS, for patients undergoing allo-HCT, the recommended duration of treatment with inotuzumab ozogamicin is 2 cycles; a third cycle may be considered for those patients who do not achieve CR or who achieve CRi with MRD-negative status after 2 cycles.

The following actions are recommended to prevent VOD after administration of inotuzumab ozogamicin

To prevent VOD

- Avoid conditioning regimens containing 2 alkylating agents, thiotepa or both for HCT
- Administer prophylaxis (e.g. ursochol)
- Avoid hepatoxic agents (azoles), if possible
- If the patient is going to have an HCT, limit inotuzumab ozogamicin to 2 cycles

Monitoring

- Monitor weight and fluids daily if VOD suspected
- Frequently monitor liver enzymes
- Before each dose of inotuzumab ozogamicin monitor transaminases, total bilirubin, alkaline phosphatase and adjust the dose of inotuzumab ozogamicin in accordance with summary of product characteristics (protocol appendices page 15)
- Close monitoring of transaminases in the first month post-HCT

Myelosuppression/cytopenias

Neutropenia, thrombocytopenia, anaemia, leukopenia, febrile neutropenia, lymphopenia and pancytopenia, some of which were life-threatening, have been reported in patients receiving inotuzumab ozogamicin. Complications related to neutropenia and thrombocytopenia (including infections and bleeding/haemorrhagic events, respectively) have been reported in patients receiving inotuzumab ozogamicin.

Complete blood counts should be performed prior to each dose of inotuzumab ozogamicin, in addition, signs and symptoms of infection should be monitored during and after allo-HCT treatment, along with monitoring for bleeding/haemorrhage and other effects of myelosuppression during treatment. As appropriate, anti-infectives should be administered prophylactically and follow-up testing should be performed during and after treatment. Treatment of severe infection, bleeding/haemorrhage and other effects of myelosuppression, including severe neutropenia or thrombocytopenia, may require discontinuation of administration, dose reduction or discontinuation of treatment.

Tumour lysis syndrome (TLS)

TLS, which may be life-threatening or fatal, has been reported in patients receiving inotuzumab ozogamicin. In patients with a high tumour burden, premedication to reduce uric acid levels and hydration prior to administration is recommended. Signs and symptoms of TLS should be monitored and treated in accordance with standard clinical practice.

QT prolongation

QT prolongation has been observed in patients receiving inotuzumab ozogamicin. It should be administered with caution in patients with a history of or predisposition to QT prolongation, who are taking medicinal products known to prolong the QT interval and in patients with electrolyte disorders. An ECG and electrolyte measurement should be performed prior to initiating the treatment with periodic monitoring during treatment.

Lactation

Breast-feeding should be discontinued during treatment with inotuzumab ozogamicin and for at least 2 months after the last dose.

Immunisation

Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to initiating treatment with inotuzumab ozogamicin, during treatment and until recovery of B lymphocytes after the last course of treatment.

5. EVALUATION AND MONITORING

The doctor responsible for the patient in each of the stages of the process must register the following information in VALTERMED.

General patient details (will be collected in VALTERMED before starting treatment to carry out the evaluation):

- NHS/Regional (CIPA) code:
- Medical Record No.:
- Sex:
- Date of birth:
- Anthropometric data prior to therapy. Weight (kg): Height (cm):

Characterisation of the haematologic disease at diagnosis

- Date of diagnosis:
- ALL diagnosis: Bone marrow aspirate, specifying percentage blasts and percentage blasts expressing CD22.
- ALL Ph+: yes/no.
- Extramedullary involvement:
    - CNS: yes/no
    - Testicular yes/no
    - Other: yes/no (specify)

Characterisation of the patient and of the hematologic disease during the relapse/progression

- Date of relapse:
- ALL diagnosis:
- Extramedullary involvement:

  - CNS: yes/no
  - Testicular yes/no
  - Other: yes/no (specify)
- Relapsed or refractory B-cell ALL:
  - Patient in relapse after at least 1 line of usual treatment: yes/no
  - Refractory patient after at least 1 line of usual treatment: yes / no
  - Relapsed patient after allo-HCT: yes / no Date allo-HCT:
  - Ph+ ALL patient with failure after 1 line of TKI therapy: yes/no.
- Recent functional status (ECOG): Date:
- Analytical tests (prior to each cycle). Date:
  - Liver function: bilirubin (mg/dl), GOT (IU/mL), GPT (IU/mL).
  - Renal function: serum creatinine (mg/dl) and glomerular filtration (CrCl: ml/min/1.73m2).
  - Complete blood count: leukocyte count (x109/L).
  - Serology:
    - Hepatitis B: HBsAg: positive/negative
      HBsAc positive/negative
      HBcAc: positive/negative
    - Hepatitis C: Anti-HCV: positive/negative
      In case anti-HCV positive RNA-HCV:
    - HIV antibodies negative: yes/no
- Uric acid: Date:
- Left ventricular ejection fraction ≥ 45%: YES/NO Date:
- History of neoplasms: yes/no Referral status:
- Presence of syndromes associated with bone marrow failure (excluding Down's Syndrome): yes / no
- Active graft versus host disease (GvHD): yes/no
- VOD/SOS YES/NO Date:
- Pregnancy: yes/no. Lactation yes/no Contraceptive use: yes/no

Inotuzumab ozogamicin administration

- **Cycle 1**: Infusion date day 1: Dose:
  Infusion date day 8: Dose: Infusion date day 15: Dose:

- **Cycle 2**: Infusion date day 1: Dose:
  Infusion date day 8: Dose: Infusion date day 15: Dose:
- Response: yes/no Date:
- **Cycle 3**: Infusion date day 1: Dose:
  Infusion date day 8: Dose: Infusion date day 15: Dose:

Dose modification

Haematological toxicity: Date: Dose:

Treatment interrupted: yes/no Date:

Treatment restarted: yes/no Date: Dose:

Hepatic impairment: Date: Dose:

Treatment interrupted: yes/no Date:

Treatment restarted: yes/no Date: Dose:

Renal impairment: Date: Dose:

Treatment interrupted: yes/no Date:

Treatment restarted: yes/no Date: Dose:

Monitoring

- Response
  1. Morphological complete remission (CR) achieved (including CR with incomplete haematologic recovery (CRi) without further therapy.
     - Date morphological complete remission achieved:
  2. CR achieved with minimal residual disease (MRD <0.01% or 10^{-4}) by immunophenotype in BM without other therapy:
     - Date MRD <0.01%:
     - Improved immunophenotypic response achieved:

3. Relapse before allo-HCT
   - Loss of morphological CR: yes/no. Relapse date:
   - Loss of immunophenotypic CR (If MRD <0.01% previously): yes/no. Relapse date:
   - Extramedullary relapse: yes/no. If affirmative, indicate location:
     1. CNS: yes/no
     2. Testicular yes/no
     3. other locations: yes/no.
4. Exitus: yes/no.
   - Date
   - Disease active at time of exitus: yes/no.
   - Main cause of exitus: progression of ALL / other
5. Allo-HCT: Date:

Response evaluation: at least two response evaluations will be conducted, an initial one (at approximately one month), one at two months and three months, then every three months for one year and every six months for the second year. The assessments will continue until progression or in accordance with local protocols. The evaluation will include at least one morphological study and FC on BM for CD22.

Safety (continuous safety monitoring will be carried out and recorded whenever relevant. In addition, all suspected adverse reactions will be reported through their pharmacovigilance centre)

1. Hepatotoxicity: yes/no Degree: Date:
2. VOD/SOS: yes/no Degree: Date:
3. Tumour lysis syndrome: yes/no
   - Date:

4. Myelosuppression/cytopenias: yes/no
   - Thrombocytopenia: Date: Degree:
   - Neutropenia: Date: Degree:
   - Pancytopenia: Date: Degree:
   - Lymphopenia: Date: Degree:
   - Febrile neutropenia: Date: Degree:
5. GvHD reactivation (if previous allo-HCT): yes/no Type: Degree:
6. Development of second neoplasms: yes/no If yes, please specify:

7. Death related to inotuzumab ozogamicin toxicity: yes/no
    - Specify cause if applicable:
8. Other adverse events potentially related to inotuzumab ozogamicin (specify):

6. APPENDICES:

Dose modifications for haematological toxicities at the start of a treatment cycle (day 1)

Haematological toxicity	Toxicity and dose modification(s)
Levels prior to BESPONSA treatment:	
ANC was $\geq 1 \times 10^9$/L	If ANC decreases, interrupt the next cycle of treatment until recovery of ANC to $\geq 1 \times 10^9$/L.
Platelet count was $\geq 50 \times 10^9$/L[a]	If platelet count decreases, interrupt the next cycle of treatment until platelet count recovers to $\geq 50 \times 10^9$/L[a].
ANC was $< 1 \times 10^9$/L and/or platelet count was $< 50 \times 10^9$/L[a]	If ANC and/or platelet count decreases, 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 $\geq 1 \times 10^9$/L and platelet count recovers to $\geq 50 \times 10^9$/L[a], 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 BESPONSA-related toxicity).

Abbreviation: ANC=absolute neutrophil count.
[a] Platelet count used for dosing must be independent of blood transfusion.

Dose modifications for non-haematological toxicities at any time during treatment

Non-haematological toxicity	Dose modification(s)
VOD/SOS or other severe liver toxicity	Permanently discontinue treatment (see section 4.4).
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 (see section 4.4).
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 (see section 4.4).
Grade ≥ 2[a] non-haematological toxicity (BESPONSA-related)	Interrupt treatment until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal; VOD/SOS=venoocclusive disease/sinusoidal obstruction syndrome.
[a] Severity grade according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

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 BESPONSA.

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