MINISTRY
OF HEALTH, CONSUMER
AFFAIRS AND SOCIAL
WELFARE

SECRETARY GENERAL FOR HEALTH AND CONSUMER AFFAIRS

DIRECTORATE GENERAL FOR THE BASIC
NHS SERVICES PORTFOLIO AND PHARMACY

PHARMACOCLINICAL PROTOCOL FOR THE USE OF TISAGENLECLEUCEL IN ACUTE B-CELL 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"

Referred to the Permanent Pharmacy Commission and the Benefits, Insurance and Financing Commission for contributions

Validated by the institutional working group

Approved by the Interterritorial Council of the National Health System (8 May 2019)

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TABLE OF CONTENTS

1. INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a heterogeneous haematological disease characterised by the proliferation of immature lymphoid cells (lymphoblasts in the case of ALL) that infiltrate the bone marrow and can invade peripheral blood and other organs.

The objective for treating precursor B-cell ALL in young patients is to cure them, which is achieved in a high percentage of children and young adults with standard chemotherapy regimens. However, approximately 15-20% of patients will relapse due to treatment failure, with a higher percentage in high-risk groups (25-30%). In relapsing/refractory disease, current treatment for these patients consists of intensive chemotherapy followed by allogeneic haematopoietic stem cell transplantation (alloHCT), conventional chemotherapy, targeted therapy, or palliative therapy. AlloHCT is the only potentially curative treatment for those patients with a suitable donor.

Tisagenlecleucel has been authorised for the treatment of paediatric and adult patients up to 25 years of age with refractory phenotype B (CD19+) acute lymphoblastic leukaemia in relapse after allogeneic haematopoietic stem cell transplantation or in a second or subsequent relapse, based on the results from a phase II clinical trial without comparator. It is a cell and gene therapy that is positioned as a new therapeutic option in the treatment of ALL in the approved indication and in patients with good functional status. Candidate patients for treatment are those with the characteristics of those included in the phase II study on tisagenlecleucel and who do not have other suitable pharmacological alternatives.

By resolution of the Secretary General for Health and Consumer Affairs, tisagenlecleucel must be administered in the centres designated for administering CAR-T in the NHS.

In order to guarantee the equitable, safe and efficient use of the drug in the National Health System (NHS), as well as to be able to carry out patient monitoring and a long-term evaluation of the results obtained from treatment in real practice, it is necessary to establish a pharmacoclinical protocol and a pharmacotherapeutic monitoring register.
Collecting this information in a register and analysis of the results will make it possible

to address any uncertainties that remain after clinical trials. Both are included in the actions contained in the Plan for Implementation of Advanced Therapies in the NHS.

2. TREATMENT OBJECTIVE

Achieve a complete response with early negative residual disease that is maintained over time (>18 months) due exclusively to treatment with tisagenlecleucel.

3. PATIENT SELECTION CRITERIA

Candidate patients for starting treatment with tisagenlecleucel are those who **meet all of the following criteria:**

- Paediatric patients[a] and young adults up to 25 years of age.
- Refractory or relapsed ALL defined by one of the following criteria:
  - Second or subsequent disease relapse after treatment with conventional doses of chemotherapy/monoclonal antibody therapy, or
  - Any relapse that occurs after allogeneic haematopoietic stem cell transplantation (alloHCT). In these cases, a period of 6 months must elapse from transplantation to the infusion with tisagenlecleucel, or
  - Primary refractory disease defined as failure to achieve a complete response after the second line of standard chemotherapy, or
  - Secondary refractory disease defined as failure to achieve a complete response after 1 cycle of standard chemotherapy in relapsed ALL.
  - Patients with Ph+ ALL are eligible if they are intolerant of tyrosine kinase inhibitors (TKI) or treatment with at least two TKIs have failed, or if TKI therapy is contraindicated.
  - Relapsed patients who are not clinically candidates for alloHCT, but who are in adequate functional status for treatment with tisagenlecleucel.
- CD19 expression in tumour cells by flow cytometry

[a] No formal studies have been performed in paediatric patients under 3 years of age.

- Performance status ≥50% on the Karnofsky index for patients aged ≥16 years or ≥50% on the Lansky index for children under 16 years of age.
- Patients with adequate renal, hepatic, pulmonary and cardiac function to tolerate treatment with tisagenlecleucel.
  - Alanine aminotransferase ≤ 5 times the upper limit of normal.
  - Bilirubin <2.0 mg/dL (except in Gilbert syndrome).
  - Minimal lung reserve: dyspnea ≤ grade 1 or SaO2 by pulse oximetry ≥ 91% in ambient air.
  - Left ventricular ejection fraction ≥45% confirmed by echocardiogram.
  - Creatinine in the ranges described in the table for each age group.

	Maximum serum creatinine (mg/dL)	
Age	Males	Females
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1.0	1.0
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

Treatment with tisagenlecleucel should not be started in the following cases:

- Isolated extramedullary ALL relapse.
- Syndromes associated with bone marrow failure (excluding Down's syndrome).
- Patients with active or latent hepatitis B, active hepatitis C, or positive for human immunodeficiency virus.
- Active ALL involvement in the central nervous system defined as CNS-3: blasts in CSF with more than 5 leukocytes/µL and/or cranial nerve involvement and/or tumour mass in the brain or meninges detected by imaging techniques.
- They have Burkitt's lymphoma/leukaemia or other active neoplasms.
- Active graft versus host disease (GvHD).

- Previous treatment with a CAR-T.
- Pregnancy or women of childbearing potential not using contraception.

4. GENERAL CONSIDERATIONS FOR TISAGENLECLEUCEL TREATMENT

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

Dosage for paediatric and young adult patients with B-cell ALL

- For patient weighing 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells/kg body weight.
- For patients over 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells (not based on weight).

When starting treatment with tisagenlecleucel, the following **considerations** should be taken into account:

- **Pre-treatment conditions**

Lymphodepletion chemotherapy: Lymphodepleting chemotherapy is recommended prior to infusion with tisagenlecleucel unless the white blood cell count one week prior to infusion is ≤1,000 leukocytes/µL. In these cases, the decision on whether to administer lymphodepletion chemotherapy or not will be made at the discretion of the doctor responsible for the treatment. It is recommended tisagenlecleucel is administered 2-14 days after completion of the lymphodepletion chemotherapy. Before starting the lymphodepletion treatment, the availability of tisagenlecleucel must be confirmed. If there is a delay of more than 4 weeks between completion of the lymphodepleting chemotherapy and the infusion, and the white blood cell count is >1,000 leukocytes/µL, the patient will need to receive lymphodepleting chemotherapy again in order to receive treatment with tisagenlecleucel.

The lymphodepletion chemotherapy recommended is:

- Fludarabine (30 mg/m^2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days, starting with the first dose of fludarabine).

If the patient has previously had cyclophosphamide-associated grade 4 haemorrhagic cystitis, or is chemorefractory to cyclophosphamide-containing therapy given shortly before lymphodepleting chemotherapy[b], then they may receive the following treatment:

- Cytarabine (500 mg/m^2 intravenous daily for 2 days) and etoposide (150 mg/m^2 intravenous daily for 3 days, starting with the first dose of cytarabine).

Pre-medication. To minimise possible acute reactions due to infusion with tisagenlecleucel, it is recommended patients are treated with acetaminophen and diphenhydramine or another H1 antihistamine approximately 30 to 60 minutes before infusion. Corticosteroids should not be used except in life-threatening emergencies.

- **Precautions for use**

Due to the risks associated with treatment with tisagenlecleucel, the infusion should be delayed if the patient has any of the following conditions:

- Unresolved adverse reactions (particularly pulmonary reactions, cardiac reactions, or hypotension) from previous chemotherapies.
- Active uncontrolled infection.
- Active GvHD.
- Significant clinical worsening of the leukaemia burden after lymphodepleting chemotherapy.

If treatment with tisagenlecleucel is indicated, the following indications should be followed:

- If the patient has required systemic therapy for GvHD, it should be suspended at least 4 weeks before the infusion to confirm the absence of the recurrence of GvHD.

[b] Although the summary of product characteristics and the ELIANA clinical trial (Maude SL, N Engl J Med 2018) refers to the possibility of substituting the lymphodepletion regimen in this case with cytarabine, etoposide, less than 5 patients received this lymphodepletion regimen alternative. In contrast, there are data in the literature on the favourable effect of fludarabine on the lymphodepletion regimen and event-free survival. (Gardner RA, Blood. 2017 Jun 22; 129(25): 3322-3331. Hay et al, Blood, prepublished online February 6, 2019; DOI 10.1182/blood-2018-11-883710)

- Withhold steroid therapy at least 72 hours before infusion with tisagenlecleucel (physiological doses <12mg/m^2/day hydrocortisone or equivalent are allowed).
- Not having received donor lymphocyte infusion in the 6 weeks prior to tisagenlecleucel infusion.
- CNS prophylaxis should be discontinued at least 1 week prior to tisagenlecleucel infusion.
- In case of anti-T lymphocyte antibody therapies, at least 8 weeks must have elapsed before the tisagenlecleucel infusion.
- Chemotherapy
  - Tyrosine kinase and hydroxyurea inhibitors: suspend at least 72 hours before tisagenlecleucel infusion.
  - Vincristine, 6-mercaptopurine, 6-thioguanine, methotrexate <25mg/m2, cytosine arabinoside <100mg/m2/day, non-pegylated asparaginase: suspend >1 week before tisagenlecleucel infusion and avoid concomitantly or after lymphodepletion chemotherapy.
  - Salvage chemotherapy (eg, clofarabine, cytarabine >100mg/m2, anthracyclines, cyclophosphamide, methotrexate >25mg/m2), excluding drugs required in lymphodepletion chemotherapy: suspend >2 weeks before tisagenlecleucel infusion.
  - Pegylated asparaginase: suspend >4 weeks before tisagenlecleucel infusion.
- Radiotherapy
  - Non-CNS radiotherapy: discontinue more than 2 weeks before tisagenlecleucel infusion.
  - CNS radiotherapy: discontinue more than 8 weeks before tisagenlecleucel infusion.
- In patients who are candidates for treatment with tisagenlecleucel, the blood products to be transfused must be irradiated blood products.

- **Monitoring after infusion**
- Patients should be monitored daily for the first 10 days after infusion for possible signs and symptoms of cytokine release syndrome, neurological reactions and other toxicities. Clinicians should consider

hospitalisation after the infusion or at the first signs/symptoms of cytokine release syndrome (CRS) and/or neurological reactions.

- After the first 10 days after the infusion, the patient should be monitored based on medical judgement.
- The patient must be informed that they must remain in the vicinity of a qualified medical facility for at least 4 weeks after the infusion.

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[c].

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 CD19.
- ALL Ph+: yes/no.
- Extramedullary involvement:
  - CNS: yes/no
  - Testicular yes/no
  - Other: yes/no (specify)

[c] During the VALTERMED development process and until this information system is operational, an Excel spreadsheet or similar created for this purpose will be used.

Characterisation of the patient and the haematological disease in relapse/progression

- Date of relapse:
- ALL diagnosis: Bone marrow aspirate, specifying percentage blasts and percentage blasts expressing CD19.
- Extramedullary involvement:
  - CNS: yes/no
  - Testicular yes/no
  - Other: yes/no (specify)
- Relapsed or refractory B-cell ALL:
  - Patient in relapse after at least 2 lines of usual treatment: yes/no
  - Patient in relapse after alloHCT: yes/no Date alloHCT:
  - Patient with primary refractory ALL after at least two lines: yes/no
  - Patient with secondary refractory ALL after at least one line of therapy: yes/no
  - Ph+ ALL patient with failure of two lines of ITK therapy, or if ITK therapy is contraindicated or not tolerated: yes/no.
  - Patient in relapse not candidate alloHCT: yes/no. Reason:
- The patient has received previous treatment with a CAR-T: yes/no
- Functional status (Karnofsky in ≥ 16 years or Lansky in < 16 years): Date:
- Analytical testing. 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).
  - CD3 T lymphocytes (mm3)
  - IgG (mg/dL)
  - 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
- Left ventricular ejection fraction ≥ 45%: YES/NO Date:

- Blood oxygen saturation (SaO2):
- History of neoplasms: Yes/no Remission situation:
- Presence of syndromes associated with bone marrow failure (Down's syndrome is excluded): Yes/no
- Active graft versus host disease (GvHD): yes/no
- Pregnancy: Yes/no. Lactation yes/no Contraceptive use: yes/no

Leukapheresis, CAR-T production

- Date of approval of tisagenlecleucel treatment by the NHS Expert Group:
- Date of leukapheresis:
- Sufficient cellularity is obtained: yes/no
- Date of dispatch of leukapheresis material:
- Bridge therapy: yes/no.
- Lymphodepletion start date:
- Regimen type:
    - Fludarabine (30mg/m^2 daily for 4 days) and cyclophosphamide (500mg/m^2 daily for 2 days).
    - Cytarabine (500mg/m2 daily for 2 days) and etoposide (150mg/m2 daily for 3 days).
    - Other:
- Lymphodepletion chemotherapy not administered, specify cause:

Prior to the infusion, an assessment of the patient will be carried out and it will be ensured they meet the clinical conditions for administration.

Tisagenlecleucel administration

- Date admitted to hospital:
- Fulfils specifications: yes/no
- Infusion date:
- Dose per (cells/kg):
- The infusion was not performed. Specify reason:

Monitoring

- Response and survival (choose one)
  1. Morphological complete remission (CR) achieved (including CR with incomplete haematologic recovery (CRi) without further therapy.
     - Date morphological complete remission achieved:
     - CR maintained at month 18: yes/no
  2. CR achieved with minimal residual disease (MRD <0.01% or 10^{-4}) by immunophenotype in BM without other therapy:
     - Date MRD <0.01%:
     - MRD <0.01% maintained month 18: yes/no
     - Improved immunophenotypic response achieved:
  3. Relapse in patients with previous CR
     - 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 received in the 18 months post tisagenlecleucel infusion: yes/no If yes, indicate:
     - Date:
     - Reason: no CR/relapse/other
  6. Antineoplastic drug treatment received in the 18 months post tisagenlecleucel infusion: yes/no.
     If yes, indicate the reason: no CR/relapse/other
- Date of last visit:
- Disease status on the date of the last visit: a) CR b) CRi c) active disease

Response evaluation: at least two evaluations of the response will be carried out, an

initial one (approximately in the third month) and another at 18 months. Other evaluations will be indicated when there is suspicion of progression or in accordance with local protocols. The evaluation will include at least one morphological study and FC on BM. If there was extramedullary disease before the infusion, a specific check on the response should be carried out in these locations.

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)

- Admission to ICU: yes/no
    - Mechanical ventilation: yes/no
    - Renal Replacement Therapy: yes/no
    - Haemodynamic support: yes/no
- Cytokine release syndrome (CRS) developed: yes/no
    - Start date:
    - Maximum grade date:
    - Maximum CRS grade:
    - Tocilizumab required: yes/no
    - Dose administered:
    - Corticosteroids required: yes/no
- Development of neurotoxicity attributed to CAR-T: yes/no
    - Start date:
    - Maximum grade date:
    - Maximum neurotoxicity grade:
    - Corticosteroids required: yes/no
- Development of Haemophagocytic Syndrome/Macrophage Activation: yes/no
- Development of tumour lysis syndrome (TLS): yes/no
- Grade 3-4 cytopenias.
    - Neutropenia <500: yes/no If yes, indicate recovery date >500 neutrophils/µL (without growth factor):
    - Platelets <20,000: yes/no If yes, indicate recovery date > 20,000 platelets/µL (without transfusion):
    - Haemoglobin <8 g/dl with indication for transfusion: yes/no If affirmative, indicate Date Hemoglobin maintained >8 g/dl without transfusion:
- Development of myelodysplasia yes/no

- Development of hypogammaglobulinemia attributed to CAR-T: yes/no
    - Replacement treatment in persistent hypogammaglobulinemia (>6 months): yes/no
- Development of B lymphocyte aplasia attributed to CAR-T: yes/no
- GvHD reactivation (if previous alloHCT): yes/no
- Development of second neoplasms: yes/no If yes, please specifiy:
- Death related to tisagenlecleucel toxicity: yes/no
    - Specify cause if applicable:
- Other adverse events potentially related to tisagenlecleucel (specify):

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