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BASIC NHS SERVICES PORTFOLIO AND
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PHARMACOCLINICAL PROTOCOL FOR THE USE OF TISAGENLECLEUCEL AND AXICABTAGENE CILOLEUCEL IN DIFFUSE LARGE B-CELL LYMPHOMA 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"

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All the experts have made a conflict of interest declaration

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1. INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in Western countries. Incidence increases progressively with age, with the median age being over 60 years, although cases have been reported in people of all ages. Primary mediastinal large B-cell lymphoma (PMBCL) is a subtype of DLBCL whose precursor is B lymphocytes present in the thymus. A situation in which a DLBCL is diagnosed in a patient also diagnosed with follicular lymphoma, either concomitantly or previously, is known as transformed follicular lymphoma (TFL).

DLBCL is a potentially curable disease. Standard therapy consists of a combination of rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP) followed or not by local radiation therapy; half of patients respond to therapy with an overall 5-year survival of approximately 60%. If the disease is relapsed or refractory (R/R), treatment consists of platinum-based salvage chemotherapy followed by autologous haematopoietic stem cell transplantation (auto-HCT). However, half of patients are not candidates for auto-HCT because of age or significant co-morbidity, and of the remainder, half do not respond well enough to salvage chemotherapy to proceed to auto-HCT, and of those who eventually reach auto-HCT, approximately 50-60% relapse.

Tisagenlecleucel and axicabtagene ciloleucel have been licensed for the treatment of adult patients with R/R DLBCL after two or more lines of systemic treatment and they are positioned as new therapeutic options in patients with good functional status who do not have other suitable treatment alternatives. Candidate patients for the drug include those with the characteristics of those included in the pivotal studies. In addition, axicabtagene ciloleucel is indicated in patients with R/R PMBCL after two or more systemic treatment lines

By resolution of the Secretary General for Health and Consumer Affairs, both drugs 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 information in the register and analysing the results will make it possible to address the 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 an early and sustained complete response over time (>18 months) as well as long-term overall survival due exclusively to treatment with these medicinal products.

3. PATIENT SELECTION CRITERIA

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

- Age ≥ 18 years.
- Histologically confirmed diagnosis of DLBCL[b] or follicular lymphoma transformed to DLBCL.
- Histologically confirmed diagnosis of PMBCL for axicabtagene ciloleucel.
- Before considering therapy with tisagenlecleucel or axicabtagene ciloleucel, the presence of refractory, persistent disease should be confirmed by biopsy. Treatment should be considered if:
    - the new biopsy confirms the diagnosis of DLBCL or
    - the re-biopsy confirms diagnosis of follicular lymphoma transformed to DLBCL
    - re-biopsy confirms diagnosis of PMBCL (axicabtagene ciloleucel)
    - or

[a] There is no evidence in patients > 75 years of age

[b] Patients with T-cell/histiocyte-rich large B-cell lymphoma and patients who relapsed after allo-HCT were not included in the pivotal CT on tisagenlecleucel (nor in the pivotal CT on axicabtagene ciloleucel).

- In the event the procedure to perform a new biopsy is unsafe, it should be confirmed that there is progressive disease at the previously documented sites of active disease and that the previous histology was DLBCL.

- **Tisagenlecleucel**: Relapsed or refractory disease after at least 2 lines of systemic treatment, defined by one of the criteria below, and either the patient had not responded to autologous transplantation or was not a candidate based on clinical criteria:
  - Patient with DLBCL who has received 2 or more lines of systemic therapy[c] and relapses after the last line or is refractory[d] to the last line of systemic therapy
- **Axicabtagene ciloleucel (DLBCL and PMBCL)**: Relapsed or refractory disease after at least 2 lines of systemic treatment, defined by one of the following criteria, or refractory to autologous transplantation:
  - Patient who has received 2 or more lines of systemic therapy[c] who does not respond (disease progression as best response from the most recent treatment regimen or stable disease (SD) as best response after at least 2 cycles of the last line of treatment with duration of SD <6 months after the last line of treatment) or refractory to auto-HCT if progression or relapse ≤12 months from auto-HCT.

For both drugs patients with transformed follicular lymphoma (FL) who have received prior CT for FL and who have received 2 or more lines of systemic therapy[c] since the transformation diagnosis and relapses after the last line or is refractory[d] to the last line of systemic therapy.

- ECOG functional status of 0 or 1.
- Patients with adequate renal, hepatic, pulmonary and cardiac function to tolerate treatment with tisagenlecleucel or axicabtagene ciloleucel.

[c] Must include at least one anti-CD20 monoclonal antibody, unless the tumour is determined to be CD20-negative, and a chemotherapy regimen containing anthracycline.
[d] Refractory disease is defined as progressive disease or stable disease (lasting <6 months) as the best response to the last line of therapy, or disease progression within 12 months after autologous transplantation.
Radiation therapy cannot be counted as a line of therapy.

- For tisagenlecleucel, adequate bone marrow reserve is defined as: neutrophils > 1000/mm^3, lymphocytes > 300/mm^3 and CD3+ T lymphocytes > 150/mm^3, platelets ≥ 50,000/mm^3 and haemoglobin > 8.0 g/dl.
- For axicabtagene ciloleucel, adequate bone marrow reserve is defined as: neutrophils > 1000/mm^3, lymphocytes > 100/mm^3, platelets ≥ 75,000/mm^3.

Treatment with tisagenlecleucel or axicabtagene ciloleucel **should not be started** in the following cases:

- Patients with Richter's transformation, Burkitt lymphoma, primary Central Nervous System (CNS) lymphoma.
- Active CNS involvement known to be lymphoma.
- With another active neoplasm, with the exception of adequately treated cutaneous squamous cell or basal cell carcinoma or carcinoma in situ (cervix, breast, bladder) treated and without evidence of recurrence for at least three years prior to treatment or primary neoplasm completely resected and in remission for 5 or more years.
- Patients with active or latent hepatitis B, active hepatitis C, or positive for human immunodeficiency virus.
- With active autoimmune neurological diseases (e.g., Guillain-Barré syndrome and amyotrophic lateral sclerosis).
- Cardiac arrhythmia without adequate cardiological control.
- Having had unstable angina or myocardial infarction in the 12 months prior to infusion.
- History of uncontrolled autoimmune disease in the previous 2 years
- History of deep vein thrombosis or severe pulmonary embolism in the previous 6 months. This will be assessed individually.
- Auto-HCT within 6 weeks prior to infusion.
- Previous treatment with a CAR-T.
- Pregnancy or women of childbearing potential not using contraception.

In case of tisagenlecleucel do not initiate treatment in patients with primary mediastinal lymphoma, primary cutaneous DLBCL or EBV+ DLBCL.

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH TISAGENLECLEUCEL / AXICABTAGENE CILOLEUCEL

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

Dose for adult DLBCL patients

- Tisagenlecleucel: 0.6 to 6 x 10^8 CAR-positive viable T cells (not based on weight).

- Axicabtagene ciloleucel: 2x10^6 CAR-positive viable T cells per kg body weight (or a maximum of 2x10^8 CAR-positive viable T cells for patients weighing 100 kg or more

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 of tisagenlecleucel. If the patient's white blood cell count is ≤1,000 cells/µl in the week prior to tisagenlecleucel infusion, lymphodepletion chemotherapy may be omitted. 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 (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 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 the lymphodepleting chemotherapy, then they may receive the following treatment:

- Bendamustine (90 mg/m^2 intravenous daily for 2 days).

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

When starting treatment with axicabtagene ciloleucel, the following considerations should be taken into account:

- **Pre-treatment conditions**

Lymphodepletion chemotherapy: Lymphodepleting chemotherapy is recommended prior to infusion with axicabtagene ciloleucel.

The lymphodepletion chemotherapy recommended is:

- Fludarabine (30 mg/m^2 intravenous) and cyclophosphamide (500 mg/m^2 intravenous), on the fifth, fourth and third days prior to infusion.

Pre-medication. To minimise possible acute reactions due to axicabtagene ciloleucel infusion, it is recommended that patients be treated with 500-1000 mg oral paracetamol and 12.5 to 25 mg intravenous or oral diphenhydramine (or equivalent) approximately 60 minutes prior to infusion. Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of axicabtagene ciloleucel.

- **Precautions for use**

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

- Unresolved adverse reactions (in particular pulmonary reactions, cardiac reactions or hypotension) from previous chemotherapies.
- Active uncontrolled infection.

- Active graft versus host disease (GvHD).
- Clinically significant worsening of lymphoma after lymphodepletion chemotherapy.

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

- The patient has not received chemotherapy other than lymphodeplection in the 2 weeks prior to the tisagenlecleucel infusion.
- Therapeutic doses of steroids should be discontinued >72 hours before leukoapheresis and >72 hours before the tisagenlecleucel infusion. Physiological doses of steroids (<12mg/m^2/day of hydrocortisone or equivalent) are allowed.
- Immunosuppression: any immunosuppressive drugs have been stopped at least 2 weeks before leukoapheresis and at least 2 weeks before the tisagenlecleucel infusion.
- Antiproliferative therapies other than lymphodeplection chemotherapy:
  - Short-acting agents (e.g., tyrosine kinase inhibitors or hydroxyurea): should be discontinued >72 hours prior to leukoapheresis and >72 hours prior to the tisagenlecleucel infusion.
  - Other cytotoxic agents (including low daily or weekly maintenance doses): should be discontinued 2 weeks before leukoapheresis and 2 weeks before the tisagenlecleucel infusion.
  - Monoclonal antibodies, including anti-CD20: should not be administered within 4 weeks prior to infusion or five half-lives of the respective antibody, always using the longest period.
- CNS prophylaxis: should be discontinued >1 week before tisagenlecleucel infusion.
- Radiation therapy: must have been given at least 2 weeks before the infusion.
- In patients who are candidates for treatment with tisagenlecleucel, the blood products to be transfused must be irradiated blood products.

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

- The patient has not received systemic therapy in the 2 weeks or 5 half-lives (whichever occurs earlier) prior to leukoapheresis. In the case of immunotherapy, at least

3 half-lives should have passed prior to leukoapheresis (e.g. ipilimumab, nivolumab, pembrolizumab, atezolizumab, etc.).

- Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to initiating lymphodepleting chemotherapy, and until recovery of the immune system after treatment with axicabtagene ciloleucel.

- **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. The doctors 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.

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

- NHS code[e]
- CIP/CITE code[e]:
- NIF/NIE[e]
- Health Card No.[e]
- Anonymised identification code:
- Medical Record No.:
- Sex[f]:
- Date of birth[f]:

[e] It is mandatory to fill in at least one of these fields
[f] Required fields

- Anthropometric data prior to therapy. Weight (kg): Height (cm):

Characterisation of the haematologic disease at diagnosis

- Date of diagnosis:
- Type of lymphoma: (choose one)
  - DLBCL N.O.S.
  - Double/triple hit high grade B lymphoma
  - DLBCL transformed from follicular:
  - Primary mediastinal large B-cell lymphoma
  - Other (specify):
- Clinical stage (Lugano criteria):

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

- Date of relapse:
- Clinical stage (Lugano criteria):
- CD19 tumor expression document (if available): yes/no
- DLBCL relapsed or refractory or unresponsive.
  - Patient with relapsed DLBCL after receiving at least two lines of chemotherapy (including rituximab and anthracycline).
  - Patient with DLBCL refractory to the last line of systemic therapy after receiving at least two lines of chemotherapy (including rituximab and anthracycline).
  - Patient with DLBCL unresponsive to two or more CT lines (including an anti-CD20 monoclonal antibody, unless the tumour is CD20 negative, and an anthracycline CT regimen)
  - Patient with relapsed TFL after receiving at least two lines of chemotherapy (including rituximab and anthracycline) since diagnosis of transformation to DLBCL.
  - Patient with TFL refractory to the last line of systemic therapy after receiving at least two lines of chemotherapy (including rituximab and anthracycline) since diagnosis of transformation to DLBCL, or an anthracycline-containing regimen prior to transformation.
  - Patient with PMBCL without response to two or more treatment lines

- Prior HCT: yes/no.
  - If yes, indicate

    - Type:
    - Date:
  - If no, indicate whether the patient is a candidate for auto-HCT: yes/no
    - If not a candidate, specify the reason:
- The patient has received previous treatment with a CAR-T: yes/no
- CNS affected: yes/no
- International prognostic index for lymphomas (IPI):
- ECOG functional status: 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/1.73m^2).
  - 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
  - LDH (IU/L),
  - β2 microglobulin (mg/L)
- Left ventricular ejection fraction ≥ 50%: yes/no Date:
- Blood oxygen saturation (SaO_2) by pulse oximetry:
- History of neoplasms: Yes/no Remission situation:
- Pregnancy: Yes/no. Lactation yes/no Contraceptive use: yes/no

<u>Leukapheresis, CAR-T production</u>

- Date of approval of tisagenlecleucel/axicabtagene ciloleucel 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 (25mg/m^2/d for 3 days) and cyclophosphamide (250 mg m^2 iv for 3 days).

  - Fludarabine (30 mg/m^2 intravenous) and cyclophosphamide (500 mg/m^2 intravenous), on the fifth, fourth and third days prior to infusion.

  -Bendamustine (90mg/m^2/d for 2 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.

Administration of tisagenlecleucel/axicabtagene ciloleucel

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

Monitoring

- Response and overall survival (OS)

1. Complete response (CR) achieved by PET-CT without other therapy. Yes/no. If yes, indicate:
   - Date CR achieved:
   - Relapse in patients with previous CR: yes/no. Relapse date:
   - CR maintained at month 18: yes/no
2. OS without other therapy. Yes/no. If yes, indicate:
   - Date CR achieved:
   - OS maintained at month 18: yes/no
3. Exitus: yes/no.
   - Patient is alive at 18 months without other lymphoma treatments: yes/no

   In case of exitus, indicate:

- Date:
- Disease active at time of exitus: yes/no.
- Primary cause of exitus: progression of DLBCL/other

4. HCT received for 18 months post-infusion with tisagenlecleucel/axicabtagene ciloleucel: yes/no

   If yes, indicate:

   - Date:
   - Reason: no CR/relapse/other

5. Antineoplastic drug treatment received in the 18 months post tisagenlecleucel/axicabtagene ciloleucel infusion: yes/no.

   If yes, indicate the reason: no CR/relapse/other

- Date of last visit:
- Disease status on the date of last visit: a) CR b) PR c) active disease d) loss of monitoring
- Assessed by the Monitoring Committee

  Yes/No If yes, ”Appropriate" Yes/no

Response assessment: at least two PET-CT response evaluations will be performed, one early (approximately month 3) and another around month 18 after the CAR-T infusion. In the case of relapse or success between both evaluations, it will be stated in the corresponding section whether to wait for the evaluation at 18 months. Other evaluations will be indicated when there is suspicion of progression or in accordance with local protocols.

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 µL: yes/no. If yes, indicate date of recovery >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
- Development of second neoplasms: yes/no If yes, please specifiy:
- Death related to CAR-T toxicity: yes/no
  - Specify cause if applicable:
- Other adverse events potentially related to CAR-T (specify):

BIBLIOGRAPHY

1. Plan for Implementation of Advanced Therapies in the NHS: CAR Drugs. Approved by the National Health System Interterritorial Council on November 15 2018. Available on: https://www.mscbs.gob.es/profesionales/farmacia/pdf/Plan_Abordaje_Terapias_Avanzadas_SNS_15112018.PDF file

2. Kymriah® (tisagenlecleucel) summary of product characteristics. Available on: https://cima.aemps.es/cima/dochtml/ft/1181297001/FT_1181297001.html [accessed:10/02/2019].

3. Yescarta® (axicabtagén ciloleucel) summary of product characteristics. Available on: https://cima.aemps.es/cima/pdfs/ft/1181299001/FT_1181299001.pdf [accessed:07/07/2019].

4. Therapeutic Positioning Report on tisagenlecleucel (Kymriah®) in the treatment of paediatric and adult patients up to 25 years of age with refractory B-cell acute lymphoblastic leukemia, in post-transplant relapse, or in second or subsequent relapse; and of adult patients with relapsed/refractory diffuse large B-cell lymphoma after two or more lines of systemic treatment. Available on: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-tisagenlecleucel-kymriah-LAL-LCGB.PDF file [accessed:10/02/2019].

5. Therapeutic Positioning Report on axicabtagene ciloleucel (Yescarta®) in the treatment of adult patients with diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma, relapsed or refractory after two or more systemic treatment lines.

6. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. DOI: 10.1056/NEJMoa1804980

7. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, and Liste TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol.2014; 32:3059-3067.

8. 22 June 2018 EMA/481168/2018 Committee for Medicinal Products for Human Use (CHMP) Assessment report YESCARTA International non-proprietary name: axicabtagene ciloleucel Procedure No. EMEA/H/C/004480/0000. Available on: https://www.ema.europa.eu/en/documents/assessment- report / yescarta-epar-public-assessment-report_en.PDF file [accessed:07/07/2019].

9. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, et al Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017 Dec 28;377(26):2531-2544.