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Hospital pharmacist's roles and responsibilities with CAR-T medicines

Funciones y responsabilidades del farmacéutico de hospital con los medicamentos CAR-T

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Abstract: The development and commercialization of cell therapy drugs with chimeric antigen receptor T cells (CAR-T) represent a new challenge for Spain's hospital pharmacy. The aim of this article is to review the key aspects of these medicines and to describe the oncohematological pharmacist's role within the multidisciplinary clinical team. This includes the different phases in the transversal process that involves a therapy with CAR-T medicines, ranging from indication to short and long term follow-up of patients treated with this type of therapy, and emphasizing on the management of its main adverse effects. CAR-T therapy offers the hospital pharmacist the opportunity to work closely with the rest of the clinical professionals involved in the process, allowing their contribution to the development of procedures, clinical practice guidelines of global approach, and establishing starting points when facing future therapies of similar complexity -and even improving previously established basic processes-.

KEYWORDS: T-cell chimeric antigen receptor, Cytokine release syndrome, CAR-T-related encephalopathy syndrome, Pharmaceutical care.

Resumen: El desarrollo y la comercialización de medicamentos de terapia celular con células T con receptor de antígeno quimérico (CAR-T) suponen un nuevo reto para la farmacia hospitalaria en España. El objetivo de este artículo es revisar los aspectos clave de estos medicamentos y describir el papel del farmacéutico oncohematológico dentro del equipo clínico multidisciplinar en las diferentes fases del proceso transversal que implica el tratamiento con medicamentos CAR-T, desde la indicación hasta el seguimiento a corto y largo plazo de los pacientes tratados con este tipo de terapias, con una importante mención al manejo de sus principales efectos adversos. La terapia tipo CAR-T ofrece al farmacéutico hospitalario la oportunidad de trabajar en estrecha colaboración con el resto de los profesionales clínicos implicados en el proceso, permitiendo su contribución en el desarrollo de procedimientos, guías de práctica clínica de abordaje global y estableciendo puntos de partida para afrontar tratamientos futuros de complejidad similar e incluso mejorar procesos base anteriormente establecidos.

PALABRAS CLAVE: Receptor antigénico quimérico de células T, Síndrome de liberación de citoquinas, Síndrome de encefalopatía relacionada con CAR-T, Atención farmacéutica..

Introduction

Over the last 15 years, scientific progress in cellular and molecular biotechnology have led to the development of cell therapy drugs with chimeric antigen receptor T cells (CAR-T), which have become one of the main immunocellular therapies treating cancer. The European Commission has authorized the marketing of the first two drugs with CAR-T cells: tisagen-lecleucel (Kymriah®) -holder of the Novartis Europharm Limited authorization-, and axicabtagene ciloleucel (Yescarta®) -holder of the KitePharma EU B.V. Gilead group-. The aim of this article is to review the key aspects of these medications and to describe the role that the oncohematological pharmacist has in the whole process, from indication to follow-up of patients treated with CAR-T cells, and emphasizing on the management of its main adverse effects.

Description of CAR-T cells

CAR-T cells consist of either the patient's own T lymphocytes -autologous-, or lymphocytes obtained from genetically modified donors in vitro -allogeneic- to express a chimeric antigen receptor that provides an antigen specificity for their binding and subsequent destruction of malignant cells. Genetic modification is made by the manufacturer using a viral vector derived from a retrovirus or a lentivirus that carries a new gene, which codes for the chimeric antigen receptor. In recent years, CAR-T has been developed in multiple academic centers with constructs against different antigens. The two currently available commercial CAR-T drugs, Kymriah® and Yescarta®, are second-generation CAR-T cells, in which the viral vector carries a gene that codes for the binding point of the specific antibody for CD19, a costimulatory domain of T lymphocytes and an intracellular domain to initiate T cell signaling. These drugs carry the same receptor, thus they are specific for the same antigen. These CAR-T cells target B - cell tumors, such as acute B -cell lymphoblastic leukemia (LAL-B), diffuse large cell B lymphoma (LBDCG), and primary mediastinal large cell B lymphoma (LBPM)^{1,2}. However, many other tumor antigens are also considered the target of CAR-T therapy in numerous clinical trials during the development phase, mostly aimed at hematological malignancies, due to the complexity associated with the use of CAR-T cells in solid tumors.

Regulatory framework for CAR-T medicines

CAR-T cells are advanced therapy drugs, so they are subject to regulation 1394/2007³, which introduces additional provisions to those established in Directive 2001/83/CE⁴ and regulation 726/2004 on medicinal products for human use⁵. This type of therapy involves its use in the hospital setting. Thus, the hospital pharmacist, as a key professional in

the efficient management of any medication within their competence, has the responsibility of contributing to the rational use of CAR-T therapies, guaranteeing and assuming the technical responsibility of their selection, ordering, product receipt, storage and preparation, and dispensing. In addition, the management of CAR-T drugs requires the establishment of an effective and safe system that guarantees their correct administration, as well as the follow up and monitoring of their efficacy and safety in the short and long term⁶.

The marketing authorization of CAR-T cells obliges to comply with a pharmacovigilance level risk management plan, as well as to register all patients treated in a centralized European registry in order to monitor the safety and efficacy of these therapies in the long term.

In November 2018, the Ministry of Health, Consumption and Social Welfare (MSCBS by its Spanish acronym) published a Plan of tackle Advanced Therapies in the National Health System: CAR⁷ medicines. One of the Plan's objectives is to organize in a planned, equitable, safe and efficient way the use of CAR medicines in the Spanish National Health System (NHS). In order to guarantee the experience and necessary means to properly carry these treatments out, the Plan establishes criteria for the selection of referral hospitals for the use of CAR-T medicines in Spain's NHS.

Pharmacist's roles and responsibilities

The implementation of this new hospital treatment modality represents an important challenge for Pharmacy Services and requires specific training in this area and availability of new resources, including great coordination with all the professionals of the multidisciplinary team who are involved in these therapies, where the Pharmacist will have an essential role to ensure its optimization. Table 1 summarizes the pharmacist's responsibilities, included in the CAR-T Medicines Management Procedure of the Spanish Society of Hospital Pharmacy and in other documents prepared by other scientific societies. Some of these points will be detailed below⁸⁻¹¹.

Table 1
Pharmacist responsibilities^{8,9}

Medicines selection and purchase
– Participate in the selection and approval of the CAR-T medication as a member of the CFyT. – Participate in the elaboration of a guide on indications and therapy criteria with CAR-T cells approved by the CFyT. – Own the hospital's accreditation for the administration of CAR-T by the Ministry of Health, Consumption and Social Welfare. – Be qualified for the hospital by the pharmaceutical company, through a contract signed by both parties. – Participate in the assessment of patients who are candidates for treatment through the CAR-T multidisciplinary committee. – Process requests to the regional health authority of the autonomous communities. – Purchase order and acceptance of the probable date of manufacture and delivery of the laboratory.
Obtaining the patient's autologous T lymphocytes (Blood bank)
– Understand the procedure established for apheresis and the identification system of the product obtained.
Reception of CAR-T cells
– Guarantee the correct receipt and integrity of the medicine.
CAR-T cell preservation
– Ensure conservation in appropriate conditions.
Chemotherapeutic conditioning or lymphodepletion
– Validate the prescription, preparation and dispensing of the conditioning protocol, according to clinical criteria and expected date of reception and CAR-T cells infusion. – Check availability of support treatments according to the treatment protocol for CRS, such as tocilizumab.
Validation, dispensing of CAR-T cells
– Confirm that the conditioning phase is complete and the patient is ready CAR-T infusion. – Have a defrosting standard operational procedure.
Administration of CAR-T cells
– Understand the key points of the administration. – Check availability of the necessary doses of tocilizumab in the hospitalization unit and/or Pharmacy Service.
Pharmacovigilance and monitoring
– Monitor within the first 10 days subsequent the for signs or symptoms of CRS and immune effector cell-associated neurotoxicity syndrome ICANS. – Record all patient's adverse events. – Patient follow-up after discharge.

CAR-T: T cells with chimeric antigen receptor; CFyT: Spanish acronym for Drug and Therapeutic Committee;
CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

Selection and purchase

The selection of CAR-T therapies should follow the same procedure as other medicines available in the hospital setting. Thus, CAR-T medicines will be evaluated by the Pharmacy and Therapeutics Committee (CFyT by its Spanish acronym) -guaranteeing their quality, safety, efficacy, cost and convenience-, and will entail the approval of the corresponding criteria and conditions of use, as well as their inclusion in the Hospital's Formulary. This inclusion implies ensuring availability of the necessary means for its ordering, reception, storage, dispensing and administration, as well as the availability of the necessary support treatments for managing the main side effects associated with the therapy, during or post administration. On the other hand, taking into account the particularities of this type of therapy, it will be necessary to have specific procedures for the governance of this process.

The purchase of CAR-T medicines for the use within the NHS can only be carried out in the hospitals selected by the MSCBS at the proposal of the autonomous communities (CCAA) according to the selection criteria established by a group of experts on CAR-T therapies appointed by the Ministry of Health¹². The pharmaceutical companies also qualify each center for the administration of their medication, signing a specific contract between the pharmaceutical companies and the hospital.

The request for a CAR-T treatment for a given patient will involve individual evaluation of each case by the CAR-T Multidisciplinary Committee of the hospital where there is a pharmacist. In such Committee, demographic, clinical and administrative data related to the patient will be reviewed, as well as the appropriateness of the requested indication, according to the established criteria. If the Committee gives a favourable opinion, the pharmacist forward an individual application to the Autonomous Community health authorities. The application consists of a standardized form and an anonymous clinical report of the patient. Once validated by the regional health authorities, this treatment request will be forward to the MSCBS Sub-Directorate of Quality and Medicines for its evaluation and final authorization, as established in the Advanced Therapy tackle Plan in Spain's NHS: CAR therapies. The group of experts on the Use of CAR medicines will assess, individually, if the patient meets the indication criteria. They will also inform and advise on the commercialized CAR-T medicines suitable for the patient according to the pharmacoclinical use protocol, as well as providing the option for the patient to access ongoing clinical trials -both academic and industrial- in the NHS^(13,14). The Department of Quality and Medicines of the MSCBS will issue a final decision regarding the request that may or may not be favourable. If the decision is favourable, the pharmacist will be responsible for:

Confirming that the CAR-T medication is correctly introduced in the pharmacy purchasing systems and prescribing systems.

Ordering CAR-T medication from the corresponding pharmaceutical company, including anonymous clinical report of the patient linked to the medical prescription and pharmaceutical validation.

Checking whether the order is accepted by the company with probable date of manufacture.

Formalizing the purchase order by accepting the conditions on the laboratory's date of manufacture.

Collecting the patient's autologous T lymphocytes

Unlike conventional medicines, the starting material for CAR-T manufacture is derived from an apheresis procedure, a clinical technique by which the necessary blood components for the production of these medicines are separated and selected: lymphocytes T⁹.

Usually, hospitals perform apheresis under a license from the National Transplant Organization, in the center's own facilities of Hematology Service. The pharmacist must know the Standard Operating Procedure (SOP) of the apheresis procedure and identification of the medicine.

Reception

Pharmacy Service must ensure the correct receipt of CAR-T medicines in an area that meets the specific conditions required for these therapies⁹.

The pharmacist is responsible for the correct receipt, also keeping in mind the following important points:

- Cryopreserved CAR-T cells are preserved and transported below -120 °C (Kymriah[®]) or -150 °C (Yescarta[®]) in a vapor phase nitrogen cryogenic container.

Vapor phase nitrogen storage entails health risks, therefore training and a specific safe handling procedure are required.

Cell therapies receipt includes:

- Review and validation of the temperature monitoring systems going along with the containers.

- Verification of the drug's integrity, labeling, and detailed certificate of analysis.

- Maximum excursion time at room temperature when transferring to the liquid nitrogen tank.

- Receipt procedure outside the usual schedule.

- Acknowledgment of receipt of the cells, including verification of the clinical criteria and the medicine's billing.

- Registration of receipt in the pharmacy purchasing systems.

Conservation

Pharmacy Service must ensure that CAR-T cells are store in adequate conditions, guaranteeing the availability of the following requirements^{8,9}:

- Continuous temperature monitoring system with 24-hour working alarm.

Notification and action plan before a temperature deviation.

Contingency plan in case of deviation of the temperature storage specifications.

Validation and dispensing

Chemotherapeutic conditioning or lymphodepletion

Most CAR-T medicines are administered after a lymphodepletion process, which involves the administration of a chemotherapeutic conditioning regimen a few days before infusion. Therefore, this phase of the process requires great coordination between the multidisciplinary team responsible for the patient, who must assess whether he/she is still a candidate to receive the CAR-T treatment, as well as establishing the expected date of the CAR-T infusion⁸.

If the patient is a candidate for lymphodepletion conditioning, the pharmacist must screen the prescription of the corresponding protocol, taking into account the validation criteria established for oncohematological treatments. The following steps are required:

Having a copy of the the conditioning protocol for CAR-T, with its associated anti-infective prophylaxis in the usual prescription system, preparation and administration of the hospital's own chemotherapy.

Verifying the CAR-T availability for the patient and that its expiration date is later than the lymphodepletion and the infusion date of the CAR-T.

Recording the preparation and dispensing of conditioning drugs.

Verifying the availability of supportive treatments that may be necessary during or after CAR-T infusion. The risk management plan requires 2-4 doses of tocilizumab, approved for the treatment of severe or life-threatening cytokine release syndrome (CRS) that may result from the CAR-T administration. Calculate the number of tocilizumab doses and setting aside the corresponding number of vials labeled with the patient's name and medical history number prior to the CAR-T infusion is recommended just in case they will be needed after the infusion. If not used, these can be returned to the main stock.

The location of the tocilizumab vials should be indicated in the local SOP, taking into account each hospital's characteristics. Alternatively, similar medicines can be used, such as siltuximab or anakinra^{15,16}, although they do not have such an indication in the label -therefore they should be included in the treatment protocol for CRS approved by the CFyT-.

The pharmacist, as part of the multidisciplinary team, must verify that the lymphodepletion phase has been completed correctly and that the patient is prepared for the CAR-T drug infusion.

CAR-T cell prescription screening dispensing

Similar to lymphodepletion therapy, the CAR-T drug infusion protocol must be available in the hospital prescribing system, allowing its prescription for the planned date and its subsequent registration and follow-up by any member of the team who is responsible for the patient. This protocol should include concomitant premedication, medicines to avoid -for instance, corticosteroids from five days before CAR-T infusion or granulocyte and macrophage colony stimulating factors-, as well as any information relevant to their prescription, screening or administration. The pharmacist must screen the aforementioned prescription, bearing in mind the previous phases and the patient's clinical criteria^{8,9}.

Once the CAR-T therapy is screened, the involvement of the Pharmacy Service is crucial for coordinating the dispensing of the CAR-T on the date and time planned for its infusion, checking along with the rest of the multidisciplinary team that the patient is prepared for the infusion⁹. This process involves the following activities:

Double-check of both the patient's name and the medicine label.

Retrieval from the nitrogen tank, with its corresponding record.

Confirmation of a correct procedure for defrosting the medication and subsequent dispensing. The Pharmacy Service must ensure that adequate equipment is available for rapid defrosting of the cryopreserved bag/s prepared for the patient, as well as making sure an aseptic technique is used to prevent medication contamination. As these drugs whose

defrosted stability is not enduring (even less than 30 minutes), defrost can be assessed in the hospitalization unit. In the case of the existence of two or more bags for a given patient, the bags will be defrosted sequentially, so that until the end of the administration of the first bag, the process of adapting the second one will not proceed, and so on. The defrosting process must be properly registered by the pharmacist for each of the defrosted bags.

Dispensing of the defrosted CAR-T to the clinical hospitalization unit for later administration, by transporting it in a specific container with dry ice, or either a Dewar during vapor phase if defrosting has been carried out outside the hospitalization unit. Said dispensation must also be registered, recording the date and time of delivery for each of the bags intended for the patient and person receiving the medication.

Confirmation of availability of a carriage of stops and the necessary doses of tocilizumab -previously agreed in the CRS treatment protocol- at the clinical hospitalization unit.

Administration

The nursing staff will be responsible for the correct administration of CAR-T cells. However, the existence of a registry is vital -preferably in electronic format- to reflect the medical prescription process, the pharmaceutical screening and administration of CAR-T medicines, as well as the support treatments required for this type of therapy and the possible adverse effects or complications derived from the infusion⁹. In this sense, the computer system used for hospital oncohematological treatments is recommended.

Administering CAR-T medicines involves taking into account a number of key points, which the pharmacist can check:

Having premedication protocols, in which the dose of all medications to be used, such as paracetamol and antihistamines, should be indicated.

Discontinuing corticosteroids before administering CAR-T medication (five days before or five elimination half-lives), except in case of a vital

emergency. Physiological replacement of an equal to or less dose than 40 mg per day of hydrocortisone or equivalent is allowed.

Manipulating the bag with gloves and glasses to avoid potential risk of infectious diseases.

Using equipment for intravenous infusion without latex and without lymphocyte depletion filter.

Administering infusion at a rate of 10-20 mL per minute.

Infusing the entire content of each and every one of the bags intended for the patient.

Using physiological serum to purge the equipment before infusion and cleaning it afterwards.

Washing the bag with 10-30 mL of physiological serum, by retro purging, when the volume of CAR-T cells dispersion has already been infused, to ensure that the maximum number of cells is infused.

Having the car stop available at the hospitalization unit where the CAR-T medication is to be administered.

Checking the supply in the nursing unit and/or in the pharmacy service of the necessary doses of tocilizumab established in the protocol, in addition to other support medications established in each center's adverse effects management protocols.

Understanding of SOP on waste management and spills of dangerous drugs.

Pharmacovigilance and monitoring

The risk management plan for commercial CAR-T medicines requires the integration of a pharmacist into the healthcare team. The pharmacist is clinically responsible for the patient and has training and experience on recognition and management of adverse effects associated with this type of therapy, particularly in CRS, tumor lysis syndrome (TLS) and immune effector cell-associated neurotoxicity syndrome (ICANS) whose symptoms and recommendations are summarized in Table 2^{10,15}.

Table 2
Adverse events of CAR-T cells^{10,15}

Adverse effect	Recommendations
Tumor lysis syndrome – High uric acid levels – High tumor burden	– Allopurinol or alternative treatment – Control signs and symptoms, management according to standard guidelines
Mild cytokine release syndrome – Fever – Fatigue – Anorexia – Flu symptoms: nausea, headache and body aches	– Patient observation – Rule out infection – Administer broad-spectrum antibiotics according to local guidelines if there is febrile neutropenia, avoiding those with a higher risk of neurotoxicity (for example, avoid imipenem) – Administration of paracetamol on demand and hydration – Rate tocilizumab if persistent and refractory fever
Moderate cytokine release syndrome – High fever – Hypoxia – Moderate hypotension	– Administration of paracetamol on demand – Oxygen – Hydration with physiological serum – Vasopressors as needed (norepinephrine) – Assess tocilizumab if persistent and/or refractory fever, refractory hypotension or hypoxia
Moderate-severe cytokine release syndrome – High fever – Hemodynamic instability despite intravenous hydration and support vasopressors – Worsening of respiratory distress, including pulmonary infiltrates, increased oxygen requirements including high flow oxygen therapy and/or need for mechanical ventilation – Rapid clinical deterioration	– Administration of a high or multiple dose of vasopressors, oxygen, mechanical ventilation and/or other supportive care – Administration of tocilizumab: • If patient weights less than 30 kg: 12 mg/kg intravenously for 1 hour • If patient weights ≥ 30 kg: 8 mg/kg intravenously for 1 hour (maximum dose 800 mg) – Repeat another dose of tocilizumab with a minimum interval of 8 hours in case there was no clinical improvement – If there were no response with the second dose of tocilizumab, to consider a third dose of tocilizumab (maximum three doses in 24 hours) or look for other alternative measures of treatment of CRS is recommended – The maximum number of tocilizumab doses in total is four – If there is no improvement with the first tocilizumab dose in 12-18 hours, or if there is even worsening at any time, start treatment with corticosteroids: dexamethasone 0.5 mg/kg/6 h or methylprednisolone 1-2 mg/kg/day, divided into 2-4 doses. In the most severe cases, 1 g per day of methylprednisolone can be administered for 3 days, with a rapid progressive withdrawal according to response
Neurological effects – Marked change in mental state – Encephalopathy – Confusional syndrome – Delirium	– Manage depending on the underlying disease and according to local guidelines: • Corticosteroids: dexamethasone or methylprednisolone • Antiepileptics such as levetiracetam, phenobarbital, diazepam • Tocilizumab only if it is associated with cytokine release syndrome
Infections and febrile neutropenia	– Antibiotic prophylaxis: broad spectrum antibiotics – Control immunoglobulin levels

CAR-T: T cells with chimeric antigen receptor; CRS: cytokine release syndrome.

The most concerning adverse effect is CRS, a systemic inflammatory response that correlates with the *in vivo* activation and proliferation of CAR T cells and cytokines, released rapid and massively in blood. Initially, it occurs with fever and flu symptoms, such as nausea, headache and body aches that are considered mild symptoms, grade 1 or 2. They are managed with supportive therapy, which includes intravenous fluid therapy based primarily on physiological serum, broad-spectrum antibiotics such as meropenem, and analgesics and antipyretics such as paracetamol. CRS may present other symptoms -such as renal failure, heart failure, arrhythmias, diarrhea or hair weakness syndrome- and progress to a macrophage/hemophagocytic lymphohistiocytosis activation syndrome, with hepatic impairment and bleeding disorders.

It is necessary to monitor any signs of worsening of CRS, such as hypotension -which may require high doses of vasopressors such as norepinephrine- or hypoxia -which may require oxygen therapy and even mechanical ventilation-. Tocilizumab must be available to start treatment in less than two hours to prevent irreversible organic damage. In severe cases it may be necessary to start treatment with corticosteroids, dexamethasone or methylprednisolone. There are other therapeutic strategies recommended by experts in some cases or situations in which the patient does not respond or is refractory to standard treatment with tocilizumab with or without corticosteroids, such as siltuximab (another anti-interleukin-6), anakinra or anti-interleukins filters (such as Cytosorb[®]), although there is no extensive experience to recommend their incorporation into clinical practice guidelines^{15,16}. Granulocyte and macrophage colony stimulating factors administration is not recommended as CRS symptoms worsen¹⁵.

The other serious adverse effect is ICANS, which manifests itself with marked changes in mental state: aphasia, drowsiness, confusion, tremors, hallucinations, agitation, speech disorders, delirium, convulsions and unconsciousness, among others. It is recommended to have a baseline neurological assessment, which should be repeated daily in case of suspected neurotoxicity. Sometimes the pathophysiology of CRS and ICANS overlaps, although they are distinct adverse effects that must be recognized and treated by a multidisciplinary team. In the event of CRS and neurotoxicity occurring concomitantly, it may need to be addressed through tocilizumab treatment. However, if only ICANS occur, its administration is not recommended because the associated symptoms can be worsened¹⁵.

The patient is recommended to stay at least 10 days from the CAR-T infusion in hospital. Nevertheless, the patient must reside in an accommodation less than two hours away from the hospital during the first 28 days after the infusion, a period in which the appearance of adverse effects is more frequent. The pharmacist must participate as part of the multidisciplinary team in the patient's long-term follow-up, and know the recommendations for action in case of:

Hypogammaglobulinemia:

-- Assess the use of prophylactic antibiotics.

- Evaluate replacement therapy with intravenous immunoglobulins, according to age and standard guidelines.

Prolonged cytopenias:

- Avoid granulocyte and macrophage colony stimulating factors administration during the first three weeks post infusion, as CRS symptoms can be worsened.

Live vaccines:

- Avoid administering these vaccines until immune recovery.

Evaluation and recording of health results

In the “Approach Plan for Advanced Therapies in Spain’s National Health System: CAR drugs”⁷ considers the need to define the model for measuring health outcomes in clinical practice, with the objective of determining the added therapeutic value of CAR-T medicines. These variables must be included in the European registry of the European Society for Blood and Marrow Transplantation Cellular Therapy. The Plan establishes that an information system will be used, which is currently under design, called “Information system to determine therapeutic value in the actual clinical practice of high health and economic impact medicines in Spain’s National Health System (VALTERMED)”⁷. The pharmacist, due to their training and involvement in drug evaluation, must actively participate in this registration and evaluation.

Conclusions

The marketing of CAR-T medicines is a new challenge for the pharmacist specializing in Hospital Pharmacy, especially when expertising in the onco-hematological patient. It is of vital importance to know all the responsibilities and implications that the pharmacist must assume during the different phases included in a CAR-T therapy. Therefore, the oncohematological pharmacist must be and active member of the multidisciplinary clinical team responsible for the management and follow-up of CAR-T treated patients. All pharmacists’ functions must be established according to standard operational procedures and local guides of each hospital.

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Author notes

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