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Brief communication

# Clinical units to set up chimeric antigen receptor T-cell therapy (CAR T-cells): Based on the recommendations of the Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC)

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## ABSTRACT

The Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) hold its eighth practice harmonization workshops on September 2017. In a workshop dedicated to chimeric antigen receptor T-cell therapy (CAR T-cells), the society issued recommendations regarding the prerequisite for hematopoietic cellular therapy programs to set up CAR T-cell therapy. In this article we focused on the prerequisite needed, in France, for a hematopoietic transplantation unit to start a CAR T-cell program with industrial manufactured cells within investigational products or after market access authorization.

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## 1. Introduction

The main objective of the SFGM-TC practice harmonization workshop [1] was to identify the prerequisites for initiating a clinical trial evaluating chimeric antigen receptor T-cell therapy (CAR T-cells). Participants focused on the situation where CAR T-cells are manufactured by pharmaceutical companies and are intended to be placed on the market, following the delivery of a market authorization through the EMA centralized procedure, and negotiations for reimbursement conditions have been concluded with national authorities. They have excluded the situation where CAR T-cells are produced as investigational medicinal products or on a non-routine basis, based on the hospital exemption defined by European regulation CE 2007-1394, and further clarified in a French regulation (November 2016). In this scenario, CAR T-cells are to be produced on a small scale by a GMP facility authorized by the French national agency of safety of the drugs (ANSM), to supply a phase I or II clinical trial conducted in a restricted number of research sites in the same member state. Participants have

considered that this situation felt outside of the scope of the current harmonization workshop, although most of the prerequisites will be similar to that of industrial CAR T-cells [1].

## 2. Methodology

This workshop used the same methodology of for the prior series of the SFGM-TC harmonization workshops dealing with many aspects of routine medical practices [2]. However, since treatments with CAR-T cells are only in the early phases of their developments, and because of the small number of patients who received such products in France so far, the term “harmonization of practices” does not here reflect the reality. Only a limited number of clinical trials with CAR T-cells involving a small number of clinical sites have been authorized by the ANSM as of today. On one hand, these guidelines are thus based on an exhaustive review of the literature, including the experience of foreign sites and, on the other hand, on the experience of certain SFGM-TC centers that are working toward initiation of industry-sponsored protocols in the near future. The limited clinical experience of autologous CAR T-cells reinjection to some French patients has been taken into account. In addition to compiling existing literature and clinical experience, participants also performed a review of regulatory

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texts of the FACT-JACIE international standards for hematopoietic cellular therapy [3]. In this article we focus on the prerequisite needed for a clinical unit to start a CAR T-cell program with industrial manufactured cells within investigational protocols or post-approval uses in France.

Therefore, we, here, excluded the recommendations specific to apheresis facility, pharmacy, cell therapy unit, as well as regulatory issues.

### 3. Background

Management of patients undergoing CAR T-cells requires two mandatory conditions:

- (1) A structured clinical unit (CU) with well-established procedures to take in charge patients developing acute immunological complications.
- (2) An intensive care unit (ICU) close to the clinical unit with a well-established collaboration between the two units (CU and ICU).

The severity and the frequency of CAR T cell-related complications along with their immunological substratum suggest that the patients could benefit from the existing organization of hematopoietic cell transplantation programs that are acknowledged by FACT-JACIE accreditation. Indeed, JACIE involves a well-established interaction between the transplantation unit and the ICU (see standard B2.6 of the guidelines, the FACT-JACIE International Standards for Hematopoietic Cellular Therapy v6.01) [4].

### 4. Recommendations

The administration of CAR T-cells requires a highly coordinated interaction of multiple specialists belonging to different infrastructures within health establishments in order to ensure the safety of the patients. For patient management, the SFGM-TC recommends minimum prerequisites likely to be completed by the specific requirements for each protocol and each type of CAR T-cells:

- A JACIE accreditation. Indeed, the JACIE committee is working on the implementation of the next edition of the FACT-JACIE standards, of a section that will be specifically dedicated to the therapeutic management of immunotherapies.
- A clinical unit with an optimal nurse/patient ratio to insure a continuous monitoring of patients at risk of developing acute immune complications (ideally 1 nurse/4 patients) [5,2].
- Medical and paramedical staff with documented experience:
  - in the administration of combinations of cytotoxic and immunosuppressive drugs
  - in the administration of previously cryopreserved cellular therapy products (Standard B3.7, B3.7.3.3, 3.7.4.3 of the FACT-JACIE International Standards for Hematopoietic Cellular Therapy v6.01)
  - in the management of patients developing acute immune complications likely to be life-threatening in a short period of time
- A physician specialized in hematology and/or transplantation on duty 24/7.

- Availability of tocilizumab (or another drug likely to attenuate the side effects according to the requirements of the sponsor and specificity of the CAR T-cell products) at the pharmacy of the establishment with a supply in the care unit that is available immediately.

Taking into account the time to occurrence of cytokine release syndrome reported in the literature, the SFGM-TC recommends that the minimum initial hospitalization duration should be of 14 days after the administration of the CAR T-cells. For patients developing profound neutropenia, the hospitalization in a protected room is recommended. It is also recommended that the CU organizes systematic evaluation of patients by an ICU specialist at regular-basis in order to undergo pre-emptive interventions whenever necessary. The ICU specialist should be familiar with the specific CAR T-cell complications.

Staff members have to be informed on the nature and risks/absence of risks for the environment/the operators associated with the administration of CAR T-cells that are GMO (refer to manual of confined use of GMOs in the setting) [6].

All this skills and expertise is brought together in allogenic hematopoietic cell transplantation (allo-HCT) units that are JACIE accredited. For the autologous hematopoietic cell transplantation units without allogenic activity, but which meet the criteria aforementioned, close collaboration with a nearby allo-HCT unit is recommended. This is all the more justified since treatment with CAR T-cells can necessitate, more or less rapidly, consolidation by allo-HCT. This latter can be indicated when CAR T-cells are used as a “bridging” to an allo-HCT or in the case of profound and prolonged cytopenias caused by “off target” toxicity of CAR T-cells.

### 5. Conclusion

To our knowledge, the SFGM-TC recommendations are the first to set up a framework that take into account primarily the safety of patients undergoing CAR T-cell therapy. These recommendations will evolve as our experience progresses.

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