EBMT European Society for Blood and Marrow Transplantation

Quality Management, 7° Edition Standard

Immune effector cells standards

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CONFLICT OF INTEREST DISCLOSURES

No disclosures

- Adoptive T cell transfer (ACT) is a new area of transfusion medicine involving the infusion of lymphocytes to mediate antitumor, antiviral, or anti-inflammatory effects.
- Durable clinical responses of otherwise treatment-refractory cancers have recently been achieved, revealing the power and potential of ACT.
- The field has rapidly advanced from a promising form of immuno-oncology in preclinical models to the recent commercial approvals of chimeric antigen receptor (CAR) T cells to treat leukemia and lymphoma.
- A gradual shift from academic research to a pharma-driven clinical practice

EBMT European Society for Blood and Marrow Transplantation

JACIE Joint Accreditation Committee ISCT | EBMT

Immune Effector Cells and JACIE Standard

- Starting with version 6.1, the Standards include new items specifically developed for other cellular therapy products, with special reference to immune effector cells (IEC).
- This reflects the rapidly evolving field of cellular therapy through mainly, but not exclusively, genetically modified cells, such as CAR-T cells.
- The Standards do not cover the manufacturing of such cells, but include the chain of responsibilities where the product is provided by a third party and ensure the competence of the personnel in the management of adverse events related to the infusion.

FACT-JACIE Standards (7th Ed) apply to:

1. Hematopoietic progenitor cells from hematopoietic sources

2. Nucleated cells or mononuclear cells from any hematopoietic tissue source collected for therapeutic use other than as hematopoietic progenitor cells

3. **Immune effector cells derived from these sources, defined broadly as any cells, in vitro modified or not, that are capable of eliciting or modulating an immune response.**

- **This broad designation includes cellular therapy products with widely diverse manufacturing methods, constructs, clinical indications, and safety and toxicity profiles.**

FACT-JACIE Standards: IECs and QM

B7.11 There shall be policies or Standard Operating Procedures addressing the administration of immune effector cells and management of complications, if applicable.

B7.11.1 There shall be a **consultation with the referring physician** prior to initiation of immune effector cellular therapy to review the goal and plan of the treatment.

B7.11.2 There shall be regular **assessment of the recipient to detect complications,** including cytokine release syndrome and neurologic dysfunction.

B7.11.3 There shall be a **written plan for rapid escalation of care**, increased intensity of monitoring, and relevant workup to address complications.

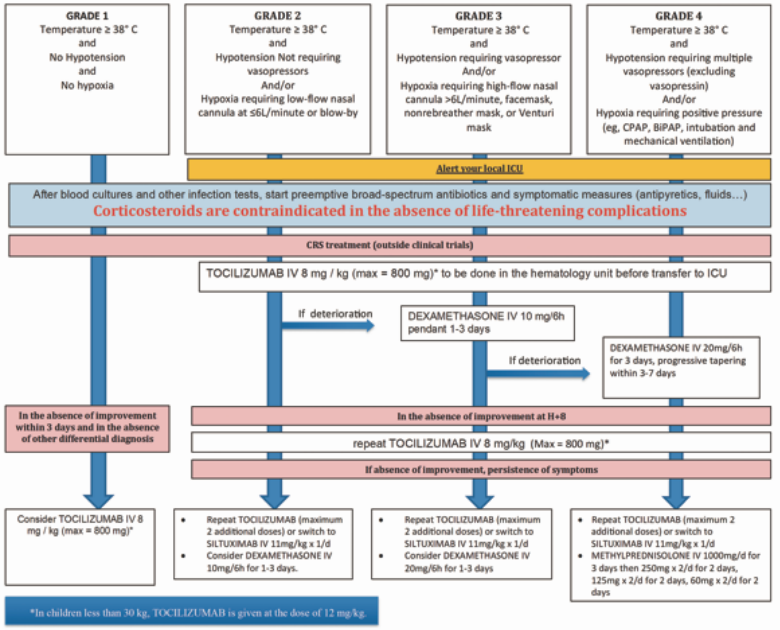
B7.11.4 **Communication** to the clinical staff, intensive care unit, emergency department, and pharmacy shall be timely.

B7.11.5 The Clinical Program shall have **written guidelines for management of complications**, including the use of **cytokine blocking agents** and corticosteroid administration.

Haematologica HAEMATOL/2019/229781 Version 3

Management of Adults and Children undergoing CAR T-cell therapy: Best Practice Recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE)

Ibrahim Yakoub-Agha[1], Christian Chabannon[2], Peter Bader[3], Grzegorz W. Basak[4], Halvard Bonig[5], Fabio Ciceri[6], Selim Corbacioglu[7], Rafael F. Duarte[8], Hermann Einsele[9], Michael Hudecek[9], Marie José Kersten[10], Ulrike Köhl[11], Jürgen Kuball[12], Stephan Mielke[13], Mohamad Mohty[14], John Murray[15], Arnon Nagler[16], Stephen Robinson[17], Riccardo Saccardi[18], Fermin Sanchez-Guijo[19], John A Snowden[20], Micha Srour[21], Jan Styczynski[22], Alvaro Urbano-Ispizua[23], Patrick J. Hayden[24] and Nicolaus Kröger[25]



Haematologica, online ed, 2019

Yakoub-Agha et Al, Haematologica, online ed, 2019

Period	SPCs and protocols	EBMT recommendations	Comments
Day 0 to Day +14 post-infusion	Some protocols require 5-14 days hospitalisation after the infusion	Ideally, 14 days hospitalisation	Shorter hospitalisation periods as well as outpatient follow-up are possible in centres that can provide 24/7 contact with immediate availability of specialist inpatient care. Patients have to be located within 30 minutes of the centre
From hospital discharge to Day +28 post-infusion	Some protocols require that patients be located within 30 to 60 minutes of the centre	Patients have to be located within 60 minutes of the treating unit or a well-equipped centre* The continuous presence of a caregiver who is educated to recognize the signs and symptoms of CRS and ICANS is required	CRS and, in particular, ICANS can occur after the patients has left the hospital. In addition, life-threatening complications may occur during this period e.g. septic shock in neutropenic patients

Table 7. Recommendations regarding the first month after CAR-T infusion

Type of therapy	SPCs	EBMT recommendations	Comments
Allo-HCT	No guidance	Patients should be off immunosuppression and GVHD-free	A minimum of one month is recommended
DLI	No guidance	Four weeks	6-to-8 weeks may be safer to rule out any GVHD
High-dose chemotherapy	No guidance	3-to-4 weeks depending on the intensity of the chemotherapy	Recovery from cytopenias is required
CNS-directed therapy	No guidance	One week	
Short-acting cytotoxic/anti-proliferative drugs	No guidance	Three days	Recovery from cytopenias is required
Systemic corticosteroids	No guidance	Ideally, seven days to minimise any effect on lymphocyte collection	A shorter period of as few as three days was considered acceptable by Kansagra *et al* (12) Regardless of timing, an ALC>0.2 x10^9/L is preferable given the likely effect of recent corticosteroids on lymphocyte quality

Table 4. Wash-out period before leukapheresis (adapted from Kansagra et al, BBMT 2018)

JACIE ACCREDITATION: APPLICANT TOOLS

The Standard

B7.11.2 There shall be regular assessment of the recipient to detect complications, including cytokine release syndrome and neurologic dysfunction.

The Manual

Example(s):

- In addition to IND requirements, investigator experience may generate ideas for detecting complications. Attending physicians may want to request additional laboratory testing, such as C-reactive protein, lactate dehydrogenase, ferritin, and fibrinogen. For example, evaluating fibrinogen periodically after CAR administration may be useful for early detection of disseminated intravascular coagulation (DIC).

Intensive Care Unit

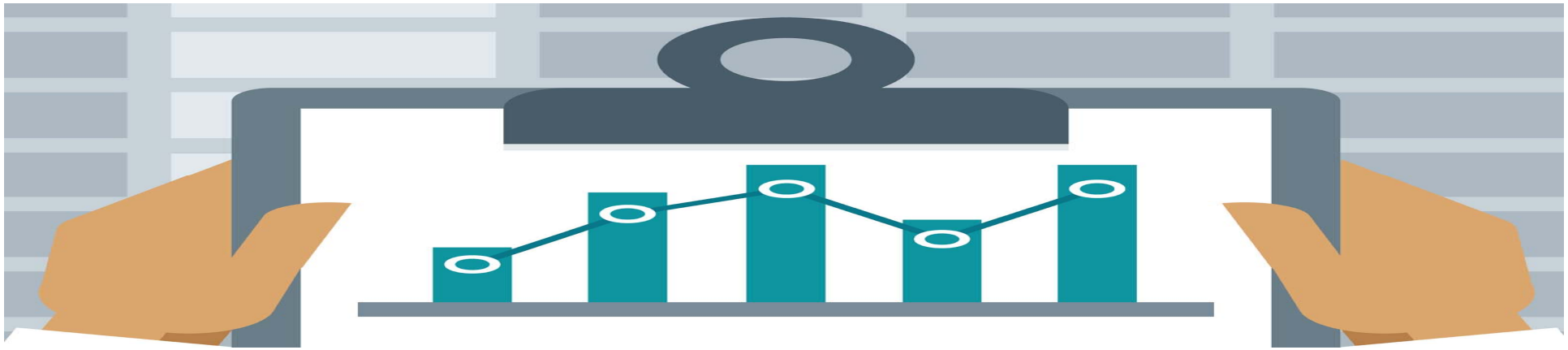
- Close interaction with ICU team
- Education for the ICU team in CAR-T adverse events
- Communication
- Patient monitoring
- Transfer of patients

- **NOTE**: substantial variation in how IC is organised; typically difficult to guarantee exclusive access for CAR-T patients

Standards: Outcome review

- B4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:
  - B4.7.3.2 For immune effector cells, an endpoint of clinical function as approved by the Clinical Program Director.
- B4.7.3.3 Overall and treatment-related morbidity and mortality at
  - thirty (30) days
  - one hundred (100) days,
  - one (1) year

  after transplantation cellular therapy product administration.



Standards: Long term follow-up

- B7.12.1 Policies or Standard Operating Procedures for monitoring by appropriate specialists of recipients for post-cellular therapy late effects, including at a minimum:
  - Endocrine and reproductive function and osteoporosis.
  - Cardiovascular risk factors.
  - Respiratory function.
  - Chronic renal impairment.
  - Secondary malignancies.
  - Growth and development of **pediatric** patients.

Personnel

- Minimum experience established
- Continuous education = 10 hours per year
    - in transplant-related areas
- Some specific areas of competency (mostly in Part B)
- No specific staffing numbers
    - “Adequate”, “satisfactory”
- Provision for trained back-up staff

IECs: personnel training

B3.7.3 **Nurses** shall have received specific training and maintain competence in the transplant-related skills that they routinely practice including:

- B3.7.3.4 Detection and management of immune effector cellular therapy complications including, but not limited to, those listed in B3.7.3.4.

Because cytokine release syndrome requires rapid care and attention, nurse training on this condition should include institutional policies on accessing and administering pertinent medications (such as tocilizumab).

B3.8.2 Training and knowledge of designated **pharmacists** shall include:

- B3.8.2.2 Adverse events including, but not limited to, cytokine release syndrome and neurological toxicities.

JACIE ACCREDITATION:

6.01ref HSCT	6,01 standard HSCT	Guidance	Applicant's assessment	Source of evidence and explanatory text	Inspector's Assessment	Inspector's Comments *(support your answers with additional information)*
B1.2.1	If cellular therapy products are received directly by the Clinical Program from a third-party provider, the following responsibilities at a minimum shall be defined in a written agreement:	**Explanation:** These standards apply to novel cellular therapy products that are manufactured by a third-party (not part of the hospital institutional structure e.g. pharmaceutical company) and routed through an accredited blood bank, accredited tissue bank, or a hospital pharmacy rather than a Processing Facility. Communication with manufacturers is critical to the safety, efficacy, and quality of the cellular therapy product, and the Clinical Program is responsible for handling products according to the Standards. Chain of custody documentation should include dates, times, and responsible parties for distribution and receipt; storage; and release for administration. The distribution conditions should be defined by the Clinical Program with documentation that those conditions were met (e.g., temperatures during transport or shipping). The program (or receiving blood bank, tissue bank, or pharmacy) should have		Please indicate here evidence that responds to this standard		
B1.2.1.1	Traceability and chain of custody of cellular therapy products.	as above		Please indicate here evidence that responds to this standard		

IECs Standards: Chain of Responsabilities

B1.2.1 If the **Clinical Program or an intermediary facility receives cellular therapy products directly from a third-party provider**, the following responsibilities shall be defined, at a minimum, by a written agreement:

- B1.2.1.1 **Traceability** and chain of custody of cellular therapy products.
- B1.2.1.2 Cellular therapy product **storage and distribution**.
- B1.2.1.3 Verification of cellular therapy product **identity.**
- B1.2.1.4 Review and verification of product specifications provided by the **manufacturer**, if applicable
- B1.2.1.5 Readily available access to a summary of documents used to determine allogeneic **donor eligibility**.
- B1.2.1.6 Documented evidence of allogeneic **donor eligibility screening** and testing in accordance with applicable laws and regulations.

JACIE
Joint Accreditation Committee
ISCT | EBMT

IEC: accreditation challenges

- Standards are a ‘work in progress’
  - Technology moving fast
- Inspector pool and lack of experience of IECs
- IEC definition is very broad in order to encompass all possible IECs
  - Maybe ‘overkill’ for low-risk CT products

Current thinking

- Take risk-based approach
- Thresholds for defining the classes of risk to be defined

Low Risk	High Risk
Tumour infiltrating lymphocytes (TILs)	CAR-T cells
Dendritic cells	NK cells
Viral specific cytotoxic T cells (vCTLs)	TILs with adjuvant therapy – IL2
Mesenchymal stromal cells (MSCs)	
Cytokine Induced Killer (CIK) cells	

CAR-T PROGRAM: RESPONSABILITA' E RUOLI

Azione	Responsabilità
Selezione e screening del paziente	Centro clinico
La raccolta mediante linfocitoaferesi (Cropreservazione -> Novartis)	
La spedizione alla cell factory	Produttore
Il trattamento delle cellule ed il loro congelamento	
L'invio del prodotto finito al Centro clinico	
Il controllo e lo stoccaggio controllato in vapori di azoto	Centro clinico
La somministrazione di una chemioterapia immunoablativa	
Lo scongelamento e la somministrazione delle cellule	
Monitoraggio clinico e trattamento delle complicanze a breve termine	
Il monitoraggio a lungo termine (15 anni)	

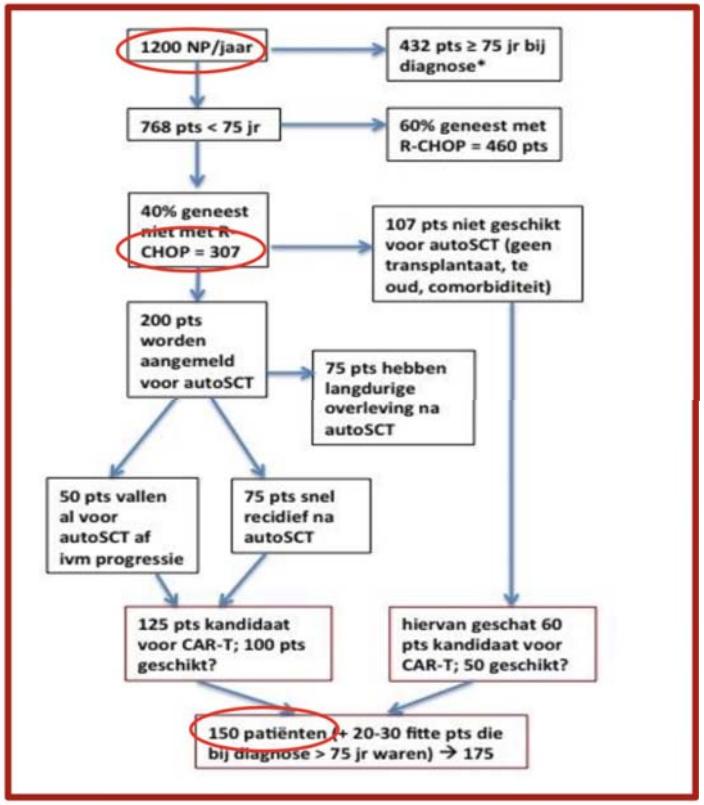
Involved Services

In all the involved areas, evidence of adequate personnel training, manpower, validated procedures, product identification and traceability, efficient communication, shall be in place

Service	Action
Outpatient	Patient selection
Inpatient/Outpatient Unit	Clinical monitoring and Therapy
Apheresis unit	Collection, Product quality
Pharmacy	Drug availability
ICU	Plan for rapid care escalation
Neurology	Clinical monitoring and Therapy
Processing lab	Storage and thawing
Data Managing	FU and Registry Report

Implementation of a IEC program

- An implementation plan aimed to fulfill all the accreditation requirements, engaging all the professionals, services and involved infrastructures is essential
- Before starting, an exhaustive estimation of eligible patients, general needs and costs has to be carried out and approved by the Competent Authority



Courtesy of Dr. Minninna, Utrecht

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Thanks!

Any questions?

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