

PERSPECTIVE

**THE ROLE OF CRYOPRESERVATION TECHNIQUES IN
MANUFACTURING, TRANSPORT, AND STORAGE OF CAR-T THERAPY
PRODUCTS**

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Abstract

Several clinical trials have proved the efficacy and safety of T-cells chimeric antigen receptor (CAR-T cells) in treatment of malignant lymphoma and the first products were registered in the European Union in 2018. The shelf-life of CAR-T cell products in the liquid state is short, so cryopreservation offers a significant benefit for logistics in manufacturing and patient management. Direct shipment of the cryopreserved CAR-T cell therapy products to the clinical department is feasible, nevertheless, intermediate storage in the hospital cryostorage facility gives significant advantage in planning of their administration to patients. Moreover, some manufacturers prefer transport of the starting material cryopreserved at the collection site. The cryopreservation protocol used for starting material by the authors is based on combining dimethyl sulphoxide (DMSO) with hydroxyethyl starch (HES) and slow controlled cooling in cryobags housed in metal cassettes. This achieves the mononuclear cell post-thaw viability of 98.8 ± 0.5 % and recovery of $72.8, \pm 10.2$ %. Transport of the starting material to the manufactures and return transport of the CAR-T therapy product is performed by authorized courier companies. Intermediate cryostorage of the final CAR-T cell therapy product is performed in a separate dry-storage liquid nitrogen container. On the day of infusion, the cryopreserved products are transported to the clinical department in a dry shipper. On the wards the product is removed from the cassette, inserted into a sterile plastic bag, thawed in a 37 °C water bath followed by immediate intravenous administration. The authors discuss the adherence of the used technology to good manufacturing practice (GMP) principles and genetic safety assurance rules.

Keywords: CAR-T, advanced therapy medicinal product, cryopreservation

INTRODUCTION

Several clinical trials (1,2) have proved the efficacy and safety of chimeric antigen receptor engineered cell therapy (CAR-T therapy) in the treatment of malignant lymphoma. The first CAR-T products tisagenlecleucel (Kymriah), Novartis Europharm Ltd., Dublin and axicaptagene ciloleucel (Yescarta), Kite, Pharma, Netherlands, were registered in the European Union in 2018. Indications for use include B-cell acute lymphoblastic leukaemia in children and young adults and diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma in adults (3,4). Brexucabtagene autoleucel (Tecartus) by Kite Pharma, Netherlands is authorized since 2020 and indicated for adult patients 26 years and older with relapsed or refractory acute lymphoblastic leukaemia and relapsed or refractory mantle cell lymphoma (5). Clinical trials with investigational CAR-T therapy products of aimed at treatment of multiple myeloma, are in progress, now (6). Direct shipment of the registered or investigational cryopreserved CAR-T cell therapy products to the clinical department and short-term storage at ultra-low temperatures in dry shippers of authorized courier companies is feasible, nevertheless as an alternative approach intermediate storage of CAR-T therapy products in the hospital cryostorage facility gives significant advantages in planning of their clinical application. Moreover, some manufacturers, prefer transport of the starting material cryopreserved at the collection site.

The collection of the starting material its processing, storage, and release for manufacturing by the responsible person of the Tissue Establishment is in hands of authorized tissue establishments (TE) and performed under strictly non-profit conditions. The final registered product is a drug for autologous use with the characteristics of an advanced therapy medicinal product (ATMP). After release by the manufacturer's qualified person the product is handled and administrated only in certified clinical CAR-T cell therapy centres. The clear rules of co-operation defining the responsibilities of individual partners must be settled among the TE s providing the starting material, CAR-T therapy product manufacturers and the clinical CAR-T therapy centres to achieve quality and safety during all collection, processing, manufacturing, and distribution

steps and to prevent deterioration of the extremely expensive product. The requirements of the European and American manufacturers on the storage and transport conditions for final CAR-T therapy products may differ as the American companies must follow the Food and Drug Administration (FDA) rules for storage of ATMPs (7). The European Society for Blood and Marrow Transplantation (EBMT) recently published a special CAR-T Handbook (8), which is oriented exclusively on the clinical aspects of this kind of therapy; generally the manufacturers expect that the cooperating collection and processing facilities as well as clinical centres are the FACT-JACIE (Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee of International Society for Cellular Therapy and EBMT) accreditation holders or are at least familiar with the FACT-JACIE Standards (9), the EBMT Handbook (10) and principles of the GMP (11). The only specific recommendation for collection, processing, storage and administration of the CAR-T products is the JACIE-EBMT recommendation from 2018 (12). In case of using investigational CAR-T therapy products the general rules for handling of genetically modified organisms (GMO) must be followed.

In this review, we express our opinion on several issues encountered in the cold chain of these products on basis of the experience of the University Hospital Hradec Králové and its Tissue Establishment (EU TE CODE CZ000426). We explore various considerations: the potential substitution of DMSO with DMSO-free cryopreservation medium (if equivalent efficacy and safety can be maintained); the use of outer metal cassettes for protection of cryopreserved products during storage and transport; the implementation of strict control of temperature records during transport and storage; the use of continuous evaluation the post-thaw viability, recovery and sterility of the starting material; and evaluation of their compliance with the instruction of manufacturers. The genetic safety assurance and adherence to the GMP principles are discussed as well. The whole collection, processing, manufacturing, and transport processes are summarized in the Fig 1.

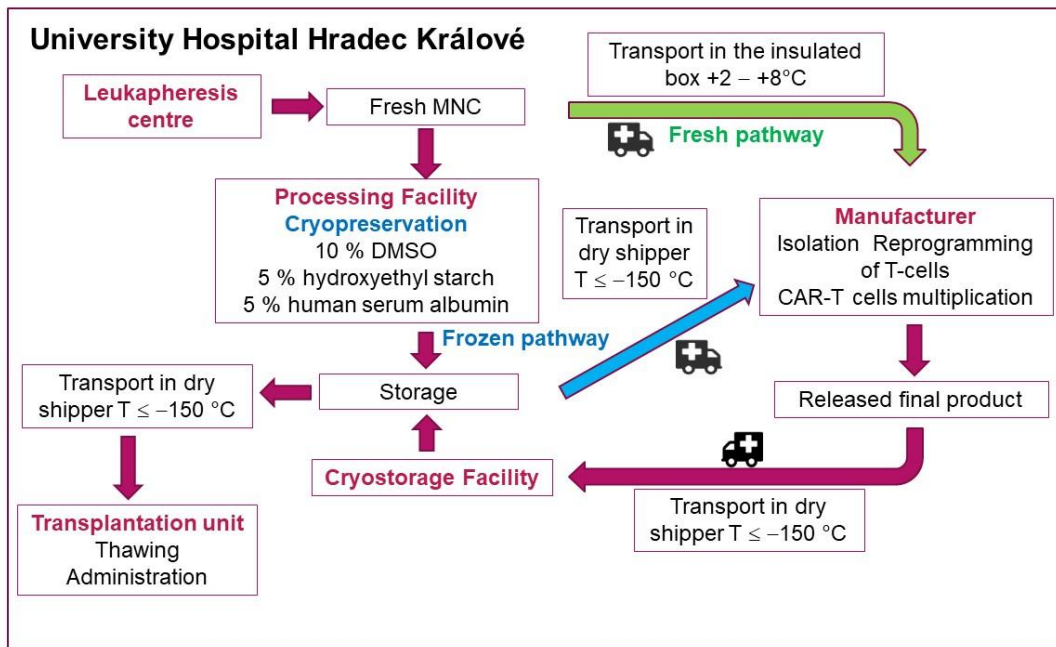


Figure 1. The algorithm of the CAR-T production process.

FUNDAMENTAL ASPECTS OF CURRENTLY USED PROTOCOL

Benefits of using cryopreservation in manufacturing the CAR-T therapy products and starting materials

In the CAR-T production and distribution pathway, the cold chain facilitated by cryopreservation is preferred by manufacturers as it allows optimal management of logistics, and provides sufficient time for testing of sterility and cell potency to fulfil release criteria of the final registered or investigational product (13). Extensive review on *in vitro* and *in vivo* tests of CAR-T cell potency was published recently by Si et al. (14). It is also recognized that cryopreservation has an important role at the start of preparing a peripheral blood mononuclear cell (PBMC) isolate, as collection sites are often distant to dedicated manufacturing sites. Cryopreservation of the starting material provides scheduling flexibility for patients, thus allowing the adequate timing of the leukapheresis procedure according to their convenience (15–17). It also prevents possible deterioration of unfrozen PBMC collections that may be caused by transport delays due to different unexpected reasons. In certain cases, it might be beneficial for the patient to undergo preemptive PBMC collection and cryopreservation to prevent use of cells with impaired potency due to planned aggressive

chemotherapy. In such cases stored starting material can be sent to the manufacturing site after several months.

Cryopreservation protocols for the starting material

Cryopreservation of the starting material – mature PBMCs has been shown to provide important benefits mentioned above, even though recoveries of total nucleated cells may be reduced by direct cryopreservation injuries and delayed onset cell death for up to 48 hours post thaw (18). Secondary cryoprotectants (CPAs) are frequently added to the DMSO; combinations with hydroxyethyl starch (6 %), human serum albumin (4 %) and/or electrolyte solution (in the most cases Plasma-Lyte A, X-Vivo, Normosol or Saline) allow reduction of DMSO to 5–7.5 % (15,19,20). HES and dextran seem to be the secondary CPAs of choice, which can modulate the osmotic effects of ice formation during slow cooling. PBMC collections are cryopreserved in volumes similar to those used for mobilized HPC (human peripheral progenitor cells) cryopreservation (19) and/or cryopreservation of non-mobilized PBMCs (16,18,19). Typically, three to four 100-mL double cryobags closed in metal cassettes are used. The TE CZ000426 uses the protocol for non-mobilized MNCs that achieves the high MNC post-thaw viability and recovery (Table 1a, b). Some protocols involve induction of ice

Table 1a. Parameters of thawed PBMC suspension collected in 16 donors, estimation from thawed control samples.

	Volume (mL)	NC concentration (10 ⁹ /L)	% MNC	NC viability (%)	MNC viability (%)	Number of viable CD3 ⁺ (10 ⁶)
Mean	355.8	37.1	95.2	98.2	98.9	7209.5
SD	150.2	15.2	2.3	0.7	0.5	4153.9
Median	300.0	34.0	95.7	98.0	99.0	5711.8

Note: NC – nucleated cells, MNC – mononuclear cells

Table 1b. Recovery of nucleated mononuclear and viable CD3⁺ cells after thawing.

	Viable NC (%)	Viable MNC (%)	Viable CD3 ⁺ (%)
Mean	73.7	72.8	73.2
SD	10.3	10.2	14.3
Median	88.3	87.9	88.6

NC – nucleated cells, MNC – mononuclear cells

nucleation by brief rapid cooling shock at –6 °C, then cooling at –1 °C per minute to –40 °C, followed by –10 °C per minute to –90 °C and storage in vapour phase of liquid nitrogen (LN₂) (21). The ISBT 128 standard is commonly used for labeling the cryobags to assure transfer of data necessary for proper labeling of the final product (22).

Cryopreservation protocols for the final CAR-T therapy product

The well-established cryopreservation

protocols for mobilized HPC or non-mobilized mature mononuclear cells (16) that were based on the use of DMSO as cryoprotectant and controlled slow rate cooling using programmable freezers (19, 23) have been applied to CAR-T cell production. DMSO at or close to 10 % v/v and cooling rate of –1 °C per minute have been used.

However only few studies have investigated aspects of the protocol, e.g. steps to minimize the impact on the cells of heat of solution when adding DMSO (24). Final CAR-T therapy

Table 2. Examples of realized transport of the fresh or cryopreserved starting material from the TE CZ000426 to the manufacturing site.

Transport number	Prescribed transport temperature	Final product	Courier	Manufacturing site
1	Fresh +2–8 °C	Yescarta	Marken	Hoofddorp, The Netherlands
2	Fresh +2–8 °C	Yescarta	Quick	Hoofddorp, The Netherlands
3	Cryo below –120 °C	Kymriah	World Courier	Stein, Switzerland
4	Cryo below –120 °C	Kymriah	World Courier	Stein, Switzerland
5	Fresh +2–8 °C	JNJ-68284528	World Courier	Beerse Antw, Belgium
6	Fresh +2–8 °C	JNJ-68284528	World Courier	Beerse Antw, Belgium

Table 3. Examples of transport of the cryopreserved CAR-T therapy product to the user, CAR-T therapy centre.

Transport number	Product/prescribed transport temperature	Courier	Distance (km)	Transport time (hours)
1	Yescarta below $-150\text{ }^{\circ}\text{C}$	Marken	994	19.4
2	Yescarta below $-150\text{ }^{\circ}\text{C}$	Marken	994	23.0
3	Kymriah below $-120\text{ }^{\circ}\text{C}$	World Courier	1323	15.9
4	Kymriah below $-120\text{ }^{\circ}\text{C}$	World Courier	1323	25.0
5	JNJ-68284528 below $-120\text{ }^{\circ}\text{C}$	World Courier	903	43.8
6	JNJ-68284528 below $-120\text{ }^{\circ}\text{C}$	World Courier	903	93.0



Figure 2 a. Liquid nitrogen container MVE (Chart, Bio Medical Ltd., USA) that uses „dry-storage“ technology; **b.** detailed close-up view on the frame in the interior of the container (Source: Tissue Establishment CZ000426, Czech Republic).

products are obtained by positive selection cell sorting leading to considerable reduction of the initial volume before genetic manipulation. They are cryopreserved in small volumes, in single polyfluoroethylene cryobags protected by metal cassettes. Exclusive storage in the liquid nitrogen vapour phase is strongly recommended by manufacturers during intermediate storage in the hospital cryostorage facility as well as during transport to the clinical department.

Storage and transport conditions for the starting material

Vapour phase of the LN_2 is recommended for storage of starting material under the

conditions settled by the EU Directives that are compatible with the American Good Tissue Practice regulation (7). We use a liquid nitrogen container with a copper heat shunt combined with automatic filling and continuous temperature recording at two levels. The high temperature alarm is set to $-160\text{ }^{\circ}\text{C}$.

Transport of cryopreserved starting material to the manufacturing site is performed by authorized courier companies in advanced dry shippers equipped with software for telemetric continuous temperature monitoring. Transport should be performed at temperatures below $-120\text{ }^{\circ}\text{C}$. In the ideal case the double bagged starting material is transported in the metal

cassettes in which it was frozen. Alternatively, the bags are removed from cassettes and transported in special paper packs provided by the CAR-T manufacturer.

Transport of the final product to the user, its temporary storage and transport to the clinical CAR-T cell therapy centre

Transport of the final CAR-T product to the user is usually provided by the same courier company that transported the cryopreserved starting material, exceptions exist, however (Tables 2 and 3). In the ideal case a single bagged CAR-T therapy product is transported closed in the metal cassette. Alternatively, the product is transported in special paper packs provided by the CAR-T manufacturer. Several CAR-T product manufacturers require the transport temperature to be below $-120\text{ }^{\circ}\text{C}$, others require the temperature below $-150\text{ }^{\circ}\text{C}$ as settled by the American federal regulation for ATMP manufacturing (25).

Exclusive storage of the final CAR-T therapy product in the separate GMP compliant liquid nitrogen vapour phase storage container placed in the hospital cryostorage facility (Figure 2) is strongly recommended (12). The Figure 2 shows the liquid nitrogen container MVE (Chart, BioMedical Ltd., USA) providing dry sample storage with vapor storage temperature of $-190\text{ }^{\circ}\text{C}$.

The common standard is the use of liquid nitrogen containers with „dry-storage“ technology and automatic filling. Each product type should be stored in a special frame marked with the its commercial name (8,12). As the size of cassettes used by different manufacturers may differ it is convenient to place the cassette with the CAR-T product into a pre-cooled larger secondary metal cassette. When the product is delivered in a paper pack, the bag is removed and placed into the secondary cassette, and fixed with sheets of non-woven texture “Perlan” (Perla a.s., CZ). Direct contact of the cassette and/ or bag with the final CAR-T therapy product with the liquid phase of nitrogen should be avoided to prevent the product leaking and cross contamination with the genetically modified product.

The storage temperature should be adjusted below $-150\text{ }^{\circ}\text{C}$, which is the upper limit for storage of ATMPs settled by American federal regulation.

Figure 3 and 4 show temperature and liquid nitrogen level records comparing traditional

vapour phase storage in a liquid nitrogen container with copper-heat shunt still routinely used for storage of HPCs with that of a liquid nitrogen container that uses „dry-storage“ technology.

Each access to the container must be recorded. When storing an investigational product labeling of the container and of the entrance of the facility with GMO warning label is mandatory. Also, an annual report on GMO manipulation must be sent to the national competent authority (Ministry of Environment in the Czech Republic). Strict access control to the cryostorage area and its videosupervision are also regarded as standard.

The transport from the hospital cryostorage facility to the clinical CAR-T therapy Centre is performed in more simple dry shippers equipped with temperature dataloggers. After the check of the patient’s data, the secondary cassette is removed from the storage container and placed into the dry shipper. Transport is performed at temperature below $-150\text{ }^{\circ}\text{C}$. The transport temperature records are downloaded and printed.

Thawing and infusion

Rapid thawing is performed at the clinical CAR-T therapy centre by immersion of the cryobag covered by the outer secondary sterile bag into a sterile water bath maintained at $37 \pm 2\text{ }^{\circ}\text{C}$ (Figure 5) or at an automated dry-thawing system (26). Before starting to thaw the CAR-T cell product, the patient should be assessed, including the administration of pre-medication to prevent any serious adverse reaction. A double check (four eyes principle) must be performed before administration to avoid any error (8).

The interval between thawing and administration is from 30 to 90 min, depending on manufacturer’s instruction. The cells are delivered intravenously at a 10–20 mL/min infusion rate. Patients must be monitored for possible side effects for at least 2 weeks (8). Examples of the thawing, manipulation and infusion times are presented in the Table 4.

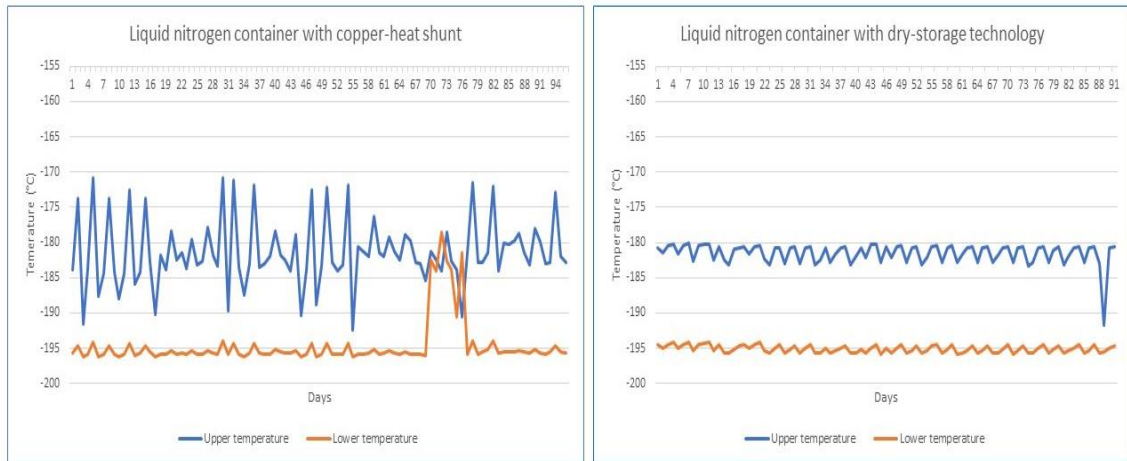


Figure 3. Temperature records comparing traditional vapour phase storage in the liquid nitrogen container with copper-heat shunt (left) and in the container that uses “dry-storage technology” (right).

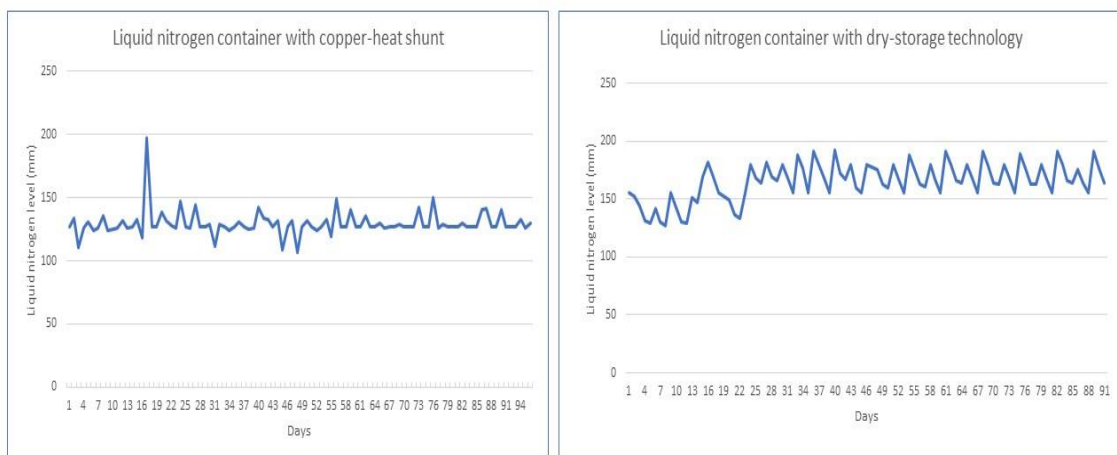


Figure 4. Liquid nitrogen level records comparing traditional vapour phase storage in the liquid nitrogen container with copper-heat shunt (left) and in the container that uses “dry-storage technology” (right).



Figure 5. Thawing of the CAR-T product in a water bath. (Source: Tissue Establishment CZ000426, Czech Republic).

Table 4. Examples of CAR-T therapy product thawing and infusion.

Case No.	Product type	Product volume (mL)	Thawing time (min)	Manipulation time (min)	Infusion time (min)
1	Yescarta	68	3	4	7
2	Yescarta	68	5	3	10
3	Kymriah	50	2	2	3
4	Kymriah	50	3	2	4
5	JNJ-68284528	70	3	2	6
6	JNJ-68284528	70	5	2	7



Figure 6. Installation, operational and process qualification performed by the supplier company.

General requirements to facilities

Facilities which cryopreserve and store the starting materials for ATMPs manufacturing must be holders of at least national Tissue Establishment license for collection, processing, storage, and distribution of mature PBMCs for ATMP manufacturing. Facilities receiving final products for intermediate storage need to have separate storage containers used exclusively for genetically manipulated material. Depending on national legislation, a storage facility may need regulatory approval as gene therapy medicinal product manufacturers. In the Czech Republic such approval has not been yet required, nevertheless a separate GMP compliant container with strict access control and validated according to the trilogy of installation, operational and process qualification (IQ, OQ,

PQ) (Fig. 6) should be used for storage of CAR-T therapy products. A GMP certificate or certificate of genetic safety issued by the national competent authority may be also required in some countries as CAR-T cell products are also genetically modified organisms. In the Czech Republic specific approval of the Ministry of Environment is required if investigational CAR-T therapy products are stored.

DISCUSSION

Chimeric antigen receptor (CAR) engineered T-cell therapy is becoming, now one of the most promising approaches in the treatment of haematological malignancies (2).

The ability of local Tissue Establishment and clinical centres to cooperate with the CAR-T therapy product manufacturers is crucial for the introduction of this novel type of therapy to the clinical practice. The technological incompatibility of the local partners with the GMP based technologies implemented by manufacturers may be an obstacle, e.g., if more procedures are needed than simple collection of fresh MNC suspension and dispatch rapidly for manufacturing and immediate clinical use of the fresh CAR-T therapy product. Such an approach is connected, however with considerable risks for product loss, e.g., inability of the patient to undergo the CAR-T therapy in the planned time because of unexpected complications. Such events are more likely to occur in the time of the COVID-19 pandemic. The authors' previous experience with implementation of the EBMT temporary recommendation to cryopreserve allogeneic HPC collections during the COVID-19 pandemic showed that such risk can be fully avoided (19,27). Nevertheless, challenges may arise in the contrary situation to cryopreservation of minimally manipulated HPCs where the receiving TE is not authorized to perform cryopreservation of the final CAR-T therapy product. For example, if the receiving TE is not the holder of the relevant ATMP manufacturing approval. The only avoidance of such events is distribution of cryopreserved product by the manufacturer and its temporary storage in the receiving hospital cryostorage facility. Our experience shows that storage in the TE is feasible if the separate GMP compliant container is available, the product receipt and delivery is performed in cooperation with the hospital pharmacy for governance oversight, and the national competent authority is informed. In case of investigational products, it is the duty of the clinical trial monitor to supervise these processes. The critical storage temperature lower than $-150\text{ }^{\circ}\text{C}$ must be assured to achieve compliance with the American regulation for ATMPs. Our institutional practice of the CAR-T product transport to the clinical centre in a dry shipper at temperature below $-150\text{ }^{\circ}\text{C}$ and its thawing by the TE staff with experience in transport and in thawing of HPCs cryopreserved

products is in accordance with recommendation of Yacoub-Agha *et al.* (12).

A good basis for achieving the quality assurance and technological compatibility between partners is the JACIE accreditation of TEs and clinical centres. However, some aspects of cooperation go beyond the JACIE standards, that are based on Good Tissue Practice principles (7). It is especially important to meet GMP requirements during storage of the final CAR-T therapy product and to involve the hospital pharmacy in the receipt, documentation, and storage of the registered CAR-T therapy products. In case of investigational products intermediate storage must be included in the study protocol and genetic safety must be assured. Some general recommendations dealing with these issues are mentioned in the consensus paper of Yacoub-Agha *et al.* (12) and EDQM recommendations (28). Nevertheless, the best way of co-operation is usually settled after certification of the TE and of the clinical centre following an audit by the manufacturer of the particular product.

The use of DMSO-free media is unlikely in the near future because of the limited availability of cryopreservation products made to appropriate standards e.g. CE Mark, ISO13485 (29), the need for secondary manipulations in certain cases (30) and their high cost. For these reasons DMSO based media will probably remain the first option in cryopreservation of both starting material and the final CAR-T product for the foreseeable future. However, the limitations of using DMSO based media as described in the EDQM recommendation version 4 should be understood (28). Because of the small volume of the infused thawed product (Table), in reality the load to the patient of DMSO is substantially lower than for example in the case of autologous HPC transplantations (31).

In cryopreservation of the starting material, we always use double packaging and protection of bags by metal cassettes when cryopreserving HPC product. Single packaging of the final CAR-T product we regard as the major weakness of the current technology. The risk of the physical and/or mechanical damage can be lowered by avoidance of direct contact with the liquid phase of nitrogen and protection by metal cassettes during storage and transport. The additional safety provided by use of the sterile outer bag during thawing is important as well.

RECOMMENDATION FOR PRACTICE AND TIPS FOR IMPROVEMENT

Based on our experience, we can suggest following recommendations for:

1. Cryopreservation of the starting material and its release for manufacturing:

MNC concentration before cryopreservation, even after volume reduction should be below 400×10^9 /L and processing should be done within 24 hours of collection. The best practice is to cryopreserve in the same day as MNC collection. It is still possible to use cryoprotection based on DMSO with limitations described in the EDQM recommendations. Double packaging and protection of bags with metal cassettes should be performed. Release of the cryopreserved product should be done after intermediate storage up to the moment when the results of all performed haematology, immunology and microbiology tests including sterility are known.

2. Receipt, storage, and delivery of the registered or investigational CAR-T therapy product:

These processes should be made in cooperation with the hospital pharmacy staff in case of the registered product or with the clinical trial monitor in case of the investigational product. Storage should be done at temperatures below -150 °C in the separate container in the hospital cryostorage facility. Use of the container based on dry vapour phase storage is the best option. In case of the investigational product approval for storage of GMO it is mandatory. The bags with the final CAR-T therapy product should be stored and transported in metal cassettes.

3. Transport of the CAR-T therapy product to the clinical department and its thawing:

Transport should be made in dry shippers at temperatures below -150 °C. Although thawing in the water bath is still accepted, the bags with the product should be placed into an outer sterile bag to contain any leakage. These processes should be done by TE staff experienced and confident in cryopreservation techniques.

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