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Quality controls of cryopreserved hematopoietic stem cells

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ABSTRACT

HPC processing has been performed routinely for many years for the preparation and cryopreservation of HPC used for autologous and allogeneic transplantation. JACIE Standards (section D) regulate HPC processing and request that processing is performed within the framework of a quality management system (QMS). Implementing QMS in HPC-processing laboratories is feasible, and many processing laboratories are already accredited according to various standards.

Before hematopoietic stem cell transplantation, it is recommended that accurate quality controls be performed to assess the median number of viable CD45+/7-aminoactinomycin-D (7-AAD) and CD45+/CD34+/7-AAD cells, the presence of microbiologic contamination, and the proliferative potential of hematopoietic progenitor cells. The guidelines for the determination of the QCs have been established by FACT/JACIE standards.

To be optimal, process and quality controls have to be performed in a real-time manner in order to ensure safe product release and an immediate recognition of deviations. Furthermore, the immediate initiation of corrective measures is crucial for risk prevention.

Introduction

Hematopoietic stem cell transplantation is a field of enormous therapeutic advances and worldwide expansion of applications over the past four decades. Studies of hematopoietic progenitor cell transplantation in humans began in the 1950s, following experiments in mice that showed protection against the lethal effects of irradiation, by the intravenous infusion of donor bone marrow containing hematopoietic cells capable of colonizing the recipient's bone marrow. HSCT has historically relied upon the steep dose–response

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Abbreviations: HSCT – hematopoietic stem cell transplantation; FACT – Foundation for the Accreditation of Cellular Therapy; JACIE – Joint Accreditation Committee European Group for Blood and Marrow Transplantation-Euro-ISHAGE; HPC – hematopoietic progenitor cell; EQA – External Quality Assessment; PT – Proficiency Testing; LI – leukocyte Immunophenotyping; SCE – stem cell enumeration; CB – cord blood; BM – bone marrow; CD – cluster of differentiation; QCs – quality controls; 7-AAD – 7-aminoactinomycin-D; HPC – hematopoietic progenitor cells; QMS – quality management system; ISHAGE – International Society of Hematotherapy and Graft Engineering; PBPCPs –

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relationship of chemoradiotherapy to maximize tumor cell kill, with the subsequent infusion of hematopoietic progenitor cells in order to circumvent the myelo and immunoablative effects of the preparative regimen [1–3]. More recently less intensive conditioning regimens have been utilized, often in older individuals, in an effort to reduce transplant related morbidity and mortality, while still capturing the potent graft *versus* tumor effect of an allogeneic HSCT. HSCT can be broadly classified according to donor source: autologous and allogeneic. Autologous HSCT involves the administration of myeloablative doses of chemoradiotherapy, followed by the infusion of previously collected autologous (self-donor) cells. Allogeneic HSCT refers to the transplantation of hematopoietic cells from a donor other than the patient [4–6].

The "quality" in a transplant program

HSCT as a discipline continues to rapidly evolve through translation of discoveries in the basic and clinical aspects of immunology, oncology, and infectious diseases into the transplant clinic. The continuing evolution of clinical care and the diverse group of patients and diseases treated with HSCT have contributed to disagreement as to how to establish measures of quality in transplant programs [7]. Quality of health care remains a topic of intense interest at all levels of the health-care delivery system. Measurement of quality in no less important in HSCT than in other areas of medicine and may even be more important, for a host of reasons. These include the life-threatening nature of the diseases, the treatment, the opportunity for cure, the intensive resource utilization, the manipulation of cells and the involvement of healthy donors in HSCT. It is quite likely that results of all transplant centers do not yield equivalent outcomes. Despite the acceptance of HSCT as the standard of care, meaningful measures of program quality are still in development [8].

The JACIE standards

Early after the initiation of FACT accreditation, the Joint Accreditation Committee European Group for Blood and Marrow Transplantation-Euro-ISHAGE (JACIE) was established. JACIE standards aim to promote and maintain the quality of medical and laboratory practice in HPC transplantation and to ensure harmonization between JACIE standards and other national/international standards. JACIE accreditation is voluntary, but provides a means whereby transplant facilities can demonstrate that they are working with a quality system covering all aspects of the transplantation process [9, 10]. The JACIE standards cover all aspects of clinical transplant programs, collection facilities and processing. The JACIE standards also apply to the use of therapeutic cells derived from blood or marrow including donor lymphocytes and mesenchymal stem cells. The JACIE accreditation system is now firmly established in Europe, and the experience of centers that have been inspected are that implementation of the JACIE standards has led to significant improvements in different aspects of their transplant programs. JACIE has further assisted with a number of training courses for preparing centers for accreditation and has issued a practical guide for quality management. JACIE has developed a close working relationship with other organizations involved in cellular therapy, which form the basis for a new global approach to harmonization of standards and accreditation systems worldwide [11, 12].

A milestone: the "Directive 2004/23/EC" of the European Parliament

In March 2004, Directive 2004/23/EC set standards for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells. For the first time in the area of tissues and cells, a binding supranational, transparent, and sound regulatory framework had arisen, providing all citizens with the same minimum guarantees of quality and safety [13]. It is well specified that each tissue center must put in place a quality control system, which must include at least the following information: guidelines; operating procedures; training and reference manuals; donor records (to be kept for at least 30 years); information on the final destination of tissues or cells. Moreover, tissue establishments must include in their operating procedures all the processes that affect quality and safety. They must ensure that the equipment used, the working environment and process monitoring conditions comply with the requirements regarding the processing, storage and distribution of tissues and cells.

The obligations for Member States dictated in Directive 2004/23/EC are:

(1) designation of a Competent Authority;
(2) supervision of human tissue and cell procurement;
(3) accreditation, designation, authorization, or licensing of Tissue Establishments and tissue and cell preparation process;
(4) implementation of a system of inspections and control measures;
(5) implementation of a system of traceability;
(6) guarantee on quality and safety of imported/exported human tissues and cells;
(7) Register of Tissue Establishments and reporting obligations;
(8) notification of serious adverse events and reactions [13, 14].

Aspects of donors selection

Donor and patient HLA match status should be used to assess the risk of transplantation and to plan treatment based on those risks. The benefits of high-resolution HLA class I and II typing have been well demonstrated, particularly in post-transplant survival [15].

Moreover, the possibility of infection transmission by infusion of cryopreserved peripheral blood stem cells concentrates (PBPC) or bone marrow (BM) is well known. For this reason, the European Blood and Marrow Transplantation