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Role of the blood service in cellular therapy

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ABSTRACT

Cellular therapy is a novel form of medical or surgical treatment using cells in place of or in addition to traditional chemical drugs. The preparation of cellular products – called advanced therapy medicinal products – ATMP in Europe, requires compliance with good manufacturing practices (GMP). Based on long-term experience in blood component manufacturing, product traceability and hemovigilance, selected blood services may represent ideal settings for the development and experimental use of ATMP. International harmonization of the protocols and procedures for the preparation of ATMP is of paramount importance to facilitate the development of multicenter clinical trials with adequate sample size, which are urgently needed to determine the clinical efficacy of ATMP. This article describes European regulations on cellular therapy and summarizes the activities of the 'Franco Calori' Cell Factory, a GMP unit belonging to the department of regenerative medicine of a large public university hospital, which acquired a certification for the GMP production of ATMP in 2007 and developed nine experimental clinical protocols during 2003–2011.

1. Introduction

Although blood transfusion may obviously represent a form of cellular therapy, evident technological, operational and regulatory differences exist between the traditional and well-established procedures used for the preparation of red blood cells, platelets, fresh frozen plasma, cryoprecipitate and peripheral blood stem cells with closed multiple bag or apheresis systems and the more recently developed protocols aimed at the therapeutic use of highly purified and thoroughly characterized cell sub-populations, frequently consisting of stem and progenitor cells obtained from multiple sources. The latter, which include bone marrow, adipose tissue, placental blood, amniotic fluid and other tissues [1–4], typically require sophisticated manipulations, including magnetic or immune-mediated fractionation, washing, ex-vivo expansion and cryopreservation by dedicated staff operating in expensive clean rooms – currently termed 'Cell Factories' – under the rules of good manufacturing practices (GMP) [5].

Because of their long experience in managing aseptic procedures for the collection, testing, labeling and distribution of labile blood products and their active involvement in hemovigilance programs including long-term product traceability and recipient look back, selected blood services with adequate resources may represent a convenient setting for the development of novel products for cellular therapy. However, this development requires specific professional training and formal qualification based on GMP.

The European framework for the full transition from classical transfusion medicine into the exciting new and broader field of cellular therapy is represented by the recent regulations related to the so called 'Advanced Therapy Medicinal Products – ATMP'. At the global level, most institutions, scientific societies and organizations involved in the development and clinical use of ATMP have formed the 'Alliance for Harmonization of Cellular Therapy Accreditation – AHCTA', *with the objective of creating a single set of quality, safety and professional requirements for cellular therapy including haematopoietic stem cell (HSC) transplantation (AHCTA mission statement).*

The aim of this article is to provide a brief overview of the European regulation of cellular therapy and to describe the programs recently developed in a public university hospital blood transfusion service primarily devoted to cellular therapy.

2. European regulation for cellular therapy

All regulatory documents and procedures relevant for ATMP are available at the website of the European Medicines Agency (EMA) [6]. The regulatory framework for ATMP is established in 'Regulation (EC) No 1394/2007 of the European Parliament and of the

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Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC Regulation (EC) No 726/2004', whose aim is 'to regulate advanced therapy medicinal products which are intended to be placed on the market in [European] Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC. Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined'. Important elements of this regulation are the definition of a centralized marketing authorization procedure and the provision of special incentives for small and medium size enterprises.

The main product categories include: (a) a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC; (b) a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC; (c) a tissue engineered product, defined as a product that 'contains or consists of engineered cells or tissues' and 'is presented as having the properties for, or is used in or administered to human beings with a view of regenerating, repairing or replacing a human tissue.'

Because of the novel and fast evolutionary development of ATMP, EMA provides guidance for product classification to industry and investigators, with particular attention to 'questions of borderline with other areas such as medical devices'. Scientific recommendations on classification are provided free of charge by the Committee for Advanced Therapies (CAT) within 60 days of a valid request receipt. The CAT maintains a monthly calendar for applications of requests of classification which is published on the EMA website. Moreover, an updated summary of scientific recommendations on ATMP classification is published in the website. During approximately two years (19 June 2009–17 May 2011), a total of 44 products have been analyzed and classified by the CAT [6]. Examples of products classified as ATMP and as non-ATMP are reported in Table 1. It is seen that products so far classified by the

Table 1
Examples of product classification by the CAT (source: www.ema.europa.eu).

Classification	Product (intended treatment or specialty)
ATMP	Buffy coat of centrifuged autologous bone marrow containing hematopoietic and mesenchymal stem cells (spinal cord injury)
Gene therapy	Living, genetically modified Lactococcus lactis bacteria, containing the human Trefoil Factor 1 (hTFF1) gene (oral mucositis)
	Lentiviral vector expressing the naturally occurring human anti-angiogenic proteins endostatin and angiostatin (age-related macular degeneration)
	Non-integrative vector including a gene coding for an anti-HSV-1 Meganuclease for the ex-vivo transduction of human cornea (cornea graft)
	Genetically modified Lactococcus lactis secreting human interleukin-10 (inflammatory bowel disease)
	DNA plasmid encoding for the human fibroblast growth factor type 1 (FGF 1) (critical limb ischemia)
	Lentiviral vector expressing the truncated form of human tyrosine hydroxylase (TH), human aromatic L-amino-acid decarboxylase (AADC), human GTP-cyclohydrolase 1 (CH1) (Parkinson's disease)
	Salmonella typhi strain genetically modified to secrete a fusion protein of the prostate specific antigen and a protein leading to an increased antigenicity (prostate cancer)
	Lentiviral vector expressing the human MYO7A gene (retinitis pigmentosa)
	Lentiviral vector expressing the ABCA4 gene, packaged into infectious VS virus envelope (retinal disorders)
Somatic cell therapy	Autologous ex-vivo pulsed dendritic cells (ovarian cancer)
	Allogeneic human placenta-derived, culture-expanded, mesenchymal-like cell population (chronic inflammatory diseases)
	Allogeneic natural killer cells activated with a lysate from a cell line which is established from a patient with acute monoblastic leukemia (acute myeloid leukemia)
	A combination of lysates of tumor cells (autologous and allogenic) and living cells of a glioblastoma cell line (glioblastoma)
	Haploidentical donor T lymphocytes genetically modified to express HSV-Tk gene (acute leukemia)
	Substantially modified human allogeneic fibroblasts and keratinocytes administered in conjunction with fibrin as structural component (venous leg ulcers)
Somatic cell therapy – combined	Hollow fiber cartridges populated with the C3A cells to be used with ancillary support equipment (hepatitis)
Somatic cell therapy – not combined	Heterologous human adult liver-derived progenitor cells (inborn errors of liver metabolism)
	Allogeneic human aortic endothelial cells cultured in a porcine gelatin matrix (vascular injury)
	Mixture of porcine beta cell and their accompanying endocrine cell populations embedded in an alginate matrix (diabetes)
	Autologous tolerogenic dendritic cells derived from peripheral blood monocytes (rheumatoid arthritis)
Tissue engineering	Allogeneic mesenchymal precursor cells (cardiology)
	Umbilical cord blood cells expanded ex-vivo using allogeneic mesenchymal precursor cells (hematology-oncology)
	Allogeneic human dermal fibroblasts (dystrophic epidermolysis bullosa)
	Allogeneic cultured corneal epithelial cell sheet in amniotic membrane scaffold (ocular diseases)
	Autologous bone marrow-derived progenitor cells (cardiology)
Tissue engineering – combined	Autologous cultured chondrocytes integrated in a scaffold (cartilage repair)
	Allogeneic human fibroblasts cultured onto a biodegradable Matrix (dermatology)
	Autologous osteoprogenitor cells, isolated from bone marrow and expanded in vitro, incorporated, as an integral part, with 3D biodegradable scaffold (odontostomatology and maxillo-facial surgery)
Tissue engineering – not combined	Suspension of expanded autologous skeletal muscle-derived cells (myoblasts) (stress urinary incontinence)
	Layer of autologous corneal epithelium containing stem cells (extended corneal lesions)
	Adult skeletal muscle-derived cells (stress urinary incontinence)
	Frozen, cultured allogeneic keratinocytes on a silicone dressing material (acute burn wounds)
Not an ATMP	Live recombinant lentiviral vectors encoding HIV epitopes (therapeutic HIV vaccination of HIV-1 infected patients)
	Naturally occurring antigen-specific CD8+ donor lymphocytes isolated with Streptamers (infectious diseases)
	Mesenchymal stem cell-derived microvesicles containing receptors, proteins, lipids, mRNA and microRNA (renal diseases)
	Fresh and freeze-dried thrombocytes isolated from autologous or allogeneic blood (wound healing in orthopedic and dental surgery)