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The survey on cellular and tissue-engineered therapies in Europe and neighboring Eurasian countries in 2014 and 2015

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Abstract

Background aims. With the support of five established scientific organizations, this report, the seventh of its kind, describes activity in Europe for the years 2014 and 2015 in the area of cellular and tissue-engineered therapies, excluding hematopoietic stem cell (HSC) treatments for the reconstitution of hematopoiesis. *Methods.* In 2015 [respectively 2014], 205 [276] teams from 32 countries responded to the cellular and tissue-engineered therapy survey; 178 [126] teams reported treating 3686 [2665] patients. *Results.* Indications were musculoskeletal/rheumatological disorders (32% [33%]), cardiovascular disorders (12% [21%]), hematology/oncology (predominantly prevention or treatment of graft versus host disease and HSC graft enhancement; 20% [20%]), neurological disorders (4% [6%]), gastrointestinal disorders (<1% [1%]) and other indications (31% [20%]). The majority of autologous cells (60% [73%]) were used to treat musculoskeletal/rheumatological (44% [36%]) disorders, whereas allogeneic cells were used mainly for hematology/oncology (61% [68%]). The reported cell types were mesenchymal stromal cells (40% [49%]), chondrocytes (13% [6%]), hematopoietic stem cells (12% [23%]), dermal fibroblasts (8% [3%]), dendritic cells (2% [2%]), keratinocytes (1% [2%]) and others (24% [15%]). Cells were expanded *in vitro* in 63% [40%] of the treatments, sorted in 16% [6%] of the cases and rarely transduced (<1%). Cells were delivered predominantly as suspension 43% [51%], intravenously or intra-arterially (30% [30%]), or using a membrane/scaffold (25% [19%]). *Discussion.* The data are compared with those from previous years to identify trends in a still unpredictably evolving field. Perspectives of representatives from plastic surgery practitioners, Iran and ISCT are presented (contributing authors D.A. Barbara, B. Hossein and W.L. Mark, respectively).

Key Words: *cellular therapy, clinical trial, regenerative medicine, tissue engineering*

Introduction

The numerous opportunities offered by emerging cellular and tissue-engineered therapies are being increasingly presented in the public media as if they will be routine medical procedures in the near future [1]. As these treatments become more widespread and visible to the public, it is beholden upon clinicians, researchers and the health care industry to raise awareness of the risks and benefits through communication of outcomes from official clinical trials [2,3]. In this context, results published in the scientific press and public databases (e.g., clinicaltrials.gov) provide insight into prospective and ongoing trials. However, these disclosures represent only a small number of the total interventions performed, and they do not specify the precise number of patients treated for separate indications with specific cells in a defined period. In fact,

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they exclude the majority of patients who are treated outside of formal clinical trials and patients treated with non-substantially modified, "homologous" cell/tissue therapies that are not regulated as medicines and not subject to formal clinical trials. Moreover, it is crucial to map the cell/tissue donor types, along with the modes of cell processing and delivery, and match them with the use for specific therapeutic indications. These data are of substantial significance in providing transparent safety reporting, predicting developing trends and possibly advances in the field.

Since 2008, this survey has aimed to offer an unbiased update on the number of patients treated using cellular and tissue-engineered therapies in Europe and Eurasian countries associated with the European group for Blood and Marrow Transplantation (EBMT) [4–9]. This has been made possible by support from the International Society for Cellular Therapy (ISCT), the European Chapter of the Tissue Engineering and Regenerative Medicine International Society (TERMIS-EU), the International Federation for Adipose Therapeutics (IFATS), the International Cartilage Repair Society (ICRS), and the EBMT. The survey comprises data of treated patients sorted by specific therapeutic indications, cell/tissue donor types, together with the processing and delivery modes, without reference to the clinical outcome, thus avoiding infringement of the publication rights for the clinical teams themselves.

In this article, we report the combined results of the seventh and eighth activity survey, covering treatments in 2014 and 2015 together with a description of some recent trends. The report includes a specific discussion on the use of fat-derived cells in plastic and reconstructive surgery, on the clinical translation of cellular therapies in Iran and on the ISCT perspective for this program.

Methods

Definitions

For the purpose of this survey, "cellular and tissue-engineered therapy" is any clinical treatment based on living cells excluding donor lymphocyte infusions (DLIs) and non-manipulated hematopoietic cells for hematological reconstitution. Data regarding DLIs and non-manipulated hematopoietic cells for hematological reconstitution are collected and reported independently by the EBMT [10,11].

Data collection and validation

Participating teams were, as in previous years, requested to report their data for 2014 and 2015 by indication, cell type and source, donor type, processing method and delivery mode. The survey followed the traditional principles of the EBMT transplant activity survey, which concentrates on numbers of patients with a first cellular therapy. For the 2014 survey, more than 600 teams known to be actively transplanting in 48 countries (39 European and 9 affiliated countries) were contacted, to which were added members of the other participating societies, who distributed the survey directly to their members in Europe by e-mail, and teams that had contributed to any earlier survey. The non-European countries affiliated with the EBMT activity survey are Algeria, Iran, Israel, Jordan, Lebanon, Nigeria, Saudi Arabia, South Africa and Tunisia. Extended questionnaires, in the format displayed in Supplementary Table SI, were received in paper form and electronically.

For the 2015 survey, due to changes in the data being collected by the EBMT for its survey, only EBMT teams that had previously reported treating patients with a cell or tissue-engineered therapy were automatically sent the extended questionnaire. During the year, EBMT teams that reported treatments with regenerative medicine were also sent the extended questionnaire, as were contributors to all past surveys. The supporting societies distributed the survey directly to their members in Europe by e-mail and/or published the survey and documents on their websites. New teams identified either through their contribution to published clinical trials or their reports on the platform clinicaltrials.gov (using the search terms "Tissue-engineer" and "Cell" associated with either "Transplant" or "Treatment" in the relevant countries) were contacted and invited to report their data.

Treatment rates

Treatment rates, defined as the reported numbers of patients receiving cellular or tissue-engineered therapies and the number of teams reporting treatments per 10 million inhabitants, were computed for each country, without adjustments for patients who crossed borders or received treatment in a foreign country. Population numbers were obtained from the 2014 and 2015 eurostat database (ec.europa.eu/eurostat).

Results

Unless described otherwise, all the reported data are displayed simultaneously for the years 2015 and 2014 (format: *number declared* 2015 [*number declared* 2014]), as this report encompasses the survey data for both the years 2014 and 2015.

Participating teams

Two hundred and five [276] teams from 32 countries (26 European, 6 EBMT-affiliated countries) responded to the cellular and tissue engineered therapy