When the best is the enemy of the good: the case of bone-marrow mononuclear cells to treat ischemic syndromes

Natividad Cuende,[1] Concha Herrera,[2] and Armand Keating[3]

[1]Andalusian Initiative for Advanced Therapies, Servicio Andaluz de Salud, Junta de Andalucía, Sevilla, Spain; [2]Cell Therapy Unit, IMIBIC, Hospital Universitario Reina Sofía, Universidad de Córdoba, Córdoba, Spain; and [3]Division of Hematology, University of Toronto, Cell Therapy Program, Princess Margaret Hospital, Toronto, Canada

E-mail: natividad.cuende.sspa@juntadeandalucia.es *doi:10.3324/haematol.2013.086231*

Stem cell and tissue-based products are subject to complex regulation that varies widely according to country and product type. This means that the boundaries between the different categories of these products are not always completely clear.[1]

To simplify the regulatory framework as much as possible, the USA and the EU share a common approach regarding what products need and do not need to get marketing authorization to be 'distributed' on the 'market'. In the case of the USA, most minimally manipulated products, intended for homologous use and not combined with other agents are regulated under section 361 of the Public Health Service Act and so do not need the pre-market approval required by products regulated under section 351.[2] In the EU, a centralized procedure to gain marketing approval is required for advanced therapy medicinal products (ATMPs) that, in the case of cells and tissue-based products, are mainly those which have been substantially manipulated or those not intended to be used for the same essential function(s) in the recipient as in the donor.[3]

The need for marketing approval does not necessarily mean a safer product. However, it has important economic and organizational consequences. This is especially the case for public healthcare systems which may or may not be involved in the development of these products but which are interested in offering them as a service (once their safety and efficacy have been demonstrated) while having no interest in their commercialization.

Learning from history

The example provided by bone marrow mononuclear cells (BM-MNCs) can be illuminating.[1] The use of cellular fractions contained in bone marrow (BM), such as BM-MNCs, or specific cells such as $CD34^+$ or $CD133^+$ progenitor cells, became commonly available in a large number of hospitals several decades ago as a variant of hematopoietic cell transplantation (HCT). In the last ten years, an increasing number of clinical trials using these selected cell types have been carried out globally for purposes other than HCT.

Nevertheless, the simplicity of the BM processing and its availability in many hospitals have facilitated the uncontrolled application of BM cells in some clinics by unscrupulous practitioners looking for a lucrative business.[4] Therefore, the definition of a clear, predictable regulatory pathway with regard to the clinical development of these products and their introduction into clinical practice is desperately needed, as well as enforcement measures to prevent illegal practices.

The use of BM-MNCs or $CD133^+$ cells is governed under the cell transplantation regulation when used for hematologic/immunological reconstitution. Therefore, transplantation regulations could provide the easiest and most convenient directives for public healthcare systems to regulate the same product when used for enhancing adult neovasculogenesis (e.g. for treatment of ischemic diseases such as ischemic heart disease or peripheral arterial disease). If these products were considered as cellular transplantation, they could be available for patients once hospitals have obtained the required transplant authorization (after rigorous and clear demonstration not only of their safety but also of their clinical efficacy), thus allowing them to offer these products/procedures as a service, just as hospitals offer HCT.

The recommendation of the European Medicines Agency (EMA) and the Committee for Advanced Therapies (CAT) regarding the classification of these products as ATMPs,[5] when used to induce angiogenesis, means that the only possible way for these products to become available for patients is for a company to distribute them after undergoing a centralized procedure and being granted marketing approval. It would not be possible for any hospital to appeal for exemption as a consequence of the foreseeable routine basis of these procedures and the large number of patients with ischemic syndromes.

Facing the facts

The EMA/CAT considers that MB-MNCs and $CD133^+$ cells used in ischemic syndromes fall within the definition of ATMPs on the basis that they "are not intended to be used for the same essential function (hematologic restoration)".[5]

The "same essential function" argument is difficult to pin down since it is not possible to establish a general legal definition regarding what should be understood to be essential or not, making it necessary for the needs of each case to be considered individually. In these particular instances, there are scientific arguments both in favor and against.

There is *in vivo* evidence that ischemic or damaged tissues physiologically recruit BM-$CD133^+$ cells which stimulate the mechanisms of neovascularization and tissue repair.[6,7] This process is cumulative with continuous recruitment of cells over a varying period of time.[8] Collecting them from BM and administering them intra-arterially simply facilitates the physiological means by which BM-$CD133^+$ cells reach the targeted tissue.

It can be argued that neovascularization is not the exclusive essential function of BM-MNCs because they contain a heterogeneous combination of different progenitors, including subtypes that have not yet been completely characterized. However, in the case of BMT, the infusion of BM-MNCs into the central venous system includes the same heterogeneous group of cells that are not considered as a medicinal product. It can also be argued that angiogenesis is not an essential function of the bone marrow because bone-marrow endothelial progenitor cells contribute no more than 1.4% of the blood vessel's endothelium under normal conditions and no more than 12% in pathological conditions.[9] Nevertheless, the legal definition recognizes that cells or tissues can have several essential functions and does not indicate that the essential function should be exclusive to those cells.

As there is scientific evidence supporting the consideration of these products as medicinal products or as cell transplant when used to treat ischemic syndromes, a line can be drawn by considering other arguments that may tip the balance. Additional arguments include:

Lack of evidence regarding safety and efficacy of BM-MNCs and BM-$CD133^+$ cells for treatment of ischemic syndromes. This is not particularly helpful as, irrespective of whether the experimental treatments are considered as medicinal products or cell transplants, pre-clinical and clinical research, approved by the institutional review board or hospital clinical research committee is required.

Maximizing safety guarantees for patients. HCT has been performed for several decades under transplant regulation without safety problems. Moreover, the HCT community, through the European Group for Blood and Marrow Transplantation and the Centre for International Blood and Marrow Transplant Research, has a successful track record of monitoring for late effects through their respective registries. Health care centers are very well placed for rigorous long-term surveillance of these treatments as an extension of HCT outcome monitoring.

Avoiding contradictions regarding requirements for the processing of the same products. If BM-MNC or BM-CD133$^+$ are considered as medicinal products, autologous BM cells should be processed under Good Manufacturing Practice (GMP) conditions when intended to be used intra-arterially for immunocompetent patients, while in HCT, allogeneic BM cells, used intravascularly via the central venous route for immunocompromised patients, are processed under Tissue Establishment conditions and follow cell transplantation regulations.

Preventing hospitals authorized for HCT having to face a contradictory situation. If these products are considered medicinal products, hospitals authorized for HCT will be able to process the BM for high-risk patients and will be obliged to send it to a company for processing (using the same procedure and technology) for lower risk patients receiving their own cells.

Reducing costs to hospitals, patients and public healthcare services. Should these products be considered medicinal products, the higher requirements for processing BM (GMP *vs.* Tissue Establishment conditions), or the attendant costs involved in sending BM to companies for processing, will have an important economic impact on hospitals, patients and, ultimately, on public healthcare services.

Favoring patients' accessibility. The classification of BM-MNCs and CD133$^+$ cells as medicinal products may reduce and delay accessibility since they would be available to patients only if a company is granted marketing authorization and distributes them. As cell transplant, they would be offered as a service (once the indication has been scientifically demonstrated) in authorized hospitals, just as in the case of HCT.

Concerns about disadvantaging companies, or even industry as a whole, by considering the use of BM-MNCs and BM-CD133$^+$ cells as cell transplantation. This fear seems unjustified as most sponsors of clinical trials using BM-MNCs or BM-CD133$^+$ cells for ischemic syndromes are hospitals, universities, research centers or foundations. Other sponsors include the company selling the technology for CD133$^+$ cell isolation that might also benefit from the more widespread requirement for cell processing by hospitals rather than the limited number of companies providing such services. Over the longer term, the development of more effective products may involve complicated cell manufacturing requiring the participation of companies to commercialize medicinal products.

Avoiding setting a precedent that could lead to other products circumventing the Medicines Legislation. There is no other cellular product introduced into clinical practice as cell transplant, as is the case with BM-MNCs or BM-CD133$^+$ cells, and at the same time is considered as a medicinal product when used for a different indication. In addition, there is no other cell product with such a vast and lengthy experience in clinic practice. These products represent a special case, thus making them unique, reducing the risk of this 'circumvention' spreading to other products.

Therefore, why not tip the balance in favor of cell transplant regulation? Regulating these products as cell transplant streamlines the entire process and offers affordability and safety, two powerful reasons to move forward.

Natividad Cuende is the Executive Director of the Andalusian Initiative for Advanced Therapies and the Deputy Director of the Andalusian Transplant Coordination, in Spain. She is a specialist in Family and Community Medicine as well as in Preventive Medicine and Public Health. Her fields of interest are donation and transplantation of organs, tissues and cells, and the development of advanced therapy medicinal products. Concha Herrera is Director of the Cell Therapy Unit of the Hospital Reina Sofia and Associate Professor of Hematology and Cell Therapy at the Department of Medicine, University of Cordoba, Spain. Her fields of interest are blood and marrow transplantation and cell-based therapies, mainly applied to the cardiovascular system. Armand Keating is Professor of Medicine and Epstein Chair, University of Toronto and Director of the Cell Therapy Program and the Orsino Cell Therapy Translational Research Laboratory at Princess Margaret Hospital in Toronto, Canada. His clinical and research interests focus on anti-cancer cell therapy, blood and marrow transplantation, leukemia, lymphoma, and cell-based tissue regeneration.

Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

References

1. Cuende N, Rico L, Herrera C. Bone marrow mononuclear cells for the treatment of ischemic syndromes: medicinal product or cell transplantation?. Stem Cells Transl Med. 2012;1(5):403-8.
2. FDA Guidance for Industry: Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) - Small Entity Compliance Guide (2007). Available at: http://www.fda.gov/BiologicsBloodVaccines/ GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073366.htm (accessed 13th of January, 2013).
3. Regulation (EC) no 1394/2007 of the European parliament and of the council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union, 10.12.2007; L 324:121-37.
4. DeFrancesco L. Adult stem cell therapies walk the line. Nat Biotechnol. 2012;30(8):739-41.
5. European Medicines Agency. Summaries of scientific recommendations on classification of advanced-therapy medicinal products. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac0580862c0 (accessed 13th of January, 2013).
6. Maltais S, Perrault LP, Ly HQ. The bone marrow-cardiac axis: role of endothelial progenitor cells in heart failure. Eur J Cardiothorac Surg. 2011;39(3):368-74.
7. Peichev M, Naiyer AJ, Pereira D, Zhu Z, Lane WJ, Williams M, et al. Expression of VEGFR-2 and AC133 by circulating human CD34+ cells identifies a population of functional endothelial precursors. Blood. 2000;95(3):952-8.
8. Takahashi T, Kalka C, Masuda H, Chen D, Silver M, Kearney M, et al. Ischemia-and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. Nat Med. 1999;5(4):434-8.
9. Crosby JR, Kaminski WE, Schatteman G, Martin PJ, Raines EW, Seifert RA, Bowen-Pope DF. Endothelial cells of hematopoietic origin make a significant contribution to adult blood vessel formation. Circ Res. 2000;87(9):728-30.