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EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

The Deputy Director-General for Health

Meeting between European Society for Blood and Marrow Transplantation (EBMT) and DG SANTE

10 November 2016

Summary Minutes

The European Society for Blood and Marrow Transplantation (EBMT)[1] is a not-for-profit medical and scientific organisation established in 1974 dedicated to fighting life-threatening blood cancers and diseases and improving patients' lives. It represents over 4700 physicians and scientists in 568 centres in 55 countries in the EU and beyond. Through a structure of committees and working parties, EBMT promotes research, education, harmonisation of practices and quality improvement through standards and accreditation. The society is funded through membership fees and corporate sponsorship. More information is available at www.ebmt.org and in the 2015 Annual Report found at http://www.ebmt.org/Contents/Resources/Library/Annualreport/Documents/EBMT_AnnualRep_2015.pdf.

In 2014, over 40,000 haematopoietic stem cells transplants (HSCT, a.o. from bone marrow) were performed, mainly to treat patients with blood cancers representing an 80% increase in activity since 2000. EBMT maintains a unique registry of transplants with data on over 500,000 transplants with around 35,000 being reported annually.

Following a short introduction of participants, the following points were raised.

- EBMT considers that the introduction of Directive 2004/23/EC has allowed for strengthening safety and quality without bringing major implementation issues or disruptions in the daily routine of transplantation programs of haematopoietic cells, including activities at clinical facilities, collection facilities and processing facilities (tissue establishments or TE). Implementation of the requirements of the Single European Coding system is expected to bring some practical challenges for TEs in the short-term as the legislation enters force in April 2017 and many TE have started to implement the ISBT 128 coding system in European and further afield, to comply with requirements of the FACT-JACIE international standards for hematopoietic cellular therapy.
- Major changes and specificities in the sector that need to be considered are:

[1] The EBMT is registered in the EU Transparency Register with identification number 652992023103-09

    - The increased use of related/family donors (haplo-identical transplantation) which could negatively impact on the need to find unrelated donors or cord blood units, and also lacking common follow-up protocols for the related donor. This shift towards lower matched donors may also threaten use of and financial sustainability of public cord blood banks.
    - The changing threat of infectious disease outbreaks that need to be taken into account in donor selection and testing strategies.
    - Notwithstanding the first point, the still increasing global exchange of HSC units, which is required due to the need for a good genetic match (HLA) or cell-rich CBU.
- There is an increased need to standardise short-term donor follow-up, in particular for related/family donors. Related donors need more attention as there are suitability issues (elderly or very young donors) and associated psychological questions. Long-term follow up, although less critical, remains important as donors are treated with colony stimulating factors (GCSF, a medicinal product) prior to collection of the cells. In addition donors may move residence over time and so their follow-up would be greatly facilitated through a central/EU data collection effort.
- EBMT has a central database collecting follow-up data of around 90% of patients treated in the EU with HSC. This database does however require significant investment to upgrade the technology, preferably with public funding such as from the Commission. This is much needed in view of the growing number and complexity of clinical and biological information that need to be collected and securely stored to provide opportunities for significant progress in our understanding of mechanisms that contribute to therapeutic efficacy or side-effects produced by hematopoietic cell transplant and cellular therapies.
- EBMT's register can also add and provide data that would be useful for Health Technology Assessment (HTA). MS explained that this topic might be on agenda of next presidency (MT), and can be addressed under the Cross-border directive, e.g., the possibility to include some haematological (rare) diseases in European Reference Networks (ERN's). It was also discussed that it might be useful to look into the possibility to obtain data for SARE reporting (legally required, serious adverse reactions and events) from registers such as this to support the task of national competent authorities.
- EBMT pointed to the several published findings that report that "more than 70-90%[2] of clinical trials of ATMPs are academic-led", also confirmed in the Innovative Medicines Initiative (IMI) consultation on ATMP. These hospitals use schemes such as Hospital Exemption (HE) or clinical trials, which, while not the original intention, for the moment are the only means to make cell-based ATMP available to citizens. EBMT observed that there is a wrong perception that hospitals/ academia - by definition - work at lower or inadequate levels of safety and quality, and that industry does better in this regard. EBMT stressed that both academia and industry have key roles to play and should rather be seen as collaborative or complementary, not as competitive. Industry brings manufacturing capacity, distribution and know-how well beyond the vast majority of hospitals' resources while academia brings medical and scientific expertise.
- Tissue establishments collecting and processing HSC could also become service providers and providers of starting materials for the ATMP-industry. Industry will need to choose either to rely on hospital TE facilities or set-up their own starting-material collection facilities. The main

[2] Forgo&al, Maciuliatis&all, AGORA project http://agora-gmp.org/about-agora/.

commercial ATMP actors are currently located in UK, DE and NL, while Eastern EU facilities would have an advantage of lower staff costs. Distribution logistics are however complicated, and it is not expected that large numbers of tissue establishments will become suppliers of HSC to industry.

- Principle of Voluntary Unrelated Donation – there is a need to be aware of the potential of new cellular therapy delivery models to impact on this principle. One scenario could see manufacturers establishing their own collection services, possibly in a distant low-cost location outside the EU, with the patient travelling for cell collection and then back home to receive his/her cells following manufacturing. Issues such as liability in case of donation-related side-effects will need to be carefully explored.
- EBMT explained that ATMP's are however, to date, still niche products. No centrally authorized ATMP is available for the moment, as there seems to be no working economic model due to small patient populations (personalised therapies), the high cost of operations and unclear or non-existent reimbursement structures. The introduction of CAR-T cells, a new therapeutic strategy that is considered ground-breaking, might change this, in particular if these can be provided from off-the-shelf, allogenic HSC but again, the reimbursement issue will require clarification.
- With regards to CAR-T cells, EBMT raised concerns on price and the consequent availability of these products and access to care. Commercially developed CAR-T cells were estimated to cost at least GBP 350,000 per patient according to an analyses by NICE, the UK HTA body[3] with similarly high costs reported in the USA. Costs might however still go down if production scale increases or if efficient point of care solutions are offered (e.g. Milteny).
  As a comparison, it is estimated that a CAR-T therapy for acute lymphoblastic leukemia (ALL) can be produced at a significantly lower cost in Spanish public hospital under HE and full oversight by the national medicines regulatory authority.[4] EBMT recognizes that hospitals or other types of academic facilities cost structures and financial flows are difficult to compare with those of for-profit pharmaceutical industry, however stresses the fact that academic facilities provide such healthcare as a not-for profit service rather than as a marketed medicinal product.
- Another comparative (dis-)advantage mentioned is that in centrally authorized ATMPs, technologies need to be fixed once trials are started until they are put on the market. In the meantime, technologies continue to rapidly evolve and improve and this can be more continuously adapted in academic settings.
- EBMT therefore asked that as the Commission and its agencies work to facilitate innovation and develop a European biotech industry, that they do not inadvertently block development of ATMPs in hospital settings where minimum safety and quality standards are met, e.g., under HE, and encourage national authorities to harmonise their approaches to HE including establishing a registry of products approved in the EU under HE.
- MS confirmed that there is a need to bridge the gap between (1) building new innovations, and (2) building access so that one does not preclude the other.

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[3] https://www.nice.org.uk/Media/Default/About/what-we-do/Science%20policy%20and%20research/regenerative-medicine-study-march2016-2.pdf. Consulted 03/11/2016

[4] http://www.lavanguardia.com/vida/20160615/402512365273/el-clinic-versiona-una-costosa-terapia-para-leucemia-con-donativos-solidarios.html. Consulted 16/06/2016