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P750

Errors, accidents and adverse events reporting—a summary of nine years' experience in the JACIE accredited center

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Registration and analysis of errors, accidents and adverse reactions (error system) are an important method guaranteeing and improving the quality in the whole organisation. Our center is JACIE accredited since 2008 for all facilities—Clinical Unit (CU), Apheresis Unit (AU) and Cell Processing Laboratory (CPL). These parts represent complex stem cell transplantation (SCT) programme with a single Quality Management System (QMS). Methods: based on the analysis of adverse event (AE) and severe adverse event (SAE) reporting we retrospectively analyzed incidence and type of this events in the period of 2008–2016. Results: In the period 2008–2016 we observed 216 adverese events, 93 (43%) in the CPL, 44 (20%) in the AU and 79 (37%) in the CU. Total of 4 severe adverse events (SAE) were found, all within the CU. Most of AE's observed in the CPL were various technical problems during cell processing (26/93, 28%), the next frequent AE was positive steritity testing in autologous and allogeneic grafts (17/93, 18%), all positive testing without affecting the recipient of the product. The most often AE reported from AU was toxicity during stem cell collection (18, 41%) and thrombocytopenia after the first apheresis (14/44, 32%). Major adverse events reported from the clinical unit were errors in documentation (29/79, 37%) and complications during autologous graft administration (12/77, 15%). We observed 4 severe adverse events, 3 of them were graft failures in the patients with very unfavorable hematologic diseases (resistant acute myeloid leukaemia, very severe aplastic anemia, paroxysmal nocturnal hemoglobinuria). In 1 patient development of secondary breast cancer 6 months after SCT was reported. Furthermore, we analyzed two periods of our transplantation programme. The early period of AE reporting (2008–2012) and the late period (2013–2016). Comparing these 2 periods statistically significantly lower incidence of AEs was detected in the last period of our transplantation programme (67% vs. 33%, $P = 0.001$).Conclusion: QMS is a means of rapidly identifying errors or accidents and resolving them so that the possibility of repetition is minimized. Comparing the number of AE's reported in the first years of QMS functioning in our department, significantly lower number of adverse events were reported in the last years. We can conclude, that QMS system is now firmly established and leads to significant improvements in different aspects of our transplantation programme.

Disclosure of conflict of interest: None.

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Validation of the Sepax® 2S-100 (Biosafe®) using a Density Gradient Automated system for the Separation of Mononuclear cells (MNC) in ABO Mismatched Allogeneic Bone Marrow Tansplantation

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In allogeneic haematopoietic stem cell (HSC) transplantation with reduced-intensity conditioning (RIC) chemotherapy regimens, there may be a time period where the coexistence of recipient and donor lymphocytes may occur and as a consequence two antibody-producing immune systems. Stem cell transplantation using major ABO mismatched bone marrow can cause severe haemolysis of donor cells which can result in delayed engraftment, red cell aplasia and even graft failure. These major complications are the result of cross-reactivity between the donor antigens and the recipient's antibodies. The quantity of infused red cells is an important factor to consider and depletion of red cells from a major ABO mismatched bone marrow is aimed to prevent early haemolysis in allogeneic HSC transplantation. The target cell dose for a bone marrow harvest is usually $2.5–3.0 \times 108$ per kg TNC which is ~10–15 ml/kg of bone marrow collected from the donor. The red cell content is considerable with a mean haematocrit (Hct) of 30–35%; this red cell load will not be tolerated by the recipient during infusion. Cellular processing of the bone marrow harvests are aimed to reduce the risk of haemolysis to the patient by red cell depletion of the bone marrow. Red cells, white cells and platelets differ in size and density and can be efficiently separated by density gradient centrifugation. Currently all processing of bone marrow products is performed on the Cobe 2991 (Terumo BCT, Lakewood, CO) cell processor. It is a manual method that is time consuming, labour intensive and requires specialised training. It also lacks reproducibility and replicability. There is therefore a requirement for a fully automated system with closed capability which can offer efficient and consistent processing of cord, bone marrow and haemopoietic blood stem cell products. Aims: To review and validate the implementation of the Sepax® 2S-100 (Biosafe SA, Eysins, Switzerland) automated cell separator in the processing of mononuclear cells (MNC) in the Therapeutic Stem Cell laboratory at Central Manchester Foundation Trust (CMFT) Methods: Red cell depletion methods were performed on the Sepax analysers using the Neatcell protocol with 18 NHSBT supplied buffy coats. Kit preparation was performed in a grade 1 GMP clean room using aseptic techniques. Ficoll-paque solution was used as a density gradient medium to separate the MNCs and to remove the red cells from the final product. Results: Mean TNC, MNC and

CD34% recovery and red cell % depletion was significantly higher after Sepax cell processing compared to the current manual Cobe 2991 method using data collected retrospectively from the previous 5 years. Both Sepax analysers showed significant correlation with TNC % recovery ($r = 0.934$). The results of the Neatcell rescue procedures also showed optimal cell % recoveries that exceeded the endpoint value set for each cell parameter, therefore concluding that the analyser is effective at recovering the mononuclear cells in the event of an equipment failure. The use of this automated technology provides an audit of traceability for cellular processes and identification of the person responsible for each significant step in recipient care, thus maintaining a requirement for the FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration. The Performance characteristics of the Sepax 2 exceed the target values set at CMFT.

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The market of cell therapies: a challenge for fair access

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In recent years, the use of cells as therapeutic agents has been seen as a potentially new method for treating diseases regarded as incurable. After successful research, from the discovery of human embryonic stem cells in 1998 by James Thomson, to the cure of the 'babies in the bubble' in 2000 and the emergence of human IPS Cells by Shinya Yamanaka in 2007, the potential of these innovative therapies has brought huge attention. It has been followed by press articles raising an undeniable hype in the media illustrated by the first successful implant in human of cardiac cells derived from human embryonic stem cells. The emphasis was then put on the industrialization of cell therapy and products. The way forward is therefore demonstrated in particular by the setting-up of two industrial structures of production unique in Europe: CELLforCURE, a group subsidiary of LFB inaugurated in 2013, and Genethon, the not-for-profit biotherapy laboratory operated by the French Muscular Dystrophy Association (AFM) operating with complementary public structures as the French blood agency. The goal is to produce innovative human cell-based products and related therapeutic methods ensuring best quality and adapted quantity to respond to the demand of the population and to tackle the problematic of the access to personalized medicine for everyone on the basis of equity. The development of cell therapies in terms of industry and fair access due to the possible success of these innovative therapies is an issue in practice. The development of a dedicated industry of cell therapy embedded in quality, safety and efficiency will need to ensure its equal access to the relevant population and will have to be accompanied by an ethical and legal assessment. Then we will have to put an emphasis on the possible limitations posed by the ethical and legal frameworks to this development and the possible options to ensure the success of the cell therapies pathways. In fact, many limitations can be encountered as already stated in the literature (Brooke Ellison, 2016) and raised by the EUcelLEX project (https://www.eucellex.eu/, FP7 Governance of Stem-cell based therapies in Europe) about the interface of science and society regarding the research and development of stem cells. As a matter of fact, a reflection must be tackled about the priority given to the research and to the availability of the scientific progress. Moreover some other limitations must be taken into account notably those encountered in the industry of cell therapies as shown by the publication of the French Society of Pharmacology and Therapeutics, in 2015 where intensive limitations have been raised (such as economy and regulatory frameworks) and where the collaboration between cell banks, and their expansion, or the engagement with the public in research, or harmonization between the regulatory agencies for example have been proposed as solutions. The purpose of this work is to make a state of the art of the various arguments proposed currently as markers of the emergence of a market and to suggest recommendations, legally and ethically sounded, to guarantee sufficient and safe access to the treatments.

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How to build an Allogeneic Hematopoietic Cell Transplant Unit in 2016: proposal for a practical framework

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Allogeneic hematopoietic cell transplantation (allo-HCT) has become standard of care for many hematological diseases. With a growing number of allo-HCT worldwide, there is a medical need for new transplant units or renewal of existing ones. Cornerstones for optimal functioning of a transplant unit are a well-trained medical team, cell collecting and processing facilities, a well-designed infrastructure of the ward and high-qualified laboratory work-up (HLA, chimerism, viral load). Surprisingly, the requirements for the construction of a unit treating patients during the acute phase of the transplantation procedure or at readmission are not well defined. In addition, the infrastructure of such a unit may be decisive for optimized care of these fragile patients. Here, we set up a framework for planning a transplant unit in order to open a discussion ending with more precise guidelines in the field of minimal infrastructural requirements for departments caring for people with severe immunosuppression. Recommendations regarding treatment of allo-HCT patients were analyzed as well as guidelines concerning infrastructural requirements for the transplant unit. Due to the lack of concrete guidelines, decisions were based on expert opinion, on-site visits and adaptation to local structural conditions. The first step is the calculation of the medical need for allo-HCT. Analyses of data from EBMT show that the number of HSCT is still increasing. This is partly explained by a higher rate of successful donor search in stem cell donor registries and by an increasing number of allo-HCT in older patients. Especially in some regions of the world where the health care systems are developing high end care only during the last decades, the number of patients with access to allo-HCT is highly increasing. A dedicated team must be composed for the planning and implementation of an isolation ward that needs a team with expertise in different fields. The infrastructure of the ward must be adapted to an existing or a new building and a policy for isolation must be decided for the rooms and the ward. Most centers install a gate for controlled entrance of medical staff and for visitors by a double door strategy. A strategy for clothing of both groups has to be implemented. A central place for monitoring of the patients must be provided. The requirements for air conditioning and monitoring of the patient are summarized in the table. A center must decide if bone marrow and peripheral stem cell collection will be performed by the department itself or cooperation with other medical departments is necessary. Decision must be in concordance with national legal rules or with certification labels such as FACT-JACIE. Today, no specific requirements except HEPA filtered air have been formulated when a new transplant unit will be opened. However, a more precise 'handbook' for construction and infrastructure of a transplant unit may have a lot of advantages. Defining minimal requirements more precisely will be time saving for centers and will help further development of more evidence based recommendations. Our proposal represents a framework usable by other centers investigating in a new transplant unit. During the meeting, we will present our method and conclusions in detail.

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Table 1 [P753]

Air conditioning	recommended	optional
HEPA filtered air patient room, ≥12 x air exchange/hour	x	
HEPA filtered air ward and on ICU, possibility for negative pressure in the rooms		x
avoidance of turbulences, temperature adaptation rooms		x
pressure gradient patient room --> ward, surveillance of pressure gradient and door closing	x	
system functioning despite a power failure, technical maintenance	x	
Patient monitoring/primary care devices	recommended	optional
ECG, Sat O2, respiration rate, blood pressure (non invasive)	x	
windows in the doors	x	
non invasive ventilation	x	
pump system for IV fluids and drugs, central venous access	x	
home trainer and physical activity		x
ultrasound device, extracorporeal photophoresis, steril bench, blood gas analysis		x

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Infusion of Thawed HPC via a Volumetric Pump

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Infusion of thawed HPC via a volumetric pump at transplant is a contentious issue. Some centres routinely infuse thawed HPC via a pump, whereas other centres have a strict policy against this and hence either draw the thawed cells into a syringe then administer as a slow push or infuse directly from the bag by gravity. The aim of this study was to run thawed HPC through a volumetric pump and measure viability and recovery of CD34 cells after using the pump. Agilia infusion pumps were tested at variable rates using thawed discarded HPC. An HPC collection was thawed as per transplant protocol, volume measured using a syringe and a 0.5 mL sample was obtained as the pre-pump sample. The infusion line was primed with saline then the entire content of cryopreservation bag was infused through the pump followed by 20 mL of saline. The collection volume was determined and a 0.5 mL sample was obtained (post-pump sample). This was performed for two pump rates (600 mL/h and 1000 mL/h). WCC were performed and vCD34 counts were measured by single platform flow cytometry on the pre and post pump samples to determine percentage recovery and any reduction in viability. For ethical reasons, fresh HPC were unable to be used, however, thawed samples represented the closest scenario to the transplant process. Pre and Post pump vCD34. There was no statistical difference between samples taken pre and post pump with respect to viable CD34 numbers. Mean and (range) for progenitor cell post-pump recoveries were 96% (94–101%) for pump rate speed 600 mL/h and 99% (92–113%) for pump rate of 1000 mL/h. Seven patient collections were included in this study. Pump rate. The two pump rates (600 mL/h and 1000 mL/h) gave comparable median vCD34 recoveries of 94.5% and 99%, respectively. This validation study demonstrates that passage of thawed HPC through a volumetric pump at two speeds had no significant effect on recovery of viable CD34 cells, with recoveries in excess of 92%. The pump rates used in this study would result in administration of the thawed bag contents plus the wash in 3.5–10.5 mins, which is in keeping with the general policy for push (syringe) administration over ~5 min and complete infusion of the thawed bag within 20 minutes. We conclude the use of the volumetric pump at 600 or 1000 mL/h settings is not detrimental in the controlled passage of HPC at transplant.

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