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Burn patient care lost in good manufacturing practices?

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SUMMARY. Application of cell therapies in burn care started in the early 80s in specialized hospital centers world-wide. Since 2007, cell therapies have been considered as “Advanced Therapy Medicinal Products” (ATMP), which are classified by European Directives along with associated Regulations by the European Parliament. Consequently, regulatory changes have transformed the standard linear clinical care pathway into a more complex one. It is important to ensure the safety of cellular therapies used for burn patients and to standardize as much as possible the cell sources and products developed using cell culture procedures. However, we can definitely affirm that concentrating the bulk of energy and resources on the implementation of Good Manufacturing Practice (GMP) alone will have a major negative impact on the care of severely burned patients world-wide. Developing fully accredited infrastructures and training personnel (required by the new directives), along with obtaining approval for clinical trials to go ahead, can be a lengthy process. We discuss whether or not these patients could benefit from cell therapies provided by standard in-hospital laboratories, thus avoiding having to meet rigid regulations concerning the use of mainly industrial pharmaceutical products. “Hospital Exemption” could be a preferred means to offer burn patients a customized and safe product, as many adaptations may be required throughout their treatment pathway. Patients who are in need of rapid treatment will be the ones to suffer the most from regulations intended to help them.

Keywords: burn patient care, cellular therapies, skin grafting, regulatory, transplantation law

Introduction

Cell therapies have been implemented for burn care for many years in specialized hospital centers world-wide, and techniques to ameliorate their quality have evolved since they were first used in the late 1980s.¹⁻² These techniques have been shown to be life-saving for severely burned victims, as the skin ultimately needs to be repaired rapidly to prevent fluid loss and infection.³ Split-thickness skin grafts remain the gold standard for the treatment of full thickness and deep partial thickness burns. In severely burned patients with a Total Body Surface Area (TBSA) of even 30%, skin graft donor sites create large surface wounds and increase fluid loss and risk for infection. Cell therapies are often used in burn centers in order to accelerate the epithelialization of donor sites and/or enhance healing of burn wounds.

Following the new European Directive (2001/83/EC) and Regulations (726/2004 amended by Regulation 1394/2007) along with the Swiss Transplantation Law, changes have adversely affected burn victims and the associated Clinical Care Pathways.^{4a-g} Since 2007, cell therapies have been considered as “Advanced Therapy Medicinal Products” (ATMP) which are classified by European Directives along with associated Regulations by the European Parliament.

The new regulatory changes intend to increase cell therapy standardization and therefore treatment safety and efficiency. Nevertheless, industry-destined GMP infrastructure requirements in cell therapy production in a hospital setting could lengthen the process before treatment finally arrives for patient use, which may be fatal for severely burned patients who need to be treated rapidly and efficiently. Indeed, private industry has not shown much interest due to costs and difficulty in logistics, with limited market impact. In this paper we will discuss whether or not these patients may benefit from cell therapies that are provided by standard in-hospital laboratories and are therefore exempt from the rigid regulations that concern the use of mainly industrial pharmaceutical products. The fact that patients in our Burn Center have benefitted from cell therapies provided by our in-hospital Cell Production Center for the last 30 years, but its full GMP licensing which began in 2007 was received only this year, is indicative of the complex regulatory labyrinth.

Materials and methods

Regulatory system requirements for Europe (European Directive 2001/83/EC and Regulations 726/2004 and 1394/2007) and Switzerland (Swiss Transplantation Law) were

evaluated with respect to treatment of burn patients with tissue and cellular therapies. New regulations were compared to those before the 2007 changes regarding this medical practice in hospital environments. The pathways were assessed to define the procedure changes and to determine methods for applying each stage of cell therapy protocols into clinical research and treatments for burn patients. Moreover, all of the tissue and cell therapies used for burn patients were assessed and described in patient care pathways and directly associated with the specific regulatory pathways and technical requirements.

Analysis of the hospital exemption ruling with regard to the European directives and the Swiss Transplantation Law was done from the clinical perspective.

Results

Within hospital settings before 2007, techniques used for severely burned patient care were regulated by the State Investigational Review Board, which approved clinical work involving amelioration of quality and clinical trials. All tissues could be used with regular clinical care, such as the use of skin grafts and adipose tissue transfer (*Fig.1*). There was no differentiation based on how tissue was treated for its classification in different categories for regulation and restrictions. Other cell therapies that needed preparatory work outside of the operating block could be used readily upon request from the medical doctor. Platelet-rich plasma preparations, skin epidermal and dermal tissue and adipose tissue cell cultures all need cell separation techniques and further manipulation of skin and adipose tissue through tissue digestion and cell culture techniques for cell expansion. When substantial manipulation was used before 2007, such as for cell culture techniques, there were no specific regulations for patient autologous cell culture. Since 2007, all of these cell therapies have been considered as standardized transplants and the level of manipulations determine the regulatory restrictions for their use in clinical trials and eventually in the clinic. Standardized transplants with minimal manipulation would be whole tissue grafting for both skin and adipose tissue along with whole skin that is treated with enzymatic digestion and direct transfer on the patient. Adipose tissue could also have cellular fractions separated by enzymatic digestion (collagenase) and centrifugation to enrich whole tissue transfer.

Therefore, minimal manipulation is when tissue is separated from the patient and transferred elsewhere on the same patient, accomplished with simple methods such as mechanical isolation or centrifugation. In addition, centrifugation of whole blood to obtain platelet-rich plasma (PRP) would also be in this category. However, whenever cell culture

techniques are introduced, the process turns into a standardized transplant with substantial manipulation and needs to fully comply with GMP regulations (*Fig. 1*).

Since 2007, clinical studies have been subject to the evolving regulatory constraints that present major challenges for clinical research in hospital settings world-wide (*Table I*). These regulations have transformed those pathways which were linear and relatively easily followed for clinical research and patient treatment (*Table I*, top) into a more complex one with multi-tiered pathways (*Table I*, bottom) which the medical doctor has to assess before deciding if techniques should be introduced or altered for patient use. A decade ago, a study was reported on the management of pediatric burns and wounds using biological bandages with fetal skin progenitor cells, which was accomplished as illustrated in the top half of *Table I*.⁵⁻⁶ Despite the fact that we have routinely used cell culture techniques in our hospital for 15-30 years (autologous keratinocytes, fibroblasts, melanocytes; foreskin cells; foetal skin progenitor), forming an intricate Transplantation Program,⁷ have IRB approval (*Table I*) and have developed a GMP infrastructure, we only received final licensing of our Cell Production Center at the beginning of 2015. Follow-up safety and regulations surrounding cell therapy for burn management have also been reported⁷⁻⁸ which will now allow us to finally progress to the new multi-tiered pathway of *Table I*.

Discussion

New Directives by the European Medicines Agency (EMA) and the associated Transplantation Law in Switzerland treat cell therapy and tissue-engineered products in the same way as drug products.⁴ However, University Hospitals and cell production centers in Europe and all over the world must adapt to Industrial Drug Manufacturing Regulations with regards to infrastructure and environmental monitoring in order to comply with Good Manufacturing Practices (GMP). Due to the vast changes in cell therapies world-wide, several initiatives have been undertaken to join forces with the public sector, charities and some industries to help advance cellular therapy activities and advancements. Already in 2009, in Europe it was reported that 50 teams from 22 countries were using cellular therapies on patients, but only 5% of all this activity was with autologous skin (keratinocytes).⁹ Each country has developed a strategy for assuring cell therapy availability in patient care but to different extents. Germany, the United Kingdom, Spain, the Netherlands, Italy, Belgium, Austria and France were very active immediately following the Regulatory changes. Those countries that found solutions to be GMP-compliant in the academic domain have advanced

significantly, as they were able to conduct clinical trials and interact effectively with regulatory bodies for assistance. In France, financing was already made available in 2005 by INSERM, the Department of Public Health and National Associations, to integrate cell therapies into Centers of Clinical Investigation (CIC) which could thus receive authorization from the French National Health Authority.¹⁰ Similarly in Spain, the Andalusian Government allotted 84 million Euros to the “Andalusian Initiative for Advanced Therapies”.¹¹ They have promoted a distinct translational phase assuring GMP infrastructure and all the support required for local research institutes and hospitals. This facilitates clinical research within the Public Health System and therefore assures high-quality patient care.¹¹ These publicly-funded initiatives are elegantly outlined in the review by Pearce et al.¹² who interviewed many of the 94 European facilities active in cellular therapies and ATMP development. They emphasize the importance of academia as the driving force of innovative therapies used in the clinic, and even though the administrative burden and cost of GMP and GCP are major hurdles and are highly underestimated for small academic “manufacturers”, they are necessary to meet the high quality standards and safety issues for patient care.¹² On the pragmatic side, there has been a recent Catapult Cell Therapy program initiative in the United Kingdom to help associate all GMP facilities available for cell therapies and clinical trials in order to have an overall picture of the capability and capacity of cell therapy manufacturing throughout the UK for future needs. It has found that 56 clean rooms are already available in academic institutes, non-profit organisations and the National Health System, and it is estimating future needs for developing an interactive program towards cell therapy development in all areas of expertise.¹³ Experts from Germany have made great efforts to develop tailored models for optimizing performance and cost estimations for GMP so that others have the tools to assure a sustainable future for cell therapies in Public Health.¹⁴

These challenges regarding GMP implementation must be met so that burn patients may continue to benefit from cell-based therapies that have been routinely used in burn treatment and in our clinical settings for over 30 years, and so that they will have access to innovative therapies in the future. However, cell therapies and ATMPs should not be unanimously considered as equivalent to drugs. The standardized, industrialized process designed for the chemical manufacturing of drugs does not address the complexity of providing a quality controlled cell therapy or ATMP suitable for clinical use. The lack of rapid harmonization between regulatory agencies world-wide has also created difficulties for manufacturing and a product definition suitable for clinical use. In the evolving regulatory environment, the choice of cell source becomes pertinent and may determine whether the

process can be easily standardized and developed into a final product to benefit burn patients. Autologous cell products are similar to tissue or organ transplants and cannot be compared to a drug molecule synthesis for which the final formulation can be more readily defined and standardized. Because of the inherent living biological nature and variability of live autologous cells, a final product would be difficult to thoroughly define. Too many variables in the production of tissues and cells from different individuals (their age, gender and/or genetic dispositions) could complicate in-process controls and specifications of final preparations. Autologous skin grafting for severe burn patients requires the use of feeder layers that have mainly been derived from embryonic mouse cell lines (3T3) for over 30 years.

Emphasis on amelioration of quality to eliminate animal cells in the co-culture of patient keratinocytes was initiated in centres to increase safety but also to better standardize as much of the technique as possible, and to allow for better coordination with surgeons for delivery to the patient. For this reason scientists and medical doctors involved in cellular research have taken a serious look at allogeneic human cell sources. The choice of available cells includes a multitude of differentiated cells and non-differentiated stem cells from tissues of living adults and cadavers (including foetal tissue regulated under organ donations). Non-differentiated embryonic stem cells provide yet another choice. The cell type chosen dictates the complexity of cellular isolation procedures. Some types need only minimal manipulation for purification and storage, but have the disadvantage of limited availability of cellular material. Other cell types require cellular expansion with more intense manipulation, but have the advantage of a substantially higher quality of material. Therefore, the choice of cell type plays a major role in the development of Master and Working Cell Banks (MCB, WCB). Ideally, the cell type should be stable and derived from only one organ donation. Both the donor and the cultured cells would be extensively screened for transmissible viral, fungal and bacterial disease. Viral screening is one of the only requirements common to all regulatory agencies. This suggests that allogeneic cell banking could adapt to the rigid 2007 guidelines and provide a safe and secure utilization of cells for therapeutic purposes.

While allogeneic cell sources used for wound bed preparation and feeder cell sources can be standardized and implemented into MCB and WCB production and stocking, autologous skin grafting is done on a patient-to-patient basis. Keratinocyte cultures from burn patients are fragile and best produced in close proximity to burn patient care so that they are readily available. Their culture has to be done over a three-week period following biopsy, and the cultures should be used once they are stratified within a given time window to be in

optimal condition for patient use. Scheduling the cell culture around the burn patient's surgical needs is of utmost importance. For the severely burned, it would be most logical to have "Hospital Exemptions" to offer individual patients customized but safe cell therapies. According to article 28 of European Regulation 1394/2007, "Hospital Exemptions" is restricted to any advanced therapy medicinal product that is not intended to be marketed, is prepared on a non-routine basis, in a non-industrial manner and is used as a custom-made product for an individual patient. Nevertheless, the European directive does not specify the meanings of "non-routine basis", "industrial process" or "custom-made". Consequently, we observe different interpretations of "Hospital Exemptions" in the countries of the European Union¹⁷. It is therefore necessary to harmonize the Hospital Exemption rules on a European level, in order to include treatments that address unmet clinical needs.

Clinical care should not be confused with "final product development" that is emphasized in GMP processing for clinical cell batches. The use of cell therapies and their integration into Clinical Care Pathways requires evolving technical alterations in cell preparations and also in delivery methods to the patients. If each minor change in the technique is treated as a "final product" and requires new regulatory submissions, clinical research could realistically come to a standstill (i.e. delivery on different scaffolds even if CE marked, or cell concentrations with varying ratios of keratinocytes/fibroblasts could be considered as a new final product). An end product represents the full final formulation and final packaging whether it is a cell suspension in a syringe, a cell suspension placed on a solid matrix, or a stratified epidermal sheet of keratinocytes and/or fibroblasts placed on a vaseline-coated gauze which is placed in a plastic container for transport. Burn patients especially would be the innocent victims of these regulatory requirements if each independent method were to be considered as a final product. The patients' needs should be at the centre of new development. Often their needs get buried under the monumental pile of documents which have to be read, understood and submitted by hospital care-takers in order to be regulatory compliant. A recent survey indicates that the European Clinical Trial Directive 2001/20/EC (CTD) has failed to simplify and harmonize the administrative aspects of governing clinical trials.¹⁵ It also reports that clinical trials in general decreased by 25% in Europe between 2007 and 2011. Even industry appears to be significantly hampered despite adequate financing. The new regulations that impose stricter criteria for the production and the environment necessary for the production of cell-based products to be used in clinical trials and treatments (GMP) have had notable effects on the cost of development. From an industry point-of-view, the priority would be for products which are more profitable than those developed for severe

burns, and there are only a few specialized centres world-wide that would be capable of conducting clinical research for the benefit of the severely burned due to lack of funding in a not so glamorous field.

Conclusion

Overall, it is important to ensure the safety of cellular therapies used in burn patients and to standardize as much as possible the cell sources and products used in culturing techniques. However, we can definitely affirm that concentrating on the implementation of GMP alone will have a major negative impact on severely burned patients world-wide, as obtaining approval for full GMP infrastructure to allow clinical trials (required by the new Directives) can be a lengthy process. Techniques are not advancing as rapidly as they could due to the time and effort put into the preparation of extensive documentation, meaning there is less time available to focus on severe burn patient needs. In the last few years, there have been many articles calling attention to the innate problems of trying to marry the clinical landscape with the challenges of manufacturing cell therapies.¹⁶⁻²³ For many diseases as for severely burned patients it would be more reasonable to adopt the “Hospital Exemption” rule,²⁴⁻²⁵ but the interpretation of this in EU member states is extremely variable.²⁶ Importantly, given the limited patient population in the Western world and particularly in Switzerland, there are not enough patients to conduct appropriate clinical trials. Therefore, Hospital Exemption could be a preferred means to offer a customized and safe product or treatment, as those who are most in need will be the ones to suffer the most from regulations intended to help them.

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Fig. 1 - Cell Therapies used for Burn Treatment

Minimal manipulation techniques including different skin grafts and adipose tissue transfers are accomplished directly in the operating room. Other techniques requiring higher manipulation are considered as substantial manipulation and need to be accomplished in accredited (GMP) laboratory facilities. To enhance sterility and safety of techniques that were once done in the operating room (i.e. preparations for platelet-enriched plasma (PRP) and whole skin digestion), they are now accomplished in controlled environmental laboratories with trained personnel. These techniques require specialized laboratory equipment for centrifugation, cell separation and cell culture procedures.

Table I - Changes in the regulation of cellular therapies

Before 2007 (Top), cell therapies were registered and activities were accomplished in hospital standard laboratories following a linear pathway for clinical trial approval. Since 2007 (Bottom), administrative and quality control measures (legal, technical and medical) along with new pathways and infrastructure (GCP and cGMP) have been necessary for cell therapy use in the clinic and have thus created a complex pathway before new techniques can finally be implemented for patient use. Double control of clinical trials has been introduced by both State and Federal agencies, and pathways for hospital environments are the same as for large pharmaceutical companies.

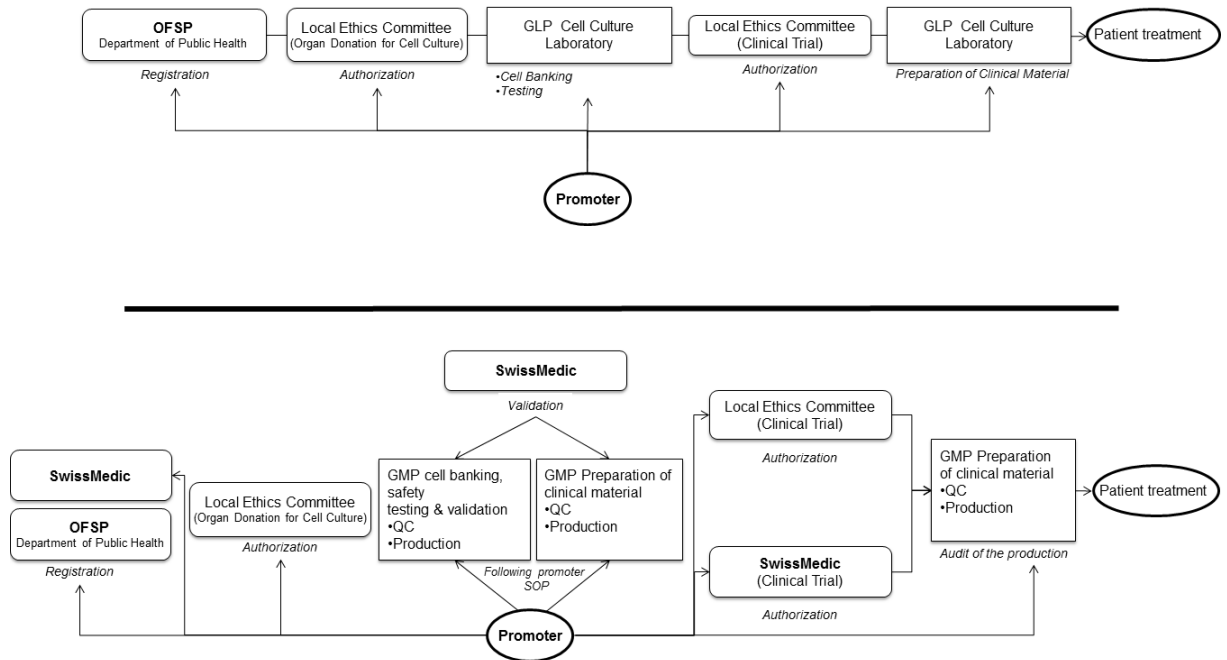
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Table 1.



Since the new Law 2007
 ("Loi sur la transplantation" 810.21)

Figure 1.

Burn Patient Treatments with Cellular Therapy



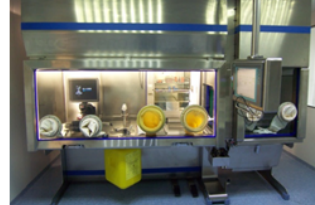
Operating room by the clinicians:
Minimal manipulation

Whole tissue grafting

- Skin
- Thin thickness mesh
- Full thickness mesh

Adipose Tissue

- Lipoaspirates
- Resection



GMP facility following SOPs
**Minimal manipulation &
Substantial manipulation***

Cell Culture*

- Skin cells
 - Fibroblasts
 - Keratinocytes
- Adipose stem cells

Tissue/Cell Transfer

- Skin enzymatically digested

Platelet Rich Plasma