Original Article

Ethical Issues in HSCT and Regenerative Medicine

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Haematopoietic stem cell transplantation (HSCT) and regenerative medicine (RM) hold great promise for the treatment of human disease, both now and in the future. Nevertheless, just like many established medical treatments and those being developed and tested, they are associated with a range of ethical issues. It is possible to consider these issues in four categories: 1) source, 2) procurement, 3) use, and 4) systems. Categorising these issues can facilitate their identification, which is a critical step since they warrant careful and explicit attention in order to help mitigate them and to best protect the rights and interests of donors, patients, and society.

Key Words: Ethics; regenerative medicine; stem cells; transplantation.

Overview

Haematopoietic stem cell transplantation (HSCT) and regenerative medicine (RM) hold great promise for the treatment of human disease, both now and in the future. Nevertheless, just like many established medical treatments and those being developed and tested, they are associated with a range of ethical issues. Whether these issues are overt or subtle, they warrant careful and explicit attention in order to help mitigate them and to best protect the rights and interests of donors, patients, and society. The purpose of this paper is to simply offer a means of categorising these issues so they may be easily identified and considered. The four proposed categories are: 1) source; 2) procurement; 3) use; and 4) systems. Each of these will be described in turn, but the particular issues falling within them will not be analysed in detail.

Sources

Sources of biological materials used for HSCT/RM include bone marrow and peripheral blood, umbilical cord blood and pluripotent stem cells. Perhaps with the exception of peripheral blood and bone marrow, most of these sources raise some unique concerns [1].

Umbilical cord blood. While UCB has now become an established treatment for some diseases it is not value free. Although in the medical context the placenta and UCB is typically viewed as waste, this is not necessarily true for all of those being asked to donate or bank it. For instance, there can be rich cultural beliefs not only about the placenta [2] but also in how it is treated [3]. Further, ethical and legal questions have arisen about whether it is appropriate to treat UCB as property that can be sold and bought.

Pluripotent stem cells. There is considerable interest in the possibility of using a variety of pluripotent stem cells for HSCT and RM. These include human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and others. From its outset, research with hESCs has been associated with moral, religious and political debates in large part since creating hESC lines necessitates the destruction of the embryo. Related debates centred on questions concerning the acceptability of using particular types of embryos, such as those discarded after *in vitro* fertilisation and those created specifically for the creation of hESCs. In addition, given differences in beliefs and laws about hESCs and the reality that hESC research typically involves collaboration across borders, ethical tensions can arise due to such differences. Further complicating these concerns is an array of ethical and legal questions about intellectual property interests and patenting of pluripotent stem cell lines, which can also differ across international borders.

While some have assumed that the creation of iPSCs would resolve the ethical issues associated with human pluripotent stem cells, unfortunately, this is not the case. For example, if iPSCs are truly able to become any cell, this would include sperm and ova, but demonstrating that these derivatives are truly functioning would require the creation of embryos, bringing the embryo debate full cycle. Moreover, as evidenced by the remarkable public response to the popular book, *The Immortal Life of Henrietta Lacks* [4], the creation of immortalised cell lines, even if they are not pluripotent, can be viewed as morally important.

Procurement

The procurement of biological materials for HSCT/RM can raise ethical issues related to privacy, fairness, consent, incentives, and donor safety.

Privacy. Privacy concerns can be relevant to the procurement of biological materials for HSCT/RM when recruiting donors as well as when testing is done to ensure the safety of the material for clinical uses. Privacy issues in recruitment can arise in workplace recruitment or in patient campaigns. In such settings, those who may not be eligible for donation for any num-

ber of reasons including for example their medical history, travel history, or sexual practices, may be put into a difficult situation by these broad social campaigns. Accordingly, it is critical to recognise these tensions in designing these approaches to recruiting donors and provide socially acceptable "opt-out" procedures.

Because it is essential that materials collected for potential use for HSCT/RM are safe for clinical use, these materials must be tested to ensure they do not harbor a broad range of infectious diseases and perhaps genetic abnormalities. As such, this information could raise privacy concerns for donors, especially if this information is in any way stigmatising. Further, policies should be set in advance about whether the results of such tests be communicated to donors. These policies should have provisions for whether there are immediate implications for the care of the donor. This can be especially challenging when donors are infants (in the case of UCB) or children.

Fairness. In order to be able to treat all patients who would stand to benefit from HSCT/RM there is a need for a diverse supply of biological materials so that an adequate match can be found for clinical use. Nevertheless, there can be social or cultural barriers to donation of these materials. Social barriers may understandably exist among members of population subgroups that have been systematically disadvantaged within health systems. Given such historical treatment, is not surprising that there may be reluctance to donate biological materials if there is a reduced opportunity to benefit from similar treatments should they be required.

While there can be unique cultural beliefs about any biological material, across the globe there is a rich set of cultural beliefs in regard to UCB. As mentioned earlier, these include beliefs and traditions regarding the placenta and the umbilical cord as well as how the placenta is treated following delivery [2, 3].

Issues of fairness also arise in relation to patient campaigns for HSCT. These campaigns, which may be organized when an individual patient can't find a suitable match, bring substantial attention to the need for donation of biological materials for transplantation. While the motivations of those organising and participating in these campaigns are laudable, the likelihood that a match for the identified patient is remote and there are substantial burdens on the collection system that result from them. For example, patient campaigns may encourage older individuals to volunteer for donation, yet at present it is less likely that material from older donors will be selected for HSCT. Further, testing these donors incurs certain costs that may have to be borne by the system. While in some programs patient campaigns include provisions for payment from volunteers, they can inadvertently divert resources in ways that don't optimise the overall fairness of the system. These realities underscore the importance of transparency regarding patient campaigns.

Consent. Consent for procurement of biological materials for HSCT/RM is an important protection for donors. While in most cases competent adults will be asked to provide consent for themselves, in UCB banking, parents are asked to make a decision on behalf of the newborn, since the newborn obviously can't make their own decisions. Consistent with international ethical and legal standards, consent for procurement involves a disclosure of the procurement process, including any inherent risks, the proposed use of the material, and information about the confidentiality of the donation and testing performed on the material. When the creation of pluripotent stem cell lines is anticipated, this arguably should be disclosed. Finally, if the creation and/or destruction of embryos are anticipated, as in the creation of human embryonic stem cell lines, this too should be explicitly mentioned.

Incentives. Since the procurement of most biological materials for HSCT/RM involves some burden and some individuals may be reluctant to provide them, incentives are sometimes offered as an encouragement. While incentives can be ethically acceptable, in the setting of HSCT/RM there are some issues that need to be addressed regarding them. Further, there can be important legal considerations that may preclude or guide their use. Regardless, a primary concern when using incentives is their potential adverse effects on decision-making such that an individual participates due to the incentive even though they have strong moral or other beliefs that would otherwise preclude their doing so [5]. A further worry that was first voiced over the issue of whether blood donors should be paid is that paid ‹donors› may pose risks to the blood supply due to their baseline health status compared to unpaid donors [6]. Accordingly, it is important to consider the potential implications of the use of incentives on the safety of the supply or biological materials for HSCT/RM. Finally, incentives may contribute to commodification, which can be seen as ethically problematic.

Donor Safety. The harvesting procedures to obtain biological materials for HSCT/RM can pose risks to the safety of donors. For example, bone marrow aspirations carry risks including infection, bleeding and pain. If growth factors are used to enhance the quality of peripheral blood collections, there can be inherent risks to donors [7]. Perhaps most poignantly are the risks associated with oocyte collections that include those due to the hormonal treatments used to stimulate oocyte development and the harvesting procedures that involve either trans-vaginal or trans-abdominal collection.

Use

The use of biological materials in HSCT/RM can raise ethical concerns in regard to their provenance for research and their allocation for treatment.

Provenance. Issues related to the provenance of biological materials have been particularly pronounced in research involving hESCs. Here, it is important to ensure that the hESC lines being proposed for use in research were ethically derived and will be used in a manner consistent with the consent provided to create the lines. While many issues are involved with determining provenance, much of this concern emanates from the markedly different views regarding the moral status of the embryo. As such, since deriving hESC lines requires the destruction of embryos, it is arguably important to ensure that consent for the creation of hESC lines made this clear. Other important considerations include that consent was obtained and that creating the lines was consistent with local norms and policies [8, 9].

Allocation. Many of the biological materials used for HSCT/RM are relatively scarce, requiring sometimes complicated approaches to allocating them for a variety of uses. Justice is the central relevant ethical principle in making allocation decisions. Justice requires that both the procedures and the ultimate distribution of these materials are fair. For instance, as a procedural matter it would be inappropriate for there to be privileged access to materials in a public bank for those who are economically better off. As a matter of fair distribution, population subgroups that provide materials should have appropriate access to them in the event that they are required.

Systems

HSCT/RM involves a diverse range of systems that are associated with ethical concerns. Dissecting such issues and developing appropriate responses to them are important tasks for those responsible for them. While such a project is beyond the scope of this manuscript, there are a few broad issues that warrant attention: private and public banking; profit and trust; and research, treatment, and innovation.

Private and Public Banking. The tensions between private and public banking have been quite pronounced in relation to UCB [10]. Here, public banks have been established primarily to provide a source of UCB for allogeneic use whereas private banks focus on banking for autologous use (although some now have mechanisms by which particular units can be made available for allogeneic use). To date, the primary use of UCB has been for allogeneic use, raising ethical questions about the propriety of private banking. As a consequence, in general, the overarching ethical justification for public banking relies upon public welfare or solidarity, whereas private banking tends to privilege individualism or self-interest.

Profit and Trust. Public systems for matching, procuring and distributing biological materials rely in large part on public participation. Here, altruistic messaging is commonly used to encourage participation, which is typically voluntary. Nevertheless, the public systems can involve profitable activities and the shipment of materials across borders. While such activities may not in themselves be problematic, when they are not transparent or are in seeming contradiction to the expectations of altruism, they can be problematic and threaten to undermine trust in the system. Accordingly, public systems should provide clear information about such issues.

Research, Treatment and Innovation. While a range of life-saving HSCTs are now accepted treatments and are commonly used, some cell-based interventions are inappropriately being delivered, often in the name of "stem cell therapies" [11]. Inappropriate use not only threatens the well-being of often desperate patients, but also may have repercussions for those engaged in the responsible clinical translation of stem cells. Accordingly, the International Society for Stem Cell Research issues Guidelines for the Clinical Translation of Stem Cells [12]. The Guidelines cover several aspects and approaches to clinical translation that are critical to address at a systems level for those engaged in clinical translation: cell processing and manufacturing; pre-clinical studies; clinical research; medical innovation; and social justice.

Concluding Comments

Despite the enormous benefits from HSCT, there are a clear set of ethical considerations related to current practice as well as anticipated advancements not only in HSCT but also in RM. Being aware of these issues and addressing them explicitly is essential in order to help mitigate them and to best protect the rights and interests of donors, patients, and society.

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Zusammenfassung

Ethische Aspekte der Transplantation von Blutstammzellen und die regenerative Medizin

Die Transplantation von Blutstammzellen und die regenerative Medizin versprechen, heute und in Zukunft wichtige Behandlungen menschlicher Krankheiten zu ermöglichen. Trotzdem werfen sie ethische Fragen auf, wie dies auch bei bereits etablierten medizinischen Behandlungen und solchen, die gegenwärtig entwickelt und getestet werden, der Fall ist. Diese können in folgende vier Kategorien unterteilt werden: 1) Quelle, 2) Beschaffung, 3) Gebrauch und 4) Systeme, wobei die Kategorisierung dazu beitragen kann, die ethischen Fragen auszumachen, was bereits ein wesentlicher Schritt ist. Den neuen Techniken sollte mit der nötigen Sorge und Aufmerksamkeit begegnet werden, um die mit ihnen verbundenen Probleme einzugrenzen und die Rechte und Interessen der Spender, Patienten und der Gesellschaft möglichst gut zu schützen.

Résumé

Les enjeux éthiques de la HSCT et de la médecine régénérative

La transplantation de cellules souches hématopoïétiques et la médecine régénérative sont porteuses de promesses importantes pour le traitement de maladies humaines, actuellement et dans le futur. Néanmoins, comme de nombreux traitements médicaux bien établis et comme ceux qui sont en développement, elles sont associées à toute une série d'enjeux éthiques. Il est possible de considérer ces enjeux selon quatre catégories: 1) la source, 2) l'obtention, 3) l'utilisation et 4) les systèmes. Cette catégorisation peut faciliter l'identification des enjeux éthiques, une étape cruciale, car une attention soigneuse et explicite est nécessaire pour limiter les problèmes qui leur sont associés et pour mieux protéger les droits et les intérêts des donneurs, des patients et de la société.

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