

1 Ethical Issues Regarding the Use of Human Tissues and Cells

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Introduction

Over the past two decades the use of human tissues and cells for transplantation has steadily increased. In the United States (USA), for example, 2,141,960 tissue grafts were distributed by American Association of Tissue Banks (AATB)-accredited tissue banks in 2007 (2007 AATB Annual Survey Results, Tissue Banks in the United States, May 2010). The AATB reported that tissue donor recoveries in the USA have continued to rise with every survey [1] (Figure 1.1).¹ Other countries, such as Spain and Slovakia, have also witnessed a rapid increase in donation of tissues. It is not clear, however, if this increase is in every case a response to need, a consequence of required death referral² or of other process improvements, or if tissue referral, procurement, and processing are growing as business opportunities.

The field of hematopoietic stem cell (HSC) transplantation has witnessed remarkable development from a highly experimental and risky procedure in the 1970s to a continuing complex procedure with inherent risks but is now a widely applied therapy for a variety of lethal conditions of the bone marrow [2].

¹Contributing to this was the establishment of first person consent registries in many states, and most important was a change in federal law that required all deaths or imminent deaths to be referred to the local organ procurement organization or a tissue bank. These organizations approach families for consent or authorization using specially trained personnel and they provide call centers that handle all referrals.

²In the USA per Centers for Medicare & Medicaid Services (CMS) Final Rule – the Conditions of Participation.

Tissue Donors Recovered

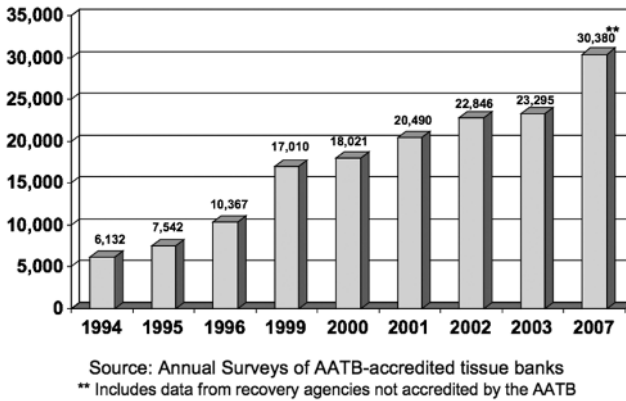


Figure 1.1 Increasing number of tissue donors in the USA [1]. (Reproduced by permission of American Association of Tissue Banks, 2007 AATB Annual Survey Results, Tissue Banks in the United States, May 2010.)

This dynamic development is in part due to scientific advances, such as in histocompatibility matching, immunosuppression, and prophylactic treatment of infections. Another reason for the rapidly expanding activities in human cells and tissues for transplantation (HCTT) is the increasing international exchange of these human donations. Collaborative efforts from more than 60 registries of unrelated volunteer bone marrow and other types of HSC donor have expanded the pool of potential donors for these patients from their immediate and extended family through to close to 14 million people globally. The success of some tissue banking systems has led to excess supply and allowed export of certain tissues to countries in need. The export of corneas retrieved in the USA, for instance, has grown from 7% (of the total number of corneas available for transplantation) in 1990 to 29% in 2000 [3]. Anecdotal reports state that 10–15% of the tissue distributed by USA tissue banks (excluding eye banks) is sent outside of the USA. The Canadian Council for Donation and Transplantation report in their surveys that more than 80% of the tissue used in Canada is imported from the USA.³

However, data on global use and exchange of tissues are patchy with poor levels of traceability. On the other hand, the unrelated HSC programs are quite tightly controlled by the bone marrow donor registries and cord blood banks, and both activity levels and adverse events data are reported annually

³ Supply of Human Allograft Tissue in Canada. April 2003, CCDT. <http://www.organsandtissues.ca/s/wp-content/uploads/2011/11/Supply-Allograft.pdf>. Accessed April 2012.

by the World Marrow Donor Association (WMDA) (<http://www.worldmarrow.org>). The World Health Organization (WHO) has also accumulated data on various organ and tissue transplantation rates derived from government sources in its Global Knowledge of Transplantation (<http://www.who.int/transplantation/knowledgebase/en>).

The idea of transplanting tissues has a longstanding history. A frequent reference is to the legend of Saints Cosmas and Damian, who attempted to transplant a limb from a deceased Moor to a white nobleman in the 3rd century AD. Van Meekeren, a Dutch surgeon, reported in 1668 the first successful bone transplant performed on a Russian soldier where a piece of canine skull was used to fill the defect in an injured soldier's skull. When this transplant was discovered he was excommunicated because the treatment was seen as un-Christian. To return to the good graces of the Church, the soldier asked for the bone to be removed but the graft had already incorporated and healed [4]. Centuries later the surgeon Alexis Carrel expressed his view of the need for organ and tissue transplantation when he stated, "if it were possible immediately after death . . . to transplant the tissues and organs . . . no elemental death would occur, and all the . . . parts of the body would continue to live. A supply of tissues . . . would be constantly ready for use . . . and could be sent to surgeons who need them" [5].

From these early times, tissue banking organizations have now grown to many hundreds of establishments providing millions of tissue grafts for transplantation annually, often with excellent success. The early Bone Marrow Registries have grown to more than 70 organizations, and perhaps 200 cord blood banks exist globally. But even if medical advances have allowed cell and tissue transplantations to become standard procedures that are readily accepted by many patients across nations, cultures, and religions, new scientific and ethical challenges have emerged.

One of these challenges is the development of a solid evidence base for clinical and policy decisions regarding HCTT. What is the need and demand for each tissue in each country every year? Can communities be self-sufficient from the tissue donations from their own population? When are cell or tissue transplants the best treatment option, and when is a product being used just as a convenient solution? For example, when is a human heart valve better or worse than a mechanical or a porcine valve? How can governments ensure that precious and rare tissues and cells be optimally used? These issues gain particular importance once donated substances of human origin are highly processed and start to be considered as tradable goods like any other.

The challenge of maintaining both confidentiality and transparency is a responsibility that exists through every step in donation, banking, allocation, and transplantation of human cells and tissues. There has been a longstanding effort in organ transplantation to establish and promote transparency about the availability and allocation of human organs. In tissue

transplantation, some health authorities are uncertain of the number of tissue establishments operating in their country, let alone the number of donated, transplanted, exported or imported tissue [6]. Transparency, however, is a key requirement for public trust. This trust is regularly challenged, for example, when bodies or component tissues are reported by the media to have been sold by Funeral Home Directors or when a young patient dies after a dubious experimental stem cell treatment. A clear and well-implemented framework of ethical principles may help avoid such scandals. Detailing how respect for autonomy, stewardship, and fair access to treatment by these special donations is going to be achieved and maintained, together with applying appropriate quality and safety standards, is an important basis for the future development of HCTT.

This chapter outlines major ethical principles and issues of HCTT. It does not enter into issues arising from tissue or cell donation as these have been treated extensively elsewhere [7]. Cell and tissue transplantation are considered separately, as they are in fact two rather distinct fields, while the use of germ line tissues and cells are covered in Chapter 20. The complexity of issues that will need consideration if and when the decision is made to use human embryonic stem cells and induced pluripotent stem cells (IPS) cells has yet to be defined as the science turns slowly from fiction to fact.

A normative framework for HCTT

There are several general ethical rules and principles that cut across the various fields of cell and tissue transplantation and, indeed, organ transplantation. The principle of respect for autonomy requires that any donation be based on informed, voluntary consent. In the case of a deceased donor who in life has not opted out from donation, this may suffice as authorization, but even in presumed consent systems the donor's family is usually asked for approval, acknowledging the psychological implications a donation may have for them. Also their cooperation is desired for providing a medical and behavioral history.

The concept of stewardship is also inspired by respect for autonomy of the donor: it wishes to honor the intention of the donor – to help another suffering person with his or her gift, a part of one's own body. Charging unjustifiable fees for processing the cells or tissues or otherwise turning the gift into a commodity just like any other would be incompatible with the idea of serving as the steward of a human tissue or cell gift that one was entrusted with.

Stewardship also requires making optimal use of the donated material. Using the donation in the most efficacious way can also be argued for within the principle of beneficence. Quality and safety requirements, on the other hand, follow from the ethical principle of non-maleficence: risks to the (live) donor, the recipient and third parties are to be minimized. The principle of

Box 1.1 Elements of a normative framework for HCTT**An international consensus has emerged on the following ethically relevant rules and concepts**

Transparency (while protecting privacy of donor and recipient)
 Evidence-based standards for procurement, processing and clinical use
 Quality, safety, and efficacy
 Informed and voluntary consent for donation as well as for receiving a transplant
 Stewardship and non-commercialization
 Equitable access and fair allocation

Underlying general ethical principles

Respect for autonomy – beneficence – non-maleficence – justice

non-maleficence could also be used to argue against paying donors or their families, as this may encourage dishonesty about the medical history, with the consequence of possible harm to the donor during the donation and to the recipient from an unsuitable product.

Paying for donation could also be considered as being in conflict with the principle of justice. More donors or families with low socio-economic status would respond to financial incentives for donation, whereas high prices for the respective cell and tissue products would favor transplantation of affluent individuals and patients from high resource countries. If human cells and tissue are to be considered not as a commodity but as a community resource their distribution becomes a justice concern, requiring criteria and processes for defining equitable access and fair allocation.

International guidance documents – such as the World Medical Association Statement on Human Organ Donation and Transplantation [8], the Council of Europe's Additional Protocol to the Convention on Human Rights and Biomedicine [9], the European Directive 2004/23/EC [10] and the WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation (2010) [11] – concur on these fundamental principles and rules (Box 1.1).

Ethical issues of HCTT

Once a normative framework of HCTT has been defined, the practical challenge lies in specifying the meaning of these overarching principles and rules in the light of ethical issues that arise in the different stages of donation and transplantation activities – from procurement to processing, testing, storage, allocation and distribution.

6 Tissue and Cell Clinical Use

Table 1.1 Central ethical issues in the regulation of human cell (HC) and human tissue (HT) transplantation. (Reproduced with permission from Schulz-Baldes A, Biller-Andorno N, Capron AM (2007) International perspectives on the ethics and regulation of human cell and tissue transplantation. Bulletin of the World Health Organization 85, 941–948.)

Issue	Agreement	Disagreement
Consent for HC/HT removal	<ul style="list-style-type: none"> • No HC/HT removal without consent • Informed consent for donation from living donors • Disclosure of possible limitations to withdrawing consent 	<ul style="list-style-type: none"> • Informed versus presumed consent in deceased donation? • Role of the next of kin (“family veto”) in deceased donation? ◦ Obligation to inform about possible profit-making, international circulation or cosmetic applications?
Confidentiality of donor data	<ul style="list-style-type: none"> • Confidentiality of donor data (with exceptions) 	
Unpaid HC/HT donation	<ul style="list-style-type: none"> • Unpaid donation • Removal of financial disincentives for donation ◦ Only not-for-profit institutions in donation discussions and the promotion of donation 	
Fair HC/HT procurement	<ul style="list-style-type: none"> • Fair criteria for donor identification and selection 	<ul style="list-style-type: none"> ◦ Binding priority of organ over HC/HT recovery?
Stewardship for donated HC/HT	<ul style="list-style-type: none"> • Obligation to honour and realize donor intent • Option to veto HC/HT use for research or education • No discriminatory restrictions of HC/HT use ◦ Stewardship, effectiveness, accountability, fair pricing, responsiveness to local and/or national needs and fair allocation are more important than institutional for-profit/not-for-profit structure 	<ul style="list-style-type: none"> ◦ Option to veto HC/HT use abroad or for cosmetic applications?
Quality and safety management	<ul style="list-style-type: none"> • Necessity of quality and safety management • Long-term follow-up of donors and recipients 	<ul style="list-style-type: none"> • Balance between quality, safety and HC/HT availability in resource-poor settings?

Table 1.1 (Continued)

Issue	Agreement	Disagreement
Fair distribution of processed HC/HT	<ul style="list-style-type: none"> • Need for allocation criteria and prioritization rules despite limited scarcity ○ General priority of HC/HT use for life-saving over life-enhancing and cosmetic purposes ○ General priority of local and/or national self-sufficiency 	<ul style="list-style-type: none"> ○ Scope of allocation criteria and prioritization rules: institutional, national, subregional? ○ Institutional reciprocity as an allocation criterion? ○ For-profit organizations in HC/HT distribution? ○ General priority of subregional self-sufficiency? ○ International HC/HT circulation to subsidize public health care?
Consent for HC/HT transplantation	<ul style="list-style-type: none"> • No HC/HT transplantation without voluntary and informed consent 	<ul style="list-style-type: none"> ○ Obligation to inform recipients about profit-making and international circulation? ○ Limits of consent for medically contested uses?

- normative agreement or disagreement was analogous to that for organ transplantation;
- normative agreement or disagreement was specific for HC/HT transplantation.

Whereas some ethical issues are highly specific to a certain kind of intervention or graft, there are also several cross-cutting themes. Table 1.1 shows issues that emerged at the 2006 International Symposium on Ethical and Policy Issues of Human Cell and Tissue Transplantation that was organized by the University of Zurich in collaboration with WHO, outlining areas of agreement and disagreement among meeting participants.

The question of financial incentives, although related to the donation, will be considered, as it relates to the larger context of commercialization of cell and tissue transplantation. The focus, however, will be on selected issues regarding processing, access and allocation and recipient consent in HCTT, respectively.

Ethical issues: tissue transplantation

Tissue transplantation comprises a heterogeneous group of grafts and procedures, including the transplantation of vessels, heart valves, bone allografts, tendons, skin, corneas, and complex tissues, such as hands and face. These grafts are used in a variety of disciplines, for example: orthopedics and sports medicine, neurosurgery, ophthalmology, craniofacial, urology, cardiothoracic, vascular, dentistry, and plastic surgery.

From an ethical point of view, there are several possible ways to categorize different allografts (Box 1.2). One relates to the degree of processing applied to the donation. There seem to be morally relevant differences between

Box 1.2 Ethically relevant criteria for distinguishing tissue transplants

Tissue transplants may be distinguished according to the following ethically relevant criteria

- Degree of processing
- Link to individual donor as source of transplant
- Temporary versus permanent transplants
- Medical purpose (life saving versus enhancing)
- Therapeutic alternatives
- Established versus experimental therapy
- Preservation methods and storage conditions
- Need for immunosuppression (hand and face transplantation)
- Availability of the type of tissue and size matching criteria
- Living donor versus deceased donor

allografts such as an entire bone versus a screw that contains a small amount of bone powder: whereas we would think of the bone segment primarily as a part of an individual donor's body we might be more inclined to consider the screw as a commercial, although somewhat special, product.

Another psychologically relevant distinction relates to how obviously the donor is the source of the graft. This particular issue is relevant in composite grafts; receiving a recognizable hand or face may trigger more far-reaching questions about the relationship between body and identity. Similarly, the questions of permanence of the graft, whether it is transient or permanent will affect the degree to which the recipient will need to confront the task of integrating the graft into his or her own body and sense of self.

Some transplanted tissues have an important impact on quality of life or even survival (such as skin allografts for burn victims), whereas others may achieve only moderate improvements or aim at enhancing an already fair quality of life (such as a knee replacement for arthritis). Some tissue transplantations, such as autologous bone, are the clear gold standard for a certain indication, whereas in other cases comparable or even superior therapeutic alternatives may exist. Some transplants (for example, human embryonic stem cells) remain highly experimental, whereas others, such as cryopreserved heart valves, have been used successfully for decades.

Tissue grafts differ in the way they are preserved and the subsequent environmental storage conditions which they need. This can affect concepts for allocation as these will need to be quite different if a tissue can only be stored short-term vis-à-vis a graft that can be stored for a long period. For instance, tissues with a short preservation time need to be used quickly and cannot be transported over long distances. Another important factor affecting access to therapy using transplantation relates to the need for

costly immunosuppression, which is required for some vascularized complex tissues such as hand and face transplantation. There may be limited availability of some graft types, especially where size matching (e.g., pediatric allograft heart valves) is required and this needs to be taken into account in determining rules for allocation.

Finally, whereas most tissues are donated by deceased donors, some may be retrieved from living donors. These include a femoral head, which can be donated when hip replacement surgery is undertaken. In such cases, the procedure resulting in the donation is to the benefit of the donor/patient and therefore poses no intrinsic risk from the donation.

Retrieval and processing

The amount of tissues retrieved differs considerably among populations. Some countries such as Sri Lanka and the USA have corneas donated in excess of domestic demand, whereas other countries import corneas to meet a considerable part of their need. What countries should aim for in regard to donation and/or self-sufficiency is a controversial ethical question. Should they strive for self-sufficiency, i.e., to procuring enough tissues to cover the needs of their own population or should they aim for the maximum number of donations to facilitate export of surplus tissues for other needy populations? And if they export what should the rules be: export to those populations with the greatest need, as a humanitarian action, or to those who have the ability to reimburse processing fees? Can a commercial company export donations to another jurisdiction when the needs of the donating population have not been met? What if no transplant program for the respective material exists in the country where the donations are made that would serve the donating population? Or, conversely, do countries carry a responsibility for their donation rates, given that they could simply import tissues if that country was not self-sufficient?

Such queries raise, of course, the underlying question of whether tissue grafts or products are commercial items, commodities that can be traded according to the rules of the market, or if they retain something of their special nature as a gift. Given the business potential of the tissue market the economic implications of this question are considerable. The monetary value of the human body after donation varies between different tissue banks. It has been reported that the value can exceed (USAD) US\$220,000, but more commonly quoted figures are between US\$30,000 and US\$50,000, with an average of 50–60 grafts made available for distribution per donor [13]. The variability is usually a result of different processing methods and the types of tissue produced. Medical devices, demineralized bone matrices, or dermal implants can yield higher reimbursement to processing facilities than do traditional grafts such as femoral heads and cancellous bone. This provides an incentive for driving donations to financially more attractive products, such as acellular dermis for wound healing or reconstructive surgery uses

(abdominal wall, bladder sling, dura replacement, etc.) rather than skin used for burns therapy.

If the concept of tissue establishments acting as stewards of a generous donation they were entrusted with is to be taken seriously, it seems problematic to simply consider human tissues as marketable products, just like equipment or furniture. As exchanges with donor family organizations have revealed, some relatives have been offended by the commercialization of the precious gift donated to tissue banks. Families may be asked to make the decision to donate at a time in their lives when they have just lost a loved one. The process of giving the “final gift” from their relative requires a lot of thought and is emotionally demanding. Families have been upset and distraught upon the discovery that tissue establishments to which they entrusted a family member’s donation may have profited from their gift. The use of terms like “products” and “sales”, in relation to tissue allografts, can be offensive.

The challenge is to find an appropriate way to appreciate the gift and to act in accordance with the concept of stewardship. This should be accomplished without hampering the development of a dynamic, innovative field as well as the efficient, state-of-the-art recovery, processing, storage and distribution of tissues for the benefit of patients who are potential tissue or cell recipients. Beyond the moral dimension there is also a pragmatic reason for honoring donations: if tissue banking is perceived by the population as reckless profiteering and exploiting peoples’ altruism and goodwill this can be expected to have a negative impact on a population’s willingness to donate.

How can the delicate balance between legitimate professionalism and unwanted commercialization be achieved? One precondition is certainly transparent pricing, so that fees can be examined and justified. The WHO Guiding Principles [11] have offered a clear criterion: whereas covering verifiable costs and expenses does not fall under the prohibition on sale or purchase, charging excess fees (independently from the market situation) should not be allowed (Box 1.3). To implement this requirement the operational schemes of both for profit and not-for-profit organizations would need to be discussed in detail. This is likely to lead to questions such as the following. What maximum level of remuneration would be appropriate for an employee in a not-for-profit organization? Are shareholder models compatible with the principle of non-commercialization?

Ethical issues about procurement of human tissue do not only relate to commercialization. Another question is the prioritization of body parts to be recovered. Usually, vascularized organs would come first, as the donor pool is more limited. However, relevant criteria include the clinical need of the recipient and the possibility of death without the graft, rather than the nature of the body part. There have been some concerns, however, that the recovery of certain grafts may put a high psychological demand on donors

Box 1.3 WHO Guiding Principles on human cell, tissue, and organ transplantation, endorsed by the 63rd World Health Assembly (2010) [11]

Guiding Principles on non-commercialization

WHO Guiding Principle 5

Cells, tissues, and organs should only be donated freely, without any monetary payment or other reward of monetary value. Purchasing, or offering to purchase, cells, tissues, or organs for transplantation or their sale by living persons, or by the next of kin in the case of deceased persons, should be banned.

The prohibition on sale or purchase of cells, tissues and organs does not preclude reimbursing reasonable and verifiable expenses incurred by the donor, including loss of income, or paying the costs of recovering, processing, preserving and supplying human cells, tissues or organs for transplantation.

WHO Guiding Principle 8

All health care facilities and professionals involved in cell, tissue, or organ procurement and transplantation procedures should be prohibited from receiving any payment that exceeds the justifiable fee for the services rendered.

or their families. Such grafts include uterus, face, limb, or hand donation. If the public feels repelled by these types of donations and transplants, the psychological demands may result in a negative impact on overall donation rates.

One way to overcome such qualms might be by providing financial incentives for donation. Implementing such policy would, however, exploit the difficult economic situation of some families who would be more vulnerable to responding to such a reward.

Another topic that has frequently been discussed is the use of donated tissues for cosmetic/reconstructive purposes. Whereas it is clear that the different uses of tissues should be disclosed to donor families when consent for donation is requested, it needs to be appreciated that the term “cosmetic use” is a broad and somewhat vague term and can be misleading. Is the use of cartilage to repair a congenital defect of a child’s ear considered to be a reconstructive or cosmetic procedure? The repair of facial scars from a traumatic accident might be seen as cosmetic use by some, but for the individual patient this type of procedure could be a major life enhancement, which could help restore their self-image. Involving the donor or donor family perspectives in the discussion regarding what constitutes appropriate use of donated body materials might be the appropriate way forward.

CASE STUDY 1.1

Directed use of tissue

Mr and Mrs Z were recently informed of the death of their only child KT. She was 17 years old and had just received her driver's license. KT lost control of her car on a slippery, icy road. Her parents are obviously distraught. Her mother had not wanted her driving to school this morning because of the hazardous roads but had agreed after a long argument. Their daughter was a beautiful, thoughtful young lady. KT was on the girls' track and field team and was planning on attending college with hopes of studying to be a doctor. She always wanted to help others. KT volunteered at the local children's hospital and assisted in the burn unit.

When she recently received her drivers' license she signed up to be an organ and tissue donor. Her parents were unaware of her wishes. There were no restrictions identified on her first person consent document. After discussing the donation process with the donation specialist, the parents decided to honor her daughter's wishes and allow organ and tissue donation. Her mother had read about some skin grafts being used for "profiting" and for "cosmetic" uses. The family insisted that her skin donation be used for children who were patients on burn units only.

Questions

1. Should the processing agency provide specific criteria to educate "consenting" specialists about all possible uses of donated tissue?
2. How can the tissue-processing establishment abide by the wishes of the family regarding these specific limitations for use?
3. How can it be expected that tissue distribution intermediaries and the hospital abide by the wishes of the family regarding these specific limitations for use? What if a surgeon uses the skin graft, which is made available in the hospital's inventory, for a breast reconstruction or repair of a facial deformity?
4. How can tissue establishment personnel know exactly what the family means by "cosmetic use," use for the treatment of "burns," or what they consider "profiting" to be? A less important issue may be what they believe the age of a "child" to be, but is that also a consideration to be addressed? Is there a limit to what wishes should be respected and which should not?
5. Because the tissue facility has the name and telephone number of the family do they have the right to call the family and explain more details and ask for permission for additional use?
6. How does "altruistic donation" relate to use of the gift (by whom and what for)?
7. What is "reasonable" regarding all of the above?

Access and allocation

Equitable access to tissue and cell transplants stands firm as an ethical principle. Its precise meaning and its practical implications are, however, far less clear. On a global scale, what does the different availability of certain tissues, which may be in part due to a differential willingness to donate, mean in terms of international solidarity? Should we think of human tissues as a global resource to be distributed according to need? That would mean, for instance, that skin could not be transformed into highly processed/higher cost products as long as there were burn victims worldwide needing cryopreserved allograft skin. Or are tissues transformed along the way into commodities that can legitimately be distributed according to a profit-maximizing strategy? So far, it is unclear at what level specific criteria for fair allocation should be defined, and what role for-profit tissue or cell establishments should have in the distribution of substances of human origin.

If the population of a certain country, which is underserved in terms of health care because of racial discrimination or economic difficulties, were hesitant to agree to postmortem donation, could they expect solidarity from other countries that did not have a similar viewpoint or situation? Alternatively should that country just be referred back to the principle of self-sufficiency or to the possibility of importing donated human substances even if the country might not have the resources to pay for them? Or what about a low-resource country that did not have significant transplantation activities for their populace but was exporting tissues with significant monetary gain? Would this be acceptable if the proceeds were invested into that country's health care system but unacceptable if the proceeds went to a private company that made considerable profit? There is an urgent need for further clarification of these types of ethical rules for cross-border circulation of human tissues.

Another issue is the trade-off between access and safety. When the supply is limited an argument might be made for lowering standards to have a larger pool of grafts available. The challenge on a policy level is to work against a downward spiral in terms of safety standards, but to uphold minimum and best practice standards and to decide on exceptions on a case-by-case basis. This should only be applicable when no other therapy or product exists and a patient will be harmed if the non-conforming allograft is not used.

Consent to receive

Recipient consent needs to follow standard rules for informed consent. Individuals need to be informed about the fact that they are receiving a human allograft, about the risks and benefits of the treatment, and about therapeutic alternatives. Instances of disease transmission would need to be reported, potentially infringing on the confidentiality of the intervention. The use of non-optimal grafts would also need to be explained when applicable, and the appropriate consent obtained. The same principle applies to the use of novel therapies.

CASE STUDY 1.2

Amputation of transplanted hand

A 48-year-old man had lost his right hand many years ago in an accident. When he received a transplanted hand and forearm from an anonymous donor, the victim of a motorcycle accident, doctors were surprised how quickly he regained function. As this was the first transplant of its kind, the case was followed closely by the press.

Two months after the transplant there were no signs of rejection, and the patient was not bothered by any adverse effects from the potent immunosuppressive drugs he needed. Psychologically, he was described as being “on top of the world.” The patient had prepared for the operation with an intensive exercise program that made sure his muscles of his handless right arm were strong enough to carry out movements with his new hand. After the operation he was in fact able to bend each finger about 25 degrees and then straighten it and to move his whole wrist around in a circle. Later, the patient was able to write with a pen and hold a glass of water. The patient was reported as stating that the hand seemed like his own, not like somebody else’s. He had made the promise to himself that when he had his new hand, it would not just be for him, “but for everyone.”

Two years later, however, the patient asked for the hand to be taken off. He admitted to not having taken his medication regularly, leading to a rejection reaction. Doctors discovered that he had been convicted of fraud and served a prison term. “This guy is a very good con man,” one of the doctors commented. The psychological testing that the patient had undergone before the transplant had concluded that he could be expected to be a cooperative patient. In the end the hand was removed in a 90-minute operation by one of the surgeons who had helped to attach it.

Questions

1. How can donor selection be improved to prevent such cases?
2. How can donor compliance be maximized?
3. Did the fact that hand transplants receive a lot of public interest and media attention have any impact on this case?
4. Is there a competitive drive between professionals in transplantation surgery (in particular with a view to “first ever” transplants), and if so, what is its potential impact on donor selection?
5. If the tissue had not been dependent on continued immunosuppression for its maintenance, should the wish of the patient have been respected?

Ethical issues: cell transplantation

Human cell transplantation covers a diverse field. It includes bone marrow, peripheral blood stem cells (PBSC), umbilical cord blood, HSCs (autologous,

related, and unrelated), mesenchymal stem cells, pancreatic islet cells, embryonic stem cells, induced pluripotent stem cells, and gametes. The common characteristic of all of these is that live human cells with uniform features are being provided to replace lost function in the recipient.

Ethically relevant distinctions can be made regarding the kind of cell (somatic versus germ line cell), the source (adults/children, embryos, deceased bodies, umbilical cord), the invasiveness of the collection process and associated risks (bone marrow aspiration and general anesthesia, peripheral blood drawing, apheresis procedures) and the clinical application.

Retrieval and processing

The retrieval of bone marrow or peripheral blood HSCs are well-established procedures, involving several stages of informed consent: for joining a donor registry, for further medical screening and testing if selected, and finally, to proceed with the donation. Still, being an HSC donor does come with certain risks, in particular the use of mobilization medicines required for PBSC donation, which need to be carefully monitored and weighed against the benefits of the procedure.

Another set of ethical issues arises when the donor decides to withdraw their offer, particular when this occurs at a moment when the recipient's own bone marrow has already been destroyed in preparation of the transplant.

CASE STUDY 1.3

Brotherly love

Mrs X was diagnosed with leukemia after a nose bleed that would not stop. A few weeks later she was ready for a bone marrow transplant. She was fortunate that she had a brother who despite living in another country was tested quickly and turned out to be a perfect tissue-type match. A medical work up in his own country revealed that he was a suitable donor and he flew to the city where his sister lived. The transplant was confirmed and the patient underwent preconditioning to destroy her bone marrow before the transplant. The day planned for the donation arrived and her brother did not arrive for admission. He was found to be at the airport on his way home. Mrs X's physician hurried to speak to him and explain that his sister would now die within a week because of the preconditioning therapy. He was aware of this and departed on the plane to his own country. His sister admitted that he had demanded more money than she and her husband could afford. They did not believe that he would carry out his threat to leave if the money was not deposited in his account before the donation. But he did.

Questions

1. How can this situation be avoided?
2. Is there anything that the transplant program can do to manage this risk to their patient?
3. What would you say to the prospective “donor” to convince them to proceed to the donation?
4. Could withdrawal from donation after preconditioning be made against the law/ethical standards?
5. What alternative options are available to the patient after preconditioning?
6. Is there a role for autologous bone marrow storage preconditioning?
7. Is there a role for unrelated HSC transplantation?

Recently, another issue has been amply discussed in the context of blood and organ donation. This is the payment of unrelated bone marrow donors to increase the number of willing individuals. This idea stems from the relatively poor availability of some individuals when they are selected for an actual donation even though they had registered to donate. It has been suggested that payment at this point might encourage both recruitment to the registries and to make the actual donation when the potential donor is called upon.

Relevant professional societies in the field, among them the National Marrow Donor Program and the WMDA, do not agree with the principle of payment for donation, for several reasons:

- The proposal is based upon the fallacy that nonavailability can be resolved by payment. In fact, payment would risk demolishing the structure of global altruistic HSC donation, possibly spreading to other fields of transplantation and leading in fact to reduced access to grafts.
- A vendor has motivation to disguise information that might jeopardize the sale of their cells. This would endanger the vendor if the hidden medical issue were of relevance to safety of cell collection and the recipient if the issue was related to risk of a transmissible disease.
- If payment was to be covered by the recipient this would make the feasibility of transplantation subject to the individual recipient’s capacity to pay, even if health insurance coverage was available.
- During the phase of preconditioning before HSC transplant the patient passes the point of no return and becomes entirely dependent on receiving the transplantation. The patient thus immediately becomes increasingly vulnerable to a fiscally driven vendor’s demands to increase the price.

Pricing is in itself a contentious issue. What is an appropriate price for a unit of PBSC? Such questions raise deeper philosophical and legal issues of ownership of the human body. Do I own my bone marrow and can I freely

dispose of it through sale? These issues have been debated ever since John Moore famously claimed a share of the profits derived from patents on a cell line that was generated from his spleen tissue [14].

Whereas pricing is a hypothetical issue while the context remains donation, it becomes very real when it comes to processing and value adding to donated tissues and cells. A transparent justification of costs that is amenable to oversight would be highly desirable. Another issue for regulatory oversight is the control of quality, safety, and efficacy, with the aim of stopping unfounded and bogus therapeutic claims and dubious, experimental treatments. An open question that would need to be reviewed in each case, is a possible difference in risk management – an individual suffering from a certain condition may be more willing to take considerable risks for the slight chance of a cure and may differ in their judgment from the position held by the responsible regulatory authority.

Access and allocation

Although there is widespread consensus on the desirability of equitable access to HSC transplantation, it is quite clear this goal has not yet been achieved. Differential access to transplants results from two different but related issues. Some ethnic groups have very similar tissue types (human leukocyte antigen, HLA) and have relatively homogeneous genetics, thus they need to have fewer individuals on the registries to have a good chance of finding a donor match. The Japanese and Korean populations are examples of this phenomenon. Indian and North American Black populations have the opposite situation, with diverse, heterogeneous tissue types leading to low chances of finding a matched donor among the same number of potential volunteers. The second problem is actually recruiting broadly representative ethnic groups to the registries in sufficient numbers to provide for patients with each particular ethnic background.

Another concern is limited access of patients without sufficient resources or appropriate health insurance coverage. In resource-poor countries, access to “gold standard” treatment will be substantially limited. The cost of creating global registries of potential HSC donors has been large with tissue typing and infrastructure costs for the unrelated registry reaching perhaps US\$300 for each of the currently 14 million registrants; adding up to a US\$4.2 billion capital investment. These costs are being borne by multiple payers: individuals providing for their own costs of typing, charitable organizations, governments, etc. HSC transplants themselves are additionally very expensive procedures with hospital costs of approximately US\$250,000 for each patient. The high expenses for an individual treatment tie into the more general debate on allocating scarce health care resources, raising the question of how much money a society is prepared to spend per quality adjusted life year (QALY). One advantage that HSC transplants have is the generally long-term survival once the initial high-risk period of the first year has

passed. Once cured of the disease for which transplantation was performed, patients may expect a fairly normal lifespan. Thus the life years per patient procedure is higher than in many economic models of other health care interventions.

Private cord blood banking is another topical issue that has enjoyed some media and commercial popularity over recent years. Parents or grandparents are offered a “life insurance” to their offspring in the form of stored cord blood, without any proof of its clinical utility and for a considerable fee. Professional societies and several physicians have voiced their concern about this practice [15], requiring, at a minimum, full disclosure of the lack of proven benefit to potential users and the problems associated with adherence to usual volume, quality and safety standards. Some alternative models that are currently under discussion suggest public-private hybrids, allowing samples stored for autologous purposes to be used for allogeneic transplantation if needed and vice versa. Regulation may well assist in clarifying what claims may be made in this area.

Regulation, on the other hand, may also threaten to cause problems. Given the dependency on suitable HLA matches, international exchanges are frequently a necessity in unrelated bone marrow transplantation. But if donor centers around the world have to fulfill different national licensing requirements, then the cost and regulatory incompatibilities are highly likely to hinder access unless effective measures are put in place to avoid this. An international harmonization of requirements will be needed [16] to avoid a situation in which measures intended to improve safety actually imperil access.

Consent to receive

Consent to receive is very complex in HSC transplantation. Whereas it shares many features with consent to any other high risk procedure it still is an ethical challenge given the high mortality and morbidity, the need for third party consent for children, the absence of other choices in certain clinical diagnoses, the complexity of the information required to fully understand the intervention, and the question as to what one is actually consenting to (Box 1.4).

HSC transplantation is not simply a single event and is more akin to being cast over a waterfall with no choice as to the subsequent turn of events. The hematologist’s task is to reduce the complexity in a way that is appropriate for the individual patient so that they can make a reasonably informed decision. What options are available will also depend on a country’s health care resources. In rich countries, the range of options is enhanced by the possibility of using very expensive medication (such as imatinib mesylate, Gleevec®) that may reduce the need for HSC transplantation. This difference needs to be taken into account when discussing equitable access on a global scale.

Box 1.4 Making meaning of mortality statistics: deciding about HSC transplantation for refractory acute myeloid leukemia

Clinical options in refractory acute myeloid leukemia (i.e., all treatment fails to achieve remission)

Option 1. No transplant

Immediate mortality risk:	Very high (90% within 3 months)
Medium-term mortality risk:	100%
Long-term survival chances:	Nil

Option 2. Transplant

Immediate mortality risk:	High (20–40% mortality within 3 months)
Medium-term mortality risk:	Very high (75–85% 2-year mortality)
Long-term survival chances:	20%

For all these reasons, consent for receiving a transplant is a delicate procedure that requires a considerable level of professional expertise. On the one hand, there is certainly no point in confusing patients with details they cannot fully appreciate or in informing them about options that may not be within reach for them. On the other hand, not informing about possible implications may lead to difficult situations, not only with a view to the recipient but, in fact, also to the donor.

CASE STUDY 1.4

Inconvenient results

RM was 12 when diagnosed with leukemia. He weighed only 27kg and despite having no siblings there was optimism that an unrelated donor would be found quickly. There were no obvious matches on the preliminary search but two cord blood units showed up on the search of the Bone Marrow Donors Worldwide database. One of the cord units was a good match and was transplanted a few weeks later. The delay in engraftment was a tense period for his parents but it all worked out well. A few months of anxiety and medications were followed by a progressive relaxation of restrictions and return to school. At one year after the transplant he had a check bone marrow biopsy to test for relapse. The good news for residual disease was that there was no evidence of relapse of his disease. The inconvenient result was that the bone marrow had been populated by the donor cord blood and those cells were abnormal. The cytogenetic diagnosis was Klinefelter's syndrome.

Questions

1. What should you tell the recipient? (There are no medical consequences of this diagnosis for the recipient.)
2. Should the possibility of such a transmission occurring have been raised during the recipient consent process?
3. Should the possibility of such an incidental diagnosis occurring have been raised as part of the consent for donation, including a discussion of feeding back such a finding?
4. What should you tell the mother of the donor of the cord blood? (There are consequences of the diagnosis for the child who has the genetic disorder. Although the diagnosis will in the end be made in the recipient, early diagnosis may help both timely medical therapy and adjustment.)
5. Should cord blood banks undertake cytogenetic testing of all cord blood units at storage, with the implication that all donors will be tested as a consequence of volunteering the donation?

Yet consent is not a sufficient requirement for transplantation. Patients may be desperate and willing to undergo or even demand exceedingly risky or unsuitable therapies. Medical indications and suitable oversight mechanisms are needed as an additional safeguard.

Conclusions and outlook

Whereas some ethical issues are specific to certain interventions, others cut across the field of HCTT, such as identifying and eliminating quackery, provision of fair, transparent pricing, and equitable access. To tackle these challenges, more data are needed on activities, on establishments, and on the effect of policies, e.g., access. Registries such as the European Registry for Organs, Cells and Tissues (EURO CET) begin to allow for an overview of what is happening in the field. Such data, as well as the development of common nomenclature, can facilitate the preparation of harmonized standards, which are essential in view of the importance of international exchange. In focusing on appropriate policy for cell and tissue transplantation, possible therapeutic alternatives should not be overlooked and preventive strategies should be strengthened, where possible.

There has been major progress over the past few years in spelling out some of the fundamental ethical principles governing the field of HCTT. Yet there is a striking gap between the level of principles and their implementation. A concrete challenge to be taken up as soon as possible consists of the need to integrate ethically relevant aspects into regulatory oversight. This is similar to what is happening in the area of clinical research, where “ethics audits,” as a follow-up to the review committee’s recommendations, are

being increasingly discussed and realized [17].⁴ Issues to be resolved in reporting or in inspections should go beyond a simple check on the consent form; they should include procedural and content aspects of consent: How were donors or their families approached? What information did they receive? Other issues that could be considered for good inspection practice might include transparency and appropriateness of pricing, or a justification of why a certain product was given priority over other options or why products were exported rather than used for the donating population. A formal system of reporting instances of “tissue trafficking” would be a useful step in implementing globally recognized ethical principles.

Yet another challenge ahead is the realization of access to evidence-based, cost-effective HCTT in low-resource countries. At the same time, patients in these countries may be particularly vulnerable to dubious treatments that are highly experimental or are offered mainly for the sake of profit. Fostering access to HCTT while taking account of public health priorities of each respective country and putting in place effective safeguards against abuses of this promising and dynamic field is an important task. It will require a joint effort from professional societies, health authorities, patient representatives, ethicists and international organizations such as the WHO.

KEY LEARNING POINTS



- Application of HCTT has expanded considerably over the past few years; cross-border circulation and global activities have intensified.
- Transparency, evidence-based standards, and an ethical framework are needed to allow for appropriate regulation and to maintain the public’s trust.
- In tissue transplantation, major ethical challenges relate to stewardship of a gift rather than commercialization and commodification driven by desire to profit.
- Ethical issues surrounding cell transplantation include access to very costly treatments, and global harmonization of regulatory standards to enable international matching of HSCs, while countering activities that are of no proven benefit.
- Future challenges consist of building a solid database for policy decisions, closing the gap between ethical principles and their implementation, and working towards equitable access to well-proven, cost-efficient treatments, including for patients from low-resource countries.

⁴The International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 2002), for instance, state that Ethical Review Committees “should be required to monitor the implementation of an approved protocol and its progression, and to report to institutional or governmental authorities any serious or continuing non-compliance with ethical standards as they are reflected in protocols that they have approved or in the conduct of the studies.” www.cioms.ch/publications/layout_guide2002.pdf, p. 29, accessed October 2011.

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