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## ETHICAL PROBLEMS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

What is hematopoietic stem cell transplantation?

The aim of our article is to present the various ethical dilemmas to which hematopoietic stem cells transplantation (HSCT) gives rise. HSCT, i.e. the transplantation of hematopoietic stem cells derived either from bone marrow (in which case called 'bone marrow transplantation') or from peripheral blood, is one of the methods of treating such hematologic malignancies as, e.g. acute and chronic leukemias, aplastic anemia, lymphoma, or hemoglobinopathies. HSCT came into common use – both with regard to adults and children – in the early 1990's. There are two types of HSCT – autologous and allogeneic. In the case of autologous HSCT (applied mainly in treating malignant lymphomas and multiple myeloma) a donor of hematopoietic stem cells is the patient himself/herself after a previous chemotherapy eliminated neoplastic cells from his/her bone marrow. This procedure is preceded by high-dose chemotherapy and is aimed to cause complete hematologic and immunologic reconstitution. In the case of allogeneic HSCT, a donor of hematopoietic stem cells is some other person – not the patient himself/herself. The donor may be either a close relative of the patient (e.g. his/her sibling or his/her parents) – in this case allogeneic HSCT is called 'haploidentical,' or a matched-volunteer unrelated donor (MUD) found in the Register of Hematopoietic Stem Cells Donors (after he/she has expressed his/her willingness and consent to donate his/her hematopoietic stem cells). Allogeneic SCT is usually applied in treating acute leukemias (and sometimes also in treating chronic leukemias and malignant lymphomas). Some additional facts about the Register of Hematopoietic Stem Cells Donors should be mentioned. A person who gives his/her blood for the purpose of determining his/her human leukocyte antigens (HLA) *ipso facto* decides to register himself/herself in the Register. Accordingly, he/she should be aware of the fact that he/she thereby becomes a potential stem cell donor: he/she is treated as a person who is willing to donate his/her stem cells to other persons (from all over the world) who have found themselves in a situation of immediate danger of their lives caused by hematologic malignancies. There are two methods for collecting hematopoietic stem cells from the donor. The most frequently used consists of obtaining stem cells from peripheral blood after mobilization by granulocyte colony stimulating fac-

tor (G-CSF). The main side effects of this method are flu-like symptoms and bone pains. The second method – less frequently implemented – consists of obtaining stem cells from bone marrow by multiple aspiration under general anaesthesia (BM harvest). The main complications that may appear after such treatment are those typical for general anaesthesia as well as pains (lasting usually a few days) in the proximity of the sacral bone. The first method is considered better, as it gives a bigger graft and, as mentioned, does not require the donor to be subject to general anaesthesia. It may be worth mentioning that patients on whom hematologic malignancies are diagnosed are usually young people, between 20–50 years old, in the prime of their lives, professionally active, building their own families, having young children.

## Ethical problems of hematopoietic stem cells transplantation

### 1. Should compensated donation be permissible?

Broadly speaking, there are two main types of motives propelling agents to donate their hematopoietic stem cells – altruistic and non-altruistic. Clearly, the latter poses special ethical problems. However, before turning to this controversial motivation, we will first devote a few words to the altruistic motivation.

Most donations of hematopoietic stem cells are purely altruistic acts. This is so both in the case of allogeneic HSCT from a related donor and allogeneic HSCT from an unrelated donor. Persons who donate their hematopoietic stem cells for their relatives do it usually for purely altruistic reasons: they do not expect any compensation for this act (we will mention some exceptions in the next section). One may argue in two ways (both, in our view, implausible) that these acts are not altruistic. First, one may note that, say, a sibling can expect gratitude from the recipient and this gratitude is the ‘reward’ for this act. It may be true but this fact does not seem to deprive the act of donation of its altruistic character. Moreover, such a donor is exposed to some additional stress which the unrelated donor avoids. Unlike transplantations from unrelated donors, in the case of transplantations from siblings, the donor and the recipient know each other very well and there usually exists a very strong emotional relationship between them. This means that the donor is likely to experience the suffering of his/her sibling very deeply, and, especially, the failure of the transplantation. Such a failure may engender in the donor the feeling of guilt, because it is *his/her* cells that caused (in some way) the patient’s death or at least failed to save the patient. Secondly, it is sometimes claimed that altruism toward kin cannot be at the same time pure altruism. This claim, however, does not seem very convincing to us. What should be stressed in this context is that persons who sustain costs for their kin usually do not do this with the intention of promoting their own self-interest but *with an intention to promote the interests of their kin*. The fact that an agent’s altruistic behaviour toward his/her kin is advantageous for the propagation of his/her genes (as evolutionary theory teaches us) is irrelevant here: at the psychological level – and this level is important when we speak about

'human altruism' – his/her behaviour is altruistic. Let us now pass to the problem of whether the motivation of unrelated donors registered in the Register of Hematopoietic Stem Cells Donors is also altruistic. The donor from this Register, i.e. a matched-volunteer unrelated donor (MUD) who decides to donate his/her blood cells, cannot know the recipient – the person whose life he/she saves. The anonymous character of the donor guarantees that his/her gift is disinterested – purely altruistic: he/she cannot expect any benefits from the recipient. The rule that the donor and the recipient cannot know each other is an expression of what may be called '*the non-market approach*' to transplantation, according to which donations for transplants cannot be regulated by market processes – they must have the character of a pure gift and not a commodity that can be sold or purchased. *This approach therefore excludes compensated donations*: it does not allow donors to get money in exchange for their donations. According to this approach, donors should be 'Good Samaritans' rather than *homines oeconomici* willing to maximize their net benefits. However, even though this approach is based on a sound ethical intuition (it is hard to deny that a donation motivated altruistically is ethically more desirable than a donation motivated by the expectation of financial benefits), it may have negative consequences. Given that the attitude of the Good Samaritan is not that widespread in society, this approach is likely to lead to a smaller supply of blood marrow donations than 'the market approach.' Does it mean that the market approach is better than the non-market approach? We think that such a claim would be too radical. The market approach creates a real danger of coerced or quasi-coerced donations from impoverished and socially disadvantaged people who are not able to make fully informed choices or whose choices to make donations are brought about by their critical financial situation and are thereby desperate means to improve their lot. Our claim is more modest: we think that *some moderate form* of the market approach (which may also be dubbed '*the quasi-market approach*') cannot be excluded as *necessarily* wrong. What does this approach consist of? It limits the role of the market in the field of transplantations in two important ways. First, it only allows compensated donations which pose little risk to the donors. Hematopoietic stem cells donations (unlike, e.g. kidney donation) seems to belong to this category. Secondly, it rejects the trade in organs between donors and beneficiaries. More precisely: it rejects the classical liberal argument in favour of the market approach which says that trade in organs or stem cells, if carefully regulated to ensure that the donor is fully informed of the consequences of his/her decision to sell his/her organs (tissues, cells), is a mutually beneficial transaction *with no negative side-effects* and thereby should be allowed. This argument, however, is not valid. It relies on a mistaken assumption that such transactions would have no negative side effects. The problem is that they violate the requirements of distributive justice and accordingly exacerbate social inequalities, as they favour rich patients. In sum, what seems to be the most attractive (at least *prima facie*) approach to transplantations is some intermediate one (between the market approach and the non-market approach) which we have called '*quasi-market approach*.' This approach allows the compensation of donors by the state but prohibits individual transactions (even if mutually beneficial) between the potential donors and beneficiaries on the grounds that such transactions exacerbate social

inequalities by promoting unequal access to medical services. This approach is likely to lead to a substantial surplus of social welfare, as it is likely to increase the supply of stem cells donors and thereby decrease the number of hematologic patients who die because of the lack of a sufficient number of such donors. Whether this *quasi*-market approach is indeed a proper one can of course only be decided after conducting a detailed analysis of its social consequences. Such an analysis has to be empirical in character, as it is close to impossible to predict in a speculative way these consequences. Finishing this part of our considerations, we would like to note that the legal systems of all states (with the sole exception of Iran which allows a market-approach) are still based on the non-market approach: they hold that donors cannot require and receive for their donation any payments or other financial benefits. As already mentioned, it is not clear if this situation is desirable or not. Let us repeat the above point that a detailed empirical analysis of the social consequences of this fact is needed to decide this question. Our intuition is that such an analysis would support what we have called a '*quasi*-market approach.' However, this is no more than an intuition, because (as far as we know) as yet no such research has been made.

## 2. Could the donation of hematopoietic stem cells be obligatory?

In most cases the donations of stem cells are non-obligatory acts: since they involve a relatively big sacrifice (though undoubtedly smaller than other types of donations, e.g. the donation of kidney) on the part of the donor, they are 'beyond the call of duty.' In moral philosophy such acts are called 'supererogatory.' However, it seems that there are two cases in which an act of stem cell donation may become obligatory or at least 'close to obligatory.' The first case is that of an allogenic HSCT from a related person. One may argue that if a tie between the patient and his/her sibling is especially strong (the closeness of this tie can be evaluated on the basis of the nature, intimacy and history of their relationship), then the sibling has a moral duty to donate his/her stem cells for his/her ill brother/sister. This case, however, is relatively unproblematic, because if there *does exist* this kind of close relationship between siblings, then the healthy sibling will usually want to help his/her ill brother/sister in a spontaneous way, so that a potential conflict between 'a call of duty' and spontaneous, emotional impulses will not arise. The second case is more interesting. It concerns the situation of a potential donor of stem cells who is registered in the Register of Hematopoietic Stem Cells Donors and who is then requested to make his/her donation. By registering himself/herself in the Register, such a person has *ipso facto* expressed for the first time his/her consent to collect his/her cells at the moment of his/her decision to register in the Register. However, when he/she is selected from among potential donors as a concrete stem cell donor for a concrete stem cells recipient he/she is asked one again whether he/she sustains his/her previously expressed consent to collect his/her bone marrow cells. Of course, the potential donor has the full legal right to refuse to donate his/her stem cells. This is fully understandable. The question arises as to whether he/she has also *the moral right* to refuse to donate his/her cells, given that he/she knows that these cells can save the life of another person. If another donor is not found, which is

highly probable given the still small number of potential donors included in the Register, this particular patient is likely to die. It is rather clear that the final consent of the donor to donate his/her stem cells is not morally obligatory; however, it does not seem to be supererogatory either. It seems that this consent is to be regarded as some kind of intermediary action between the obligatory and supererogatory. Clearly, the dilemma does not arise if the potential donor finds out that his/her donation of his/her stem cells may have dangerous effects for his/her own health. Such circumstances transform her final consent into a purely supererogatory act. The dilemma arises, however, if the circumstances that make him/her hesitate to express his/her final consent are of less serious nature, e.g. the objection of his/her family, the fact that collecting stem cells interferes with his/her plans (e.g. holidays), or his/her (ungrounded) fear of complications resulting from the very procedure of collecting stem cells. One should note that in such situations the role of a physician who is to conduct the HSCT is extremely important. The physician's obvious task is to provide the potential donor with all of the necessary information about the procedure of collecting stem cells and its possible side effects. What is controversial is whether the physician can – or even should – encourage the potential donor to give his/her final consent to collect hematopoietic stem cells if the physician is sure that this procedure will not have any harmful side effects for the donor (which is usually the case). One might argue that this is justified given that the case concerns two goods of clearly different values: the life of the patient and some relatively small inconveniences of the potential donor. However, one should also remember that no one has the duty to donate his/her stem cells to other people; as we have already argued: even though the potential donor's final consent to donate his/her stem cells is no longer a purely supererogatory act, it is still not obligatory. For this reason, the doctor does not seem to have the moral right to encourage the potential donor to donate his/her stem cells. What the doctor can do is only to provide him/her with all the information about the procedure of collecting stem cells and the side effects of this procedure.

### 3. Unethical and 'overly ethical' behaviour of siblings in the case of allogenic HSCT

Two situations are worth considering here. In the first, the problem is the unethical behaviour of a sibling – a potential donor. In the second, the problem is the opposite – it is, so to say, the 'overly ethical' behaviour of a sibling – a potential donor.

In the case of allogeneic HSCT from the patient's sibling, it may happen that the donor decides to donate his/her stem cells on the condition of receiving some financial benefits from the patient; the demands that the potential donor makes usually concern a family legacy: land, flat etc. The patient, knowing that transplantation is the only way of saving his/her life, is very likely to agree to the conditions imposed by the sibling. Such demands made by the potential donor are not only immoral but also illegal. Fortunately, they are relatively rare: they take place when siblings are in some kind of conflict. When they do happen,

however, they may lead to an ethical dilemma on the part of the physician who is to make the HSCT. Usually, only the siblings themselves or – additionally – a few other family members know about the potential donor's unethical demand. Sometimes, however, the physician who is to conduct the HSCT finds out about it. The physician then faces the following dilemma: should he/she inform the court that the law is being violated and thereby decrease the chance of making the transplantation (since the sibling is then likely to refuse to give his/her final consent to have his/her stem cells collected), or pass over the demands in silence and make the transplant? Even though there seems to be no easy theoretical solution of this dilemma, the doctors usually solve it in practice without much hesitation – they make the transplant. As it seems, a theoretical reflection on this dilemma would support this spontaneously made decision.

The second dilemma is connected with the question about the limits of love, solidarity and friendship between siblings. Imagine that a sister – a potential stem cells donor for her brother – finds out that she is pregnant. Assume that the collection of stem cells and transplantation cannot be made after the child's birth – it must be made immediately since otherwise there is a serious risk of irreversible progress of the brother's hematologic malignancy. Clearly, a solution to this problem might be finding another – unrelated – donor from the Register of Hematopoietic Stem Cells Donors. However, if we assume also that such a donor cannot be found (which is sadly a common situation). The question arises as to whether the sister should risk the life of her unborn child in order to protect her sibling or, rather, whether she should avoid such a risk and thereby allow her brother to die. Is it possible to make any kind of rational decision in this situation? How can we compare two evils: the risk to the life of an unborn child and the lost life of an adult person? Can the gift of stem cells made at the cost of the health – or perhaps even the life – of the donor's unborn child still be regarded as a genuine gift? It is not clear how sharp this dilemma in fact is, because to date no research has been made in terms of how often it appears and, more importantly, what risk his/her mother's stem cell donation poses for the unborn child. Nonetheless, it remains the fact that such dilemmas do appear in the practice of HSCT.

#### 4. How to ethically justify stem cell donation from minor siblings?

Allogeneic bone marrow transplantation is regulated in the statute (adopted on October 26, 1995) on collecting, storing and transplanting cells, tissues and organs. Unlike the transplantation of organs, in the case of which a donor must usually be a person at whom brain death has been ascertained (exceptions being transplantations of kidneys and fragments of liver), a donor of stem cells for HSCT is always a living person (thus, HSCT is always a transplantation *ex vivo*). Each person of full age and non-incapacitated can be a donor (a pregnant woman can be a donor only of cells and tissues, not organs). Clearly, in the case of collecting stem cells from a donor, the lack of objection on the part of the donor is not sufficient (as it is in the case of transplantations which involve taking organs from a dead person, i.e. in the case of transplantations *ex mortuo*) – what is required is written consent. In situations of the immediate danger of the pa-

tient's life a donor can be his/her minor sibling if the collection of his/her stem cells is not likely to cause any impairment of the functions of his/her organism. In order to collect stem cells from a minor, the consent of his/her legal representative (usually, his/her parents) as well as the permission of custodial court are required. If a minor is more than 13 years old, his/her consent is necessary as well. Not surprisingly, the ethical justification for minor siblings' stem cells donation poses a special problem: this is so because minor persons lack adequate decision-making capacity. In order to justify permitting this kind of donation, the following two arguments are usually advanced. The first argument says that the risk involved in donation is small. In the case of harvesting bone marrow stem cells, the donor faces the risk typical for general anaesthesia. Harvesting peripheral blood stem cells, in turn, requires the use of a growth factor that involves some risk. Both methods require multiple needle use (thus, they result in temporary pain) and involve the possibility of anaemia. However, these risks are relatively small compared with their potential benefit – saving the life of the minor's sibling. The second argument says that the donation has positive psychological effects for the donor: it increases his/her self-esteem, makes him/her proud of donating etc. The problem with this justification is that the donation only increases the likelihood of saving the life of the minor's sibling – it does not guarantee that the sibling's life will indeed be saved. Now, if it happens, as it does in many cases, that HSCT is not successful, then the donor – given his/her emotional ties with the ill sibling – is likely to experience an especially acute psychological distress caused, e.g. by his/her feeling guilty of the sibling's death. Thus, instead of the feelings of self-esteem and pride, the donor may experience the feeling of guilt and responsibility for causing the brother's death. Clearly, this counterargument against the traditional way of justification does not undermine this way but only weakens it by sensitizing us to the negative psychological effects of the failure of HSCT that should be taken into account while making a decision to collect stem cells from a minor sibling.

### Concluding remarks

The aim of our presentation was to present the main ethical dilemmas related to HSCT rather than to solve them. The narrow scope of this presentation is due to the fact that, as with most bioethical dilemmas, 'hematological dilemmas' cannot be solved in any straightforward way. The 'solutions' to these dilemmas necessarily depend on the general ethical perspective (utilitarian, personalist, contractualist, right-centred etc.) one assumes for tackling them, and there seem to exist no obvious criteria for selecting between those perspectives. Our approach to these dilemmas – which, depending on the point of view, can be dubbed 'reasonable' or 'timid' – can be justified by the fact that our task in this paper was descriptive rather than normative. Clearly, we have not described all of the dilemmas related to HSCT. Our focus was on ethical ones (even though we have assuredly omitted some of them, e.g. the classical dilemma called 'the tyranny of the gift,' which consists of the fact that the patient – the beneficiary of the

donation – is overwhelmed by the altruism of the donor and feels severe distress because of his/her inability to reciprocate the gift). Accordingly, we have not discussed more ‘technical’ dilemmas, e.g. the problem of under what circumstances one should recommend HSCT rather than more conventional treatment (this problem has both a medical and economic aspect – the latter one is related to the fact that HSCT is a very expensive treatment and thereby may not be recommendable when financial resources are limited), the problem of the relationship between treatment and research goals in a situation in which physicians recommend HSCT, the problem of what method of HSCT should be applied in a given case, or the problem of the proper time at which HSCT should be used.