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The ethical dilemma of granulocyte transfusions

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Abstract

Granulocyte transfusions have been administered to patients with life-threatening infections for more than five decades. However, to what extent this should be the case is far from established. On the one hand, the clinical effects of these transfusions are difficult to prove in clinical studies, and the donors of granulocytes may be exposed to certain risks. On the other hand, clinical experience seems to support the idea that granulocyte transfusions do play an important role for severely ill patients, and the donors are primarily motivated by altruistic reasons. In this paper, we first discuss the ethical issues that arise from the fact that there is a conflict between clinical experience and the results from the attempts to perform randomized control trials, and second, the risk/benefit assessment that has to be made between two different parties, namely the recipient and the donor of granulocyte transfusions.

Keywords

Granulocyte transfusions, ethics, medical ethics, G-CSF, RCT

Introduction

Patients who have undergone cytostatic treatment for blood cancer treated by stem-cell transplantation may suffer from bone marrow failure. This involves risks of serious, life-threatening infections due to a lack of white blood cells (granulocytes). Transfusion of granulocytes to some of these patients has been used for more than 50 years.[1] However, whether these transfusions should be performed, and if so how and to what extent, remains contentious.

On the one hand, the evidence for the clinical effectiveness of granulocyte transfusions is quite weak. There are, for example, no randomized control trials (RCTs) supporting the hypothesis that patients who receive granulocytes are doing better than a control group not receiving them. Furthermore, it has been argued that the harvesting of granulocytes exposes donors to the risk of harm. On the other hand, clinical experience supports the notion that granulocyte transfusions represent a crucial treatment of last resort for severely ill patients.[2–5]

In this paper, we shall discuss the ethical issues that are raised by granulocyte transfusions. The discussion is structured around (but not exhausted by) the classical principles of medical ethics[6] in relation to the recipient as well as the donor of granulocytes. As the more pressing ethical issues relate to the principle of beneficence, the principle of non-maleficence, and the principle of autonomy, we shall primarily focus on them and, accordingly, leave potential aspects actualized by the principle of justice aside in the following.

Background

Method for literature search

In this paper, we make claims about the potential risks and benefits of granulocyte transfusions. These claims are based on a literature review. The search strategy was the following. Relevant literature was identified

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from an extensive search in PubMed 24th October 2019 (see Appendix 1). The search resulted in 240 hits. Of these, 140 articles were selected from the titles and abstracts and read in full. They were supplemented with an additional seven articles from the reference lists for the selected articles.

A brief history of granulocyte transfusions

Confidence in the clinical effectiveness of granulocyte transfusions has changed over time among health care practitioners. In the late 1980s, relatively few granulocyte transfusions were administered[2] as improved alternatives for antibiotic treatment had been developed, and reports on adverse reactions in connection with granulocyte transfusions were published.[3,4] Furthermore, the results of treatment with granulocyte transfusions were considered so modest that they could only in exceptional cases justify the risks to which patients were exposed.[2,5]

Over the past two decades, studies have been published that support the hypothesis that the dose (number of granulocytes) given is crucial to treatment outcomes.[1] It was also shown that treating the donors with granulocyte colony-stimulating factor (G-CSF) together with other new techniques enabled about four times more granulocytes to be harvested. This created significantly better opportunities to obtain enough granulocytes in the recipients' blood circulation.

Scientific evidence—Patient benefit and risks for donors

Almost 30 clinical studies have been published on the effects of granulocyte transfusions since the introduction of pretreatment with G-CSF 20 years ago.[7–13] Most of them are case studies, some with controls, and others without. Even though the research designs used were insufficient, the overall evaluation of these studies indicates *some* clinical benefit of granulocyte transfusions, especially when a large number of granulocytes have been given.[1,2] The most ambitious study in the field, the so-called RING study, was designed to be a randomized and controlled study. Unfortunately, it could not be completed as planned, primarily due to difficulties in having the patients accepting the randomization process.

The most commonly reported side effects of G-CSF treatments are mild such as transient fatigue, skeletal pain, fever, and diffuse gastrointestinal symptoms.[14–17] More severe symptoms are rare and often reported in connection with stimulation prior to stem-cell harvest (when using 5–20 times higher dose of G-CSF than in granulocyte harvest).[15]

Since G-CSF stimulates stem cells, there have been discussions whether the treatment of donors with G-CSF could lead to cancer of blood-forming cells.[18–20] However, registry studies do not support these theories.[21,22]

Hence, it seems right to assume that the adverse effects for granulocyte donors are mild.

Ethical and methodological challenges for a well-designed RCT

As the scientific basis is insufficient and the use of the treatment often is based on clinical experience, it is crucial to consider the possibilities of providing a more solid scientific basis, for example, by conducting well-designed RCTs. However, it is important to stress that, in the case of granulocyte transfusions, there are a number of ethical and methodological challenges that need to be handled when designing an RCT that meets the requirements for good research practice.

One of the more pressing ethical challenges relates to one of the defining characteristics of RCTs, namely, the need for a control group: a group that receives placebo or traditionally used treatment for the condition. However, since granulocyte transfusions are given to seriously ill patients, it is problematic from an ethical point of view to design a study with such a control group—patients in the control groups would certainly die, and researchers would have good reasons to believe that they would. In the RING study, this ethical issue translated into a practical problem for researchers as research subjects did simply not accept to be a part of the randomization process.

Furthermore, there are at least two methodological challenges for conducting a study that would meet the requirements for good evidence. First, it is a relatively small group (for example, in Sweden, about 100 granulocyte transfusions are given every year to a significantly smaller number of patients, since each patient usually receives several transfusions). This challenge is not unique for granulocyte transfusions but is also the case with other patient populations, for example, those that suffer from rare diseases. Nevertheless, this presents a difficulty in providing sufficient scientific evidence. Second, these patients are seriously ill, and they are usually treated with several different therapies, which are also changing over time. Hence, it is particularly difficult to separate the potential clinical effect of the granulocyte transfusion from the potential clinical effects from these other therapies. There is a substantial risk for confounders.

Despite these ethical and methodological challenges, it is crucial to emphasize the importance of discussing how a study could be designed that is both ethically

defensible and scientifically sound in order to investigate the benefits of granulocyte transfusions.

How to make sense of these data from an ethical perspective?

Beneficence versus non-maleficence

The principle of beneficence constitutes a central part of the ethical foundation of health care and is often interpreted as a positive principle that says something about what *should be done*. For example, health care should promote people's health, quality of life, and reduce their suffering. One of several implications of this is that there is no reason to provide patients with futile treatment. Hence, the question about how granulocyte transfusions affect patients is of outmost importance from an ethical perspective.

A closely related principle is the principle of non-maleficence. Although the principle of non-maleficence may look like the principle of beneficence in several respects, there are important differences. The principle of non-maleficence is a negative principle that says something about what *should not be done*. For example, health care should, as far as possible, avoid causing discomfort, injuries, expose patients to risks and death, and, as far as possible, minimize unavoidable discomfort, injuries, and risks.

Patients versus donors

Granulocyte transfusions have a direct impact on at least two parties: (a) the recipient and (b) the donor (there is a sense in which a third party may be affected which is discussed below). While the principle of beneficence is actualized in relation to the patient, the principle of non-maleficence is actualized in relation to the patient *as well as* the donor. Early studies indicated that granulocyte transfusions may expose patients to potential harm.[23] However, more recent studies have not substantiated such risks.[24] Therefore, the principle of non-maleficence is primarily relevant in relation to the donor.

Blood donors are important for health care practices. Most blood donors donate blood for altruistic reasons. That is, the main motive for giving blood is the consideration of their fellow human beings rather than their own benefit. This is an action disposition that is generally praiseworthy and one that society should cherish. But the will to do good for others may mean that donors partially ignore their own risks associated with blood donation or potential pretreatments. Hence, although the risks to which donors are exposed seem relatively small (since the common side effects are mild and the more serious ones are uncommon and associated with relevantly higher doses of G-CSF), this still** is a reason for the staff responsible for blood donation to pay close attention to the principle of non-maleficence. More specifically, this stresses the importance of the way in which the donors are informed,[25,26] something that we discuss further below.

Moreover, there is often a tension between the principle of beneficence and the principle of non-maleficence. The extent to which the patient can be benefited must be weighed against risk, injury, and discomfort. This risk assessment is usually done for one and the same person: are the risks associated with a given procedure worth the potential benefits of that procedure? What makes granulocyte transfusions particularly complex is that health care exposes one person (the donor) to the risk in order to being able to benefit another person (the patient). This type of interpersonal risk/benefit assessment is characteristic of medical research but rarer in health care practices.

One may argue that it is reasonable to make stronger claims about the effect of a treatment when the risk/benefit assessment is inter- rather than intrapersonal. In the ethical guidelines developed by the International Society of Blood Transfusion (ISBT), such a position is stated quite clearly.[26]

An additional potentially relevant party

There is a sense in which granulocyte transfusions may affect the health of third parties. A follow up of the RING study[24] investigated immunization after granulocyte transfusions. Increased immunization could not be detected after short-term observation of the patients. However, the authors emphasize that the low rate of immunization may be due to patients receiving immunosuppressive cytostatic therapy. Hence, immunization does not appear to be a health risk in the short term. However, in a longer-time perspective, immunization risks may become a disadvantage as it may result in impaired responses to treatments that are particularly relevant for this patient group.

Moreover, when a person has donated granulocytes, the same person should not donate blood, platelets, or plasma for three months. This means that if a large number of granulocyte transfusions are performed, the availability of platelets and plasma may decrease, which may affect other patients. However, this scenario is largely dependent on the fact that it is usually platelet donors who are asked if they can also donate granulocytes. To some extent, this problem could be managed with a donor bank at transfusion medical units, where granulocyte concentrate is produced. This has, for example, been suggested by a Swedish expert group.[27]

The severity of the condition

From an ethical perspective, there is a further crucial issue, namely the severity of the condition that is targeted by granulocyte transfusions. Since the targeted condition of the patient is life-threatening, slightly higher risks for the donors may be acceptable compared to a condition of a less severe kind. Note that this does not say anything about the risks that donors can be exposed to in absolute terms, but only that the greater the severity of the patients, the greater the risks for the donor seem justifiable.

Cost-effectiveness

Hitherto, we have discussed the clinical effect in relation to the risk to which the donor is exposed. However, there is a further ethically relevant tradeoff in this context, namely, the alternative cost of allocating scarce health care resources to granulocyte transfusions if these resources could have been better spent elsewhere in the system. According to the price list 2018 for Clinical Immunology and Transfusion Medicine at the University Hospital in Linköping in Sweden, a granulocyte concentrate costs approximately 1112 €. Given the low cost of granulocyte transfusions, it would be enough with a very small clinical effect in order to reach a reasonable relation between costs and health benefits.

Autonomy

Considerations of autonomy and granulocyte transfusions

Hitherto, we have discussed granulocyte transfusions in relation to the principle of non-maleficence and the principle of beneficence. A further central aspect to medical ethics is the principle of autonomy.[6] Considerations of autonomy, or self-determination, are normally understood as the right to make one's own decisions about oneself. In clinical practice, considerations of respecting the autonomy of individuals are often operationalized by asking patients to give informed consent. In short, this means that persons should have the relevant information, be able to understand the information, and be able to act on the basis of this decision.[6] This means that patients should have the opportunity to understand, participate in, be informed, and make relevant decisions when a given measure is being used.

Free choice

The more pressing autonomy-related issue for granulocyte transfusions is that participation should be voluntary in the sense that one is free from pressure. Therefore, the donor should be informed that he or she has the right to say no without having to explain why. From the autonomy point of view, it is therefore crucial that blood donors, especially those who are at risk, for example in conjunction with pretreatments, are carefully informed about the opportunities that their efforts entail and about the risks that blood donation may pose.[16] It is also central how the donor receives information and the way in which health care approaches the donor with the question of donating granulocytes. These considerations are relevant to the risk that the donor process could entail in its own right, but also what benefit the donation can mean for the patient.

Special relations and free choice

It is important to point out that those who give granulocytes are not always blood donors, but they may also be relatives. If the health care organization cannot provide donor granulocytes, relatives may be approached. Hence, being informed as a donor that you have the right to reject is one thing. But if relatives are approached, the pressure can be great; this also applies to other situations in health care (e.g. if a relative needs a kidney donation). One possible consequence may be that those who do not have relatives will be disadvantaged. However, it is again a question of the way in which health care approaches the donors and how they are informed.

Professional values

Primum non nocere

Can values in the relevant health care professions affect the use of granulocyte transfusions? Drawing on the Hippocratic oath, several different Codes of Ethics in the medical field are partly constituted by something to the effect that the physician must always have the patient's health as the primary goal and, if possible, cure, often relieve and always comfort. In such codes, the starting point is always the patient. In the case of granulocyte transfusions, we have said above that there are primarily *two* parties that are affected. But this also means that there are two different perspectives from which health care professionals may have their respective "patient's health as the primary goal." Thus, there is a potential risk that the health care personnel responsible for the donors place higher demands on the effect of granulocyte transfusions and attaches a particularly high importance to the potential risks for which the donors are exposed. However, there is the same potential risk on the other side. The health care professionals

treating severely ill patients with bone marrow failure may be able to accept a slightly greater risk for donors as they primarily look after *their* patient's health. This strongly suggests that the risk/benefit assessment should be done by a third more impartial party.

Professional ethical codes

In the above-mentioned ethical guidelines,[26] developed by ISBT, it is emphasized that if donors are to be given drugs in order to increase the concentration of certain components in the blood, health care professionals should take special care in relation to the donor and carefully consider that the donor is not at all benefited by the procedure. Furthermore, it is emphasized that medicines can only be given to donors for this purpose when "... there is good evidence of specific benefits to the recipient. ..."[26] It is further stated that unless this is the case, the current action must be carried out as research which must therefore be preceded by a research ethics review.

Based on the examination of the scientific evidence above, it seems quite clear that there is a conflict between the ISBT guidelines and the treatment option of performing granulocyte transfusions, since the current scientific evidence for this treatment hardly can be described as "good evidence." This raises a more general discussion about the weight which should be ascribed to professional ethical codes which we shall not pursue here. We believe that a plausible standpoint on this question is that a professional ethical code cannot reasonably necessarily outweigh other relevant ethical considerations about complex ethical issues in medicine. When it comes to such ethical issues, there are usually several different aspects that need to be considered. For example, the ISBT Code of Ethics does not address the question of how clinical experience should be compared to scientific evidence or the severity of the condition to be treated by the patient, two aspects that form a central part of the general discussion in medical ethics and health care guidelines.

Conclusion

Patients with the most serious infections due to insufficient number of granulocytes in the blood have been administered granulocytes from healthy donors for more than 50 years. While the effect of these transfusions has not been proven in well-controlled scientific studies, observational studies have reported benefits of the treatment. Although the scientific evidence is insufficient, clinical experience and the severity of the condition for which patients are to be treated constitute grounds for suggesting that granulocyte transfusions may be given on established indications.[27] The information provided to donors should be neutral and reflect the scientific evidence and clinical experience. To further increase the knowledge in this area, national registers for recording the effects of granulocyte transfusions should be established.

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Appendix 1

((“granulocytes”[MeSH Terms] OR “granulocytes”[All Fields] OR “granulocyte”[All Fields]) OR (“leukocytes”[MeSH Terms] OR “leukocytes”[All Fields] OR “leucocyte”[All Fields])) AND ((“blood transfusion”[MeSH Terms] OR (“blood”[All Fields] AND “transfusion”[All Fields]) OR “blood transfusion”[All Fields] OR “transfusion”[All Fields]) AND (“blood component removal”[MeSH Terms] OR (“blood”[All Fields] AND “component”[All Fields] AND “removal”[All Fields]) OR “blood component removal”[All Fields] OR “apheresis”[All Fields])) AND ((“leukopenia”[MeSH Terms] OR “leukopenia”[All Fields] OR “leucopenia”[All Fields]) OR (“infection”[MeSH Terms] OR “infection”[All Fields]).