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Editorial

Ethics of using a bone marrow donor with Klinefelter syndrome

For many patients who require an allogeneic stem cell transplant, a human leukocyte antigen (HLA)-matched sibling or an appropriate unrelated donor can be identified. However, there are some pediatric patients who require transplantation for whom the best outcome and/or the only option is the collection of umbilical cord blood following the birth of an HLA identical sibling. This scenario occurs most often in children from ethnic minority groups for whom banked samples are scarce and in patients affected with certain genetic disorders, such as the immune deficiency diseases. In the latter situation, preimplantation or prenatal genetic testing for the specific disorder and HLA typing can ensure that the pregnancy will result in an unaffected-matched donor for the affected sibling.

Indeed, over the past decade advances in preimplantation technology have allowed the reliable determination of HLA tissue matching and the status of the embryo with regard to the specific genetic disease. These advances permit families with a child in need of a stem cell transplant to conceive and deliver an HLA-matched donor for their existing child. This approach has generated substantial controversy among ethicists, the medical community, and the public. Some of the attention surrounding these situations has focused on concerns about the genuine desire of the family to have another child and the psychological impact on the donor conceived specifically for purpose of saving the sick child. Despite this attention, this approach continues to be used and programs for the creation of stem cell donors for children with non-malignant diseases in need of stem cell transplantation have arisen.

In the article by Balsi et al. (1) in this issue, a three-yr-old boy with Wiskott–Aldrich syndrome (WAS) received HLA identical bone marrow and cord blood stem cells stored at birth from an 11-month-old brother who was prenatally identified as unaffected with WAS. The authors do not state whether or not the brother was specifically conceived for the purposes of being a donor for the older brother but do note that the pregnancy had not been terminated after the prenatal identification of Klinefelter syndrome as the parents wanted to provide a donor for the other son who had no other transplant option. Thus, it would appear that the family elected to continue a pregnancy that they may have otherwise terminated based on the fact that the fetus was an HLA identical match and was unaffected with WAS.

Klinefelter syndrome is a chromosomal abnormality that is most commonly due to a non-dysjunction event that results in a 47, XXY karyotype. During childhood boys with Klinefelter syndrome may have learning disabilities and difficulty with speech and language development. At puberty, male sexual development does not occur normally and affected men typically have low levels of testosterone, gynecomastia, reduced facial and body hair, and primary infertility. Men with Klinefelter syndrome also have an increased risk of developing breast cancer and there have also been reports linking Klinefelter syndrome with an increased risk for hematologic malignancies.

Balsi et al. comment that they had a discussion about the ethics of using a Klinefelter syndrome donor due to the theoretical risk of a hematologic malignancy arising in the recipient. Notably they did not address the ethical issue related to the parents' decision not to terminate the Klinefelter syndrome pregnancy due their desire to provide a donor for the affected son. In reality the parents of the child with WAS had a very difficult choice to make. They could try to create another HLA-matched child to be a stem cell donor and possibly rescue their dying son from his fate. They could also accept the fact their son would die from the disease and try to have another child

who was free of genetic disease. Their choice, however, was complicated by two further facts: time was of the essence and prenatal testing revealed that the child they conceived was both HLA identical with the dying child and also had Klinefelter syndrome, which the physicians perceived as a concern due to the potential risk of a hematologic malignancy arising from the donor cells.

Many clinicians and bioethicists would try to resolve this dilemma by invoking the principle that the decision should be made in "the best interests" of either the child with WAS or the donor child. Some might determine that having Klinefelter syndrome coupled with the fact that the parents otherwise might have terminated the pregnancy were it not for the desire to have a donor available for the older brother could deprive the donor child of "the right to an open future" (2). Alternatively using the child with Klinefelter syndrome as a donor could pose a risk of a hematologic malignancy in the child with WAS who would then be deprived of his "right to an open future." Finally, some may take the view that the importance of preserving the life of the existing child and his best interests take precedence.

This view that bioethics should aim at "the best interest" is dangerously misleading and does not provide the support that families in such situations need. First, guiding decisions by identifying "the best interest" is inherently intolerant. By definition, that standard declares that there is only one answer to every controversial situation. However, as demonstrated above, one could argue both for and against the transplant in terms of the best interests. Taking the best interests stance also is intolerant of respect for autonomy in that it fails to recognize that people have different values and different priorities which may lead individuals to different conclusions.

In circumstances such as those presented in this case it is hard to know what is "the best" and who should be the locus of the decision. These factors make the standard vague. Focusing on the dying child could lead to the conclusion that rescue at any course would be best. But it could also lead to the conclusion that the child had already suffered enough, that stem cell transplantation was another huge ordeal, and that the added risk of developing a hematologic malignancy because of the status of the donor was too much for anyone to bear. Focusing on the donor child with Klinefelter syndrome could lead someone to conclude that the pain and risks of bone marrow aspiration coupled with the risk that either the transplantation would not work or that the donor might later develop a hematologic malignancy would create too much pain and guilt for the donor child. Hence, stem cell donation would not be in his best interest, particularly as he had no previous attachment to his brother. Furthermore, focusing on the Klinefelter-related problems associated with language and speech acquisition and male sexual development could further persuade someone that creating a life with Klinefelter syndrome would be a burden for the donor child.

Typically, we think that we should consider the effects of our actions on others who might be impacted. People who think only about what is best for themselves are characterized as selfish egoists and may be reviled for their insensitivity to others. Yet, when it comes to medical decisions, champions of "the best interest" standard behave as if we should ascribe only egoist values to patients and take no other individuals into account. At the very least, invoking "the best interest" standard as if it represented the voice of the patient is inconsistent with our view of what morality requires.

Indeed, it is very hard to know what is in "the best interest" of others. The parents' attachment to the child with WAS could be very strong, or not. They could have cultural or religious attachments that could make it very difficult to continue to support one, let alone two children with special needs, or conversely make it very difficult for the parents to accept the death of their dying child. There could also be definitive differences in parents' emotional and economic wherewithal and also huge differences in their ability to accept the language, speech, and sexual development issues associated with raising a child with Klinefelter syndrome. Details such as these could be determinative and also hard to assess and harder still to factor together.

The health professionals' role is to use their knowledge and skill to help their patients to achieve their goals. When patients cannot make decisions for themselves because they are children, their parents have the authority to make medical decisions on their behalf. The clinicians' role then is to assure that parents do not choose anything unreasonable, such as foregoing a treatment that is very likely to confer a significant benefit or withholding a treatment that will result in a significant harm. In these circumstances, refusing treatment would be unreasonable. Unless a parents' decision is unreasonable, health professionals should not oppose it. Instead they should support parents in helping them to achieve their goal for their child. After

all, the parents are the ones who will have to bear the burdens of their choices for the rest of their lives.

In this case, the physicians involved became concerned about the theoretical risk of a hematologic malignancy developing in the recipient. It is likely that this concern presented another hurdle for the parents to overcome in making their decision about allowing the transplant. Therefore, it is important to look at the magnitude of the risk. Mamunes et al. described the first case of acute leukemia in patient with Klinefelter syndrome (3) and since that report a number of individual reports and small series of similar associations between Klinefelter syndrome and hematologic malignancy have been reported (4). However, studies of male patients with leukemia have not found an increased rate of Klinefelter syndrome suggesting that the occurrence of leukemia in men with Klinefelter syndrome may be a chance association (2, 5). Therefore, it is not a medical certainty that Klinefelter syndrome confers an increased risk for hematologic malignancy. Indeed, the National Marrow Donor Program does not include Klinefelter syndrome as a contraindication to donation (6) and the ethical debate on this point might have unnecessarily raised the anxiety of the family in this situation.

Based on the medical facts and because there is no clearly unreasonable choice on the parents' part, the clinicians' role in this case is to support the parents. That involves adhering to the professional standard of non-judgmental regard, which will require that they refrain from deciding what is ''the best'' for themselves and imposing that decision on the parents. It also entails providing the parents with honest and timely communication of the information that they need to make the decision that in the parents' judgment best serves their needs, assuring the parents that there was no wrong answer in this case, and providing caring support through the ordeal.

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References

1. Balci YI, Turul T, Daar G, et al. Hematopoietic stem cell transplantation from a donor with Klinefelter syndrome for Wiskott–Aldrich syndrome. Pediatr Transplant 2008: 12: 597–599.
2. Buchanan A, Brock DW, Daniels N, Wikler D. From Chance to Choice: Genetics and Justice. Cambridge, UK: Cambridge University Press, 2001.
3. Mamunes P. Acute leukemia and Klinefelter syndrome. Lancet 1961: ii: 26–27.
4. Keung YK, Buss D, Chauvent A, Pettenati M. Hematologic malignancies and Klinefelter syndrome a chance association. Cancer Genet Cytogenet 2002: 139: 9–13.
5. Horsman DE, Pantzar JT, Dill FJ, Kalousek DK. Klinefelter syndrome in acute leukemia. Cancer Genet Cytogenet 1987: 26: 375–376.
6. National Marrow Donor Recruitment Assessment Tool. Available at: http://www.samarinfo.org/medical.pdf (last accessed 20 February 2008).