

Ethical Considerations in Pediatric BMT Donors and Recipients

Naynesh Kamani,¹ John D. Lantos,² Doug Myers,² Jeffrey P. Kahn³

BONE MARROW TRANSPLANTATION FOR SICKLE CELL DISEASE: IS IT TIME FOR A PARADIGM SHIFT?

Naynesh Kamani, MD

Just over 25 years ago, an 8-year-old girl with acute myelogenous leukemia (AML) who coincidentally had sickle cell disease (SCD) underwent a successful matched sibling donor bone marrow transplant (BMT) for her leukemia from her otherwise healthy brother who had sickle cell trait. This was the first time that BMT had been shown to “reverse” SCD even though SCD was not the indication for BMT [1]. A few years later, Lucarelli et al. [2] published results of BMT in children with β -thalassemia major, demonstrating 87% thalassemia-free survival in patients with Class 1 thalassemia. A subsequent national trial of BMT for SCD using matched sibling donors initiated in 1991 showed promising results with 55 of 59 recipients surviving, 50 of them free of SCD [3]. Despite these promising outcomes, to date, only a few hundred children have undergone BMT for SCD despite the fact that there may potentially be thousands of eligible children with severe SCD and available allogeneic donors. There are many factors that contribute to this significant disparity between numbers of transplants and eligible patients.

Although children with SCD demonstrate a variable phenotype with only 7% to 20% having the severe phenotype, the progressive organ damage that occurs in many patients contributes to a poor quality of life, rapid decline in survival during early adulthood, and

a significant risk for premature mortality. Thalassemia major, on the other hand, has a much less variable clinical course, with most patients requiring regular blood transfusions starting in late infancy or early childhood. Allogeneic BMT from either a matched sibling or unrelated donor has become the “standard of care” for β -thalassemia major. This is also true of other inherited diseases of the lymphohematopoietic system such as Wiskott-Aldrich syndrome where early BMT soon after diagnosis is now recommended when a well-matched allogeneic donor is available. Yet, among patients with SCD who end up on chronic transfusion therapy because of severe SCD-related morbidity, many who have matched sibling donors do not undergo BMT. Whereas unrelated donor BMT has been carried out for thalassemia and WAS since the 1990s, it has been considered experimental for children with SCD and is only recently being investigated in a clinical trial setting. It is worth exploring why the application of this “curative” therapeutic approach to SCD is different than in thalassemia and perhaps considering a paradigm shift.

Based on the experience with children with inherited primary immune deficiency diseases who have now been followed for almost 4 decades after BMT, there is no reason to believe that patients with SCD who undergo BMT will not derive a long-lasting benefit. Mounting evidence points to resolution of SCD-related symptomatology and stabilization or improvement of organ function after successful BMT for SCD. Long-term complications such as sterility and a slightly increased risk of cancer aside, BMT survivors should be “cured” of their underlying hemoglobinopathy. The medical literature is rife with articles that talk of cure of thalassemia by BMT, yet this term is infrequently used for SCD and BMT. Most contemporary informational and educational brochures on SCD rarely mention BMT as a therapeutic option. A recent publication from the Centers for Disease Control and Prevention states “Symptomatic treatments exist, but there is no cure for SCD.” The parents alert brochure for those whose children have screened positive for SCD from the Texas Department of State Health Services states that “there is no cure for SCD but with

From the ¹Children’s National Medical Center, Washington, DC; ²Children’s Mercy Hospital Bioethics Center and Division of Oncology, Kansas City, MO; and ³Center for Bioethics, University of Minnesota, Minneapolis/St. Paul, Minnesota.

Financial disclosure: See Acknowledgments on page S136.

Correspondence and reprint requests: Naynesh Kamani, MD, Children’s National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010 (e-mail: NKamani@cnmc.org).

© 2011 American Society for Blood and Marrow Transplantation 1083-8791/\$36.00

doi:10.1016/j.bbmt.2010.11.007

penicillin and good care, most serious infections and almost all the deaths in young children can be prevented.” The guidelines for the management of SCD complications for healthcare providers from the SCD Care Consortium (supported by the Texas DOH), however, states: “Successful allogeneic hematopoietic stem cell transplantation provides a hematologic cure for SCD.” The FAQ section on the Website of the SCD Association of America, Inc. (a leading community SCD organization) makes no mention of BMT, and categorically states that there is no universal cure for SCD, but that research in gene therapy, the ultimate universal cure, is underway. This dichotomy between the information provided to healthcare teams on the one hand and to the patients, parents, and the lay public on the other lends credence to the perception that medical paternalism has long been practiced in the management of this disease.

Surveys of adults with SCD and of parents of children with SCD have shown that there is no agreement between the recommendations of healthcare providers and the risks that patients and parents are willing to accept to obtain a “cure” for their disease. In view of the substantial patient interest in curative therapy, the authors recommended that education about and consultation for BMT in patients with SCD be encouraged [4,5]. During the conduct of the national matched sibling donor trial for SCD, Walters et al. [6] looked into the barriers to BMT. Although the lack of an HLA-identical sib donor was the major barrier, physician refusal was more frequently encountered than parent refusal. The increasing availability of well-matched unrelated donors should alleviate the most significant barrier to BMT for eligible patients with severe SCD. With the ever increasing exposure to media and wide availability of access to the Internet, more and more patients and families are empowering themselves with scientific information in order to reject medical paternalism. Patient and parent education and empowerment and an honest discussion of risks, BMT outcome uncertainties and benefits of BMT should be fostered.

A report by Smith et al. [7] details the important gaps that exist in the equity of funds (both federal and private sector) allocated to research and in the implementation of advances in clinical care for sickle cell disease compared to cystic fibrosis. Although mortality in children with SCD has significantly decreased over the past 4 decades, the widespread adoption of best clinical practices and quality improvement efforts have lagged behind. This is especially true for adults with SCD for whom removing barriers of access to health insurance and implementation of quality comprehensive care can improve quality of life and survival.

In order that parents of children with SCD are made aware of not only the uncertain prognosis for their child but all potential therapeutic options at the

time of diagnosis, it is important to include accurate information detailing the role of BMT, its indications and potential toxicities, in parent brochures and education. This is an important consideration in the paradigm shift. As physicians, our Hippocratic oath tells us: *Primum non nocere*, or first, do no harm. Does this only mean not considering a therapeutic option that may be potentially fatal? Are we perhaps not doing harm by not offering a potentially curative therapy and subjecting the patient to a lifetime of morbidity, decreasing neurocognitive function, poor quality of life and the prospect of premature lethality?

The ethical challenges of offering a potentially curative therapeutic option with a small but finite risk of treatment-related mortality in a disease where the patient and family are not faced with the prospect of mortality in the short term (unlike refractory leukemias or severe aplastic anemia) are clearly difficult and fraught with controversy. Both the patient and family and the healthcare team have to be willing to accept this mortality risk in exchange for potential cure. This ethical dilemma is explored in more detail below.

ETHICAL CHALLENGES IN TRANSPLANT DECISIONS FOR NONMALIGNANT DISEASES

John D. Lantos, MD, Doug Myers, MD

SCD and thalassemia are 2 nonlethal conditions in which a bone marrow transplantation cures the disease. The 2 offer interesting contrasts that shed light on the ethical paradigms that govern the use of BMT for nonlethal conditions. Both β -thalassemia major and SCD can be reliably diagnosed. The clinical course in SCD, however, can vary widely. Some children have virtually no sequelae or complications from their disease. Others are debilitated by strokes, acute chest syndrome, or recurrent vaso-occlusive crises. Life expectancy is lower in β -thalassemia than in SCD disease and is more heavily dependent upon the availability of hypertransfusion and chelation.

The severity of the disease and the lack of variation in clinical course make the decision to transplant children with thalassemia less controversial, particularly if they have a sibling who is an excellent match. By contrast, the variable course in SCD makes it crucial to rely upon prognostic factors other than the diagnosis itself. Children with SCD do not become eligible for BMT unless they have other morbidity. Even then, the decision is complicated. To offer BMT for SCD, doctors must understand that they are offering a treatment that has a chance of significantly shortening the patient's life.

The ethical challenges of evaluating such a proposed therapy are daunting. SCD is a chronic disease that is usually not immediately life threatening. Today, in the United States, most patients with SCD survive

well into adulthood. Some, however, have significant morbidity from their disease. The most worrisome morbidities are from either strokes or from recurrent vaso-occlusive pain crises. Strokes can leave people seriously debilitated. Pain crisis sometimes require dozens of hospitalization each year with frequent use of high doses of narcotic analgesics. How does one balance the risks and burdens of the disease against the risks of treatment? Who should do the balancing?

One of the interesting features of transplant decisions for patients with SCD is that patients seem willing to take more risk for a chance to cure their disease than doctors or institutional review boards (IRBs) are willing to allow them to take. Kodish et al. [8] studied parents who had children with sickle cell disease, using standard reference gamble techniques. These techniques present parents with a gradually increasing level of risk, both for mortality from a transplant and morbidity from graft-versus-host disease (GVHD). A third of parents were willing to accept a 15% short-term mortality risk for a chance at cure. Thirteen percent would accept that plus a 15% risk of GVHD. Many IRBs consider any risk of death above 5% unacceptable. There are no studies of children's own views, but 15% of adults with SCD are willing to accept a mortality risk of 35% for a chance at cure. Actual outcomes, for carefully selected patients, are an overall mortality rate of about 7% with event-free survival rates of 85%.

These numbers suggest that we either underestimate the burden of SCD or have standards of acceptable risk for patients that are much more cautious than the standards that they would make for themselves. These studies raise questions about patient autonomy, about professional integrity, about the possibility of truly informed consent, and about the proper locus of responsibility for decisions such as this one.

Three factors shape any decision to offer BMT for a nonlethal condition. First, how bad is the health-related quality of life for the people with the disease? Second, are there any prognostic factors that allow more accurate predictions of the clinical course for individual patients—that is, if we knew which patients with SCD were most likely to have debilitating strokes or vaso-occlusive crises, we could selectively transplant them rather than others. Finally, we must consider the likelihood of success or failure of the transplant and do so in light of the quality of the match that is available. These factors then lead to a 2-stage decision process. First, doctors must decide if they are willing to even offer a transplant. There may be situations in which parents or patients want a transplant but in which doctors feel it is too risky. We know from studies of practice variation between centers that different groups of transplanters have different thresholds of risk and benefit. If doctors are willing to offer a transplant, then parents and patients must participate in a rigorous

process of informed consent. This is, after all, a more elective treatment than some. Meticulous attention to patient understanding is crucial. It may take time, but, given the nature of the disease and the treatment, there is time.

The informed consent process needs to deal with some issues that go beyond merely the statistics on prognosis with and without transplant, mortality risks, or the risks (and nature of) GVHD. One of the issues concerns timing of the transplant. Generally, outcomes are better when transplants are done earlier in life. Generally, prognostic accuracy is worse early in life. A program of early transplantation will result in the transplantation of some children who may not have needed it, but will likely lead to better outcomes overall for the population of transplanted children. A related issue concerns preservation of fertility. Generally, transplantation leads to infertility. For BMT recipients who have gone through puberty, fertility can be preserved by harvesting sperm or ova for later use in an *in vitro* fertilization setting. Transplantation prior to puberty does not allow this option. This, too, must be factored into the decision, along with other variables that favor either early or late transplantation.

In this transplantation situation, as in others, the donor faces a set of challenges that may be underestimated or ignored by the transplant team. Donation is not without risk, even though the risk is relatively low. More importantly, donors have well-described psychologic problems. They may feel used, neglected, or, if the transplant fails, guilt-ridden. A recent survey of HCT centers in the United States revealed that transplantation physicians were involved or potentially involved in overlapping care of the hematopoietic cell transplant (HCT) donor and the recipient in >70% of centers with similar practices for both adult or pediatric donors and recipients [9]. A policy statement from the committee on bioethics of the American Academy of Pediatrics recommends that specific criteria be met before minors can serve as stem cell donors [10]. Many pediatric programs now have donor advocacy programs that are specifically designed to attend to the physical and psychologic needs of the donor. However, it is not clear whether the AAP recommendations have gained wide acceptance among the HCT community. More studies need to be done to better understand the experience of donors in nontraditional transplantation situations.

Another issue that has recently come to the forefront is the question of whether it is ethical to give granulocyte colony stimulating factor (G-CSF) prior to a bone marrow harvest to sibling donors who are minors. The federal government was asked by the COG to review and comment on this issue during the approval process for a phase III, multi-institutional, randomized trial of G-CSF stimulated bone marrow versus conventional bone marrow as a stem cell source

in matched sibling donor transplantation. In its review, the FDA's Pediatric Ethics Subcommittee first determined that G-CSF administration involved more than a minor increase over minimal risk, with no benefit to the donor. However, they also felt that the research presented "a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." Therefore, they felt, "the research can be conducted in accord with sound ethical principles (with 1 dissenting vote), assuming that provisions were made to strengthen protection of the donors. These extra protections included additional donor exclusion criteria, mandating a donor advocate, mandating stricter criteria for the data safety monitoring board, and giving preference to older donors over younger ones [11].

THE ETHICS OF CREATING A STEM CELL DONOR

Jeffrey P. Kahn, PhD

In the years after preimplantation genetic diagnosis (PGD) was developed and first introduced, its use had been restricted to avoiding disease in future children for couples at risk of passing on genetic disease. In cases where PGD is used to select HLA-matched in vitro fertilized (IVF) embryos for the purpose of creating a hematopoietic stem cell donor, however, the distinction between testing for a disease and testing for some other, nondisease trait was ignored. The second stage, however, crossed the line between avoiding genetic disease and selecting for some nondisease trait by testing the remaining embryos for HLA status. Further complicating the analysis, the selection of HLA status is not to benefit the child that would develop from the tested embryo, but to ensure immune compatibility with the future child's sibling. For some, the concern about selecting traits for this purpose is softened by the argument that were it not for the fact that the child born from the selected embryo was both disease-negative and HLA-matched to his or her sibling, the child would not have been born. In other words, if a couple had selected an embryo only based on its FA-negative status, in all probability another child would have been born because numerous disease-negative (but HLA incompatible) embryos are usually available earlier in the process.

Does Motivation Matter?

The concern is that parents could use predictive genetic testing technologies like PGD for reasons that serve themselves or their existing children but have very little to do with the interests of the future child. Given the wide range of reasons and motivations

for having children, it is difficult to argue convincingly that having a child to save the life of an existing sick child is such a bad parental motivation.

Parents are prevented from abusing or neglecting their children, with the state stepping in and even removing children from their parents when their health and safety are threatened. We, unfortunately, can envision cases in which parents might create children to serve their own or their other children's interests in ways that could violate those limits. More successful would be efforts to oversee the treatment of the children after they are born, and to make sure that an appropriate risk-benefit balance exists when children are used as donors.

The Policy Gap

Using IVF and PGD for the purpose of creating a stem cell donor relies on a new combination of existing technologies—creation of embryos by IVF, use of PGD for selection of traits, and collection and use of umbilical cord blood for transplant. There are 3 areas that together point to a policy gap in the oversight of the new use of these technologies: (1) multiple sites leading to no locus of overall responsibility, (2) limited mechanisms for assessing acceptable creation and uses of human embryos, and (3) limited third-party payer oversight of the medical technologies involved [12].

First, the experience with these cases (eg, the Molly Nash case and others) makes clear that whatever controls we might suggest, the fact that the various elements of the process can take place at different sites makes coordinated review and oversight difficult. In the Nash case, IVF was performed at a clinic in Denver, PGD in Chicago, and the cord blood transplant in Minneapolis [13]. Rules or oversight dictated by the IVF clinic have little impact on behavior at the PGD clinic or in the transplant unit, and vice versa. The upshot of having multiple sites for the individual elements is that there is no locus of overall responsibility for the process, which creates an environment in which each of the individuals and institutions involved can make decisions at their own discretion and then claim that the implications resulting from the combination of technologies are out of their control.

Second, there are few if any mechanisms for assessing the acceptable creation and uses of human embryos, particularly in the medical context. Part of the policy gap is related to the practice of reproductive medicine and the creation of human embryos. Reproductive medicine clinics in the United States and abroad create embryos as part of routine, high-tech medical care for infertility. Such creation is subject to little oversight or review. Recent surveys suggest that in the United States alone there are nearly 400,000 frozen embryos in storage, left over from

IVF procedures [14]. These so-called “spare embryos” are subject to private contracts with the lab and infertile couples and individuals, but otherwise are subject to few legal restrictions, if any, on their future use, including experimental uses.

In the research context, U.S. policies and practices for decades have effectively prohibited the use of federal funds in any research that harms or destroys human embryos. This funding limitation has a complex policy history that has been well-documented elsewhere [15], and is a reflection of the political and moral controversy surrounding abortion. However, in the absence of federal research funding, funding-related rules or restrictions do not exist: embryos can be created, destroyed, experimented upon, and used for any purpose so long as no federal dollars are used. In addition, much of the work that takes place in reproductive clinics typically has not been classified as research, but rather as innovative clinical practice, an area that in law and policy historically has been left to the discretion of individuals and institutional policies. Indeed, as numerous others have pointed out [15-17], reproductive medicine is among the least regulated or controlled areas of medicine.

A third component of the policy gap is a product of the limited third-party payer oversight of reproductive medicine. Reproductive medicine long has enjoyed a market-oriented approach to oversight, in part because such a large proportion of the costs of reproductive medicine services are born by patients directly and not by third-party payers. Because insurers pay so few of the costs of IVF and other reproductive medicine services, they have little say over the appropriate uses of the technologies involved. Instead, market forces decide the restrictions, if any, that should exist. Likewise, any attempts at self-regulation by reproductive medicine specialists are more influenced by patient demand and willingness to pay than by any criteria that the profession might deem appropriate.

To summarize, efforts to control or oversee the creation of immune-matched stem cell donors falls neatly into a policy gap, a gap that could easily occur again in other overlapping technology uses. This policy gap stems from the combination of multiple sites of responsibility and lack of any locus of responsibility for the overall process; the limited oversight of IVF and other reproductive medicine services owing in part to the embryo research ban; and the market-driven nature of reproductive medicine. This gap has implications not only for the use of the individual technologies involved, but also for how they might be used in combination in the future.

Policy Recommendations

What can be done to improve the policy environment for intervention and/or oversight in the creation

of stem cell donors? (1) Move the debate from the clinic to the public policy arena, (2) avoid reactive policymaking, (3) create local mechanisms for review of and advice on controversial uses of biomedical technologies, and (4) consider lessons from others, particularly oversight efforts in other countries.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

REFERENCES

1. Johnson FL, Look AT, Gockerman J, et al. Bone marrow transplantation in a patient with sickle-cell anemia. *N Engl J Med.* 1984;311:780-782.
2. Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassemia. *N Engl J Med.* 1990;322:417-421.
3. Walters MC, Patience M, Leisenring W, et al. Stable mixed hematopoietic chimerism after bone marrow transplantation for sickle cell anemia. *Biol Blood Marrow Transplant.* 2001;7:665-673.
4. Kodish E, Lantos J, Stocking C, et al. Bone marrow transplantation for sickle cell disease—a study of parents’ decisions. *N Engl J Med.* 1991;325:1349-1353.
5. Besien KV, Koshy M, Anderson-Shaw L, et al. Allogeneic stem cell transplantation for sickle cell disease. A study of patients’ decisions. *Bone Marrow Transplant.* 2001;28:545-549.
6. Walters MC, Patience M, Leisenring W, et al. Barriers to bone marrow transplantation for sickle cell anemia. *Biol Blood Marrow Transplant.* 1996;2:100-104.
7. Smith LA, Oyeku SO, Homer C, et al. Sickle cell disease: a question of equity and quality. *Pediatrics.* 2006;117:1763-1770.
8. Kodish E, Lantos J, Siegler M, et al. Bone marrow transplantation in sickle cell disease: the trade-off between early mortality and quality of life. *Clin Res.* 1990;38:694-700.
9. O’Donnell PV, Pedersen TL, Confer DL, et al. Donor Health and Safety Working Committee from Center for International Blood and Marrow Transplant Research (CIBMTR). Practice patterns for evaluation, consent, and care of related donors and recipients at hematopoietic cell transplantation centers in the United States. *Blood.* 2010;115:5097-5101.
10. Children as hematopoietic stem cell donors. Committee on Bioethics. *Pediatrics.* 2010;125:392-404.
11. Available at: http://www.hhs.gov/ohrp/children/Letter_to_Nemours_061109.pdf
12. Kahn JP, Mastroianni AC. Creating a stem cell donor: a case study in reproductive genetics. *Kennedy Inst Ethics J.* 2004;14:81-96.
13. Grewal SS, Kahn JP, MacMillan ML, et al. Successful hematopoietic stem cell transplantation for Fanconi anemia from an unaffected HLA-genotype-identical sibling selected using preimplantation genetic diagnosis. *Blood.* 2004;103:1147-1151.
14. Hoffman DL, Zellman GL, Fair CC, et al. Cryopreserved embryos in the United States and their availability for research. *Fertil Steril.* 2003;79:1063-1069.
15. Parens E, Knowles LP. Reprogenetics and public policy: reflections and recommendations. A special supplement to the *Hastings Center Report.* *Hastings Center Rep.* 2003;33:S1-S25.
16. Andrews LB, Elster N. Regulating reproductive technologies. *J Legal Med.* 2000;21:35-65.
17. Knowles LP. Reprogenetics: a chance for meaningful regulation. *Hastings Center Rep.* 2002;32:13.