nature publishing group

Commentary

Hope vs. caution: ethical and regulatory considerations for neonatal stem cell therapies

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The Annual Review issue of *Pediatric Research* contains important reviews and original reports focusing on stem cell therapy for the treatment of neonatal lung disease (1), pediatric brain injury (2), congenital anomalies (3), and congenital heart disease (4). The authors describe the potential of these approaches to advance the care of children with life-threatening conditions and those with significant long-term chronic morbidities. The authors also describe the promise, ethical challenges, and limitations of these evolving therapeutic approaches. In considering these important advances, several themes are worthy of consideration, especially as related to potential cell-based therapies in neonates. These themes can be broadly categorized into study design, recruitment, funding and sponsorship, and ethical and regulatory complexities.

STUDY DESIGN AND RECRUITMENT

A clear understanding of the unique characteristics, cell source, and potential of the cellular therapies under development in each study is important in evaluating these emerging therapies. It is inevitable that clinical trials in children will result in conflicting results due to differences in study populations, cellular therapy administration regimens, and outcome measures. As such, proper description and evaluation of the characteristics of individual clinical trials are critical, especially for neonates, for whom developmental and physiological immaturities impart additional challenges.

The complexity of the conditions being investigated also warrants thoughtful consideration, especially as related to study inclusion criteria. It is important to avoid bias participant selection toward the healthiest patients. This issue is particularly complex in high-risk patient populations, where there is a natural tendency to exclude patients deemed too ill to participate.

Other important considerations in studies involving neonates include the timing of eligibility determination and informed consent discussions with the parents. For interventions that occur in the immediate perinatal period, enrollment may need to occur shortly before or after delivery (5). Special consideration of the difficulties of expectant or new parents' ability to engage in the informed consent process for complex and potentially risky studies is essential in the setting of unexpected preterm delivery or critical illness. Funding proposals, recruitment, and informed consent must be balanced and honest in the way that both risks and potential benefits are presented, with acknowledgment of unknowns about long-term risks. The allure of innovative, high-tech, and high-reward treatments may result in public calls for more access to experimental treatments, whereas ethical controversies (e.g., around human embryo-derived stem cells) and perceived risks may heighten the sense that the research is a dangerous endeavor from which patients need protection. The balance of access and protection is further complicated by inequities in access to cutting-edge experimental and innovative treatments that are likely to favor populations of social and economic advantage, whereas the burdens of translation from research to clinical settings may disproportionately accrue to disadvantaged and vulnerable populations.

Funding and Sponsorship

A unique challenge of the introduction of stem-cell-related therapies into the care of the youngest patients relates to the need for long-term surveillance to assess the benefit and adverse effects following cell-based treatments. Of concern, the duration of such long-term follow-up studies is likely to exceed typical funding periods. Investigators, funding agencies, and industry need to work together to ensure that long-term safety studies be included as part of study proposal design. The development of registries to follow these children in the long term should also be considered. Innovative funding models, which require iterative application to the sponsor for continued support for outcomes surveillance, or include engagement by patient and community stakeholders, might be helpful in upholding the scientific community's commitment to long-term safety monitoring.

Regulatory and Ethical Complexities

Although it is laudable that many clinical trials of this exciting and new therapeutic modality are taking place at academic medical centers under watchful eyes, it is important to recognize that cell-based therapies are being offered at private centers. Recent complications related to these treatments have

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Received 6 November 2017; accepted 19 November 2017; advance online publication 10 January 2018. doi:10.1038/pr.2017.320

resulted in the Food and Drug Administration (FDA) closing several commercial centers following patient harm. As tempting as the commercial potential may be, it is essential that federal agency oversight, free from political influence, take place before such treatments become mainstream.

It is crucial that ethical and regulatory considerations be interpreted in the broader context of both consensus and controversies about stem cell research and stem cell donation for and by children. Debate continues about the moral status about human embryo-derived stem cells, the use of stem cells in research, and the influence of commercial entities that stand to benefit from proprietary discoveries (6,7). Additional consideration must be given to ethical complexities when children are potential stem cell donors (8) and to routine umbilical cord blood cell banking, which is costly for families and likely never to be used for treatment (9).

CONCLUSION

Amidst the many challenges for the scientists and clinician investigators working to advance these therapeutic approaches, we need to close the gap in understandings and nomenclature of specific cellular products as they are developed. We must remain cognizant of evolving ethical, policy, and regulatory issues. We must also consider each of these areas in the design and execution of clinical trial development, recruitment processes, and informed consent discussions to maximize the benefit for children's health, given the great promise that they hold.

Disclosure: The authors declare no conflict of interest.

REFERENCES

1. Kang M, Thebaud B. Stem cell biology and regenerative medicine for neonatal lung diseases. Pediatr Res 2017 (this issue).
2. Niimi Y, Levison SW. Pediatric brain repair from endogenous neural stem cells of the subventricular zone. Pediatr Res 2017 (this issue).
3. Fauza DO. Transamniotic stem cell therapy: a novel strategy for the prenatal management of congenital anomalies. Pediatr Res 2017 (this issue).
4. Zhong J, Wang S, Shen WB, Kaushal S, Yang P. The current status and future of cardiac stem/progenitor cell therapy for congenital heart defects from diabetic pregnancy. Pediatr Res 2017 (this issue).
5. Rich WD, Auten KJ, Gantz MG, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. Pediatrics 2010;126: e215–21.
6. Lo B, Parham L. Ethical issues in stem cell research. Endocr Rev. 2009;30: 204–13.
7. Lowenthal J, Sugarman J. Ethics and policy issues for stem cell research and pulmonary medicine. Chest 2015;147:824–34.
8. American Academy of Pediatrics, Committee on Bioethics. Children as hematopoietic stem cell donors. Pediatrics 2010;125:392–404.
9. Lubin BH, Shearer WT. Cord blood banking for potential future transplantation. Pediatrics 2007;119:165–70.