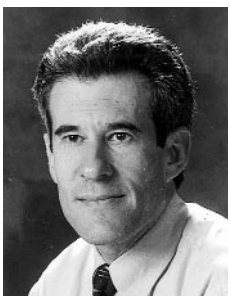
Editorial

Bioethical Issues in Autologous Stem Cell Transplantation in Children and Adults with Arthritis



In this issue of *The Journal* the proceedings of two separate meetings are presented. In June 2000, the National Institutes of Health (NIH) invited clinicians and investigators to a two day meeting to focus on the need for new treatments for pediatric rheumatic diseases and the role of stem cell transplantation therapy for these diseases[1]. In March 2000, a similar group met under the auspices of the International Bone Marrow Transplant Registry to review outcomes of trials of autologous hematopoietic stem cell transplantation (HSCT) in adult rheumatoid arthritis (RA) and to plan future transplantation studies. Several investigators reviewed their experiences with HSCT in patients with RA.

In general, despite a variety of induction regimes, almost all patients with RA have an excellent initial response to HSCT, even if previous treatment with multiple disease modifying antirheumatic drugs (DMARD) had failed, including tumor necrosis factor (TNF) antagonists in some cases[2-8]. However, despite this initial excellent response, most patients had a flare of disease 3–6 months posttransplant. The flares responded much more readily to DMARD treatments that had been unsuccessful prior to the transplant. Most protocols now suggest maintaining the excellent immediate posttransplant result with methotrexate, TNF blockade, or a combination of the two. Critical to further understanding of the place for this treatment are multicenter trials that have rigid and consistent inclusion criteria and an agreed upon conditioning regime[9-14].

Over the last decade, there have also been major advances in the treatment of children with juvenile rheumatoid arthritis (JRA). The recognition that the outcome for children with all types of JRA is poor[15] has resulted in a more "aggressive" treatment approach than had been recommended until recently. The use of intraarticular corticosteroid therapy and methotrexate has improved the outcome and quality of life of such children[16,17]. Recently, the use of targeted anticytokine therapy with etanercept[18-23] and infliximab[23-25] has resulted in even greater short term benefit. Yet despite these advances, there remain a significant number of children who do not have an adequate response to even these more advanced treatments[18,22]. For example, about 26% of children with polyarticular course JRA failed to respond by as little as 30% to etanercept, and a 70% response rate was only seen in 36% of patients. Patients with systemic onset JRA and a polyarticular course had the worst overall response to etanercept[18]. Further, as reported in adults with RA, children and adolescents who have an excellent initial response to etanercept often develop a flare of their arthritis requiring additional second-line therapy. Currently, there are no pharmacologic alternatives for these children, and the option of autologous stem cell transplantation (ASCT) has been proposed. Data presented by Wulffraat, representing the European Blood and Marrow Group Registry, using a variety of treatment protocols for ASCT in children with severe polyarticular course JRA have shown full or partial remission in 79% of patients, and in those patients whose arthritis has returned, it has been relatively easy to control with less therapy than was required for disease control prior to the transplant[26]. New protocols with NIH funding have been developed and studies to evaluate the role of ASCT in patients with treatment resistant JRA are currently under way. However, the mortality rate associated with this procedure has been significant, with about 14% of patients having died shortly after transplant. Deaths occurred from infection and macrophage activation syndrome, and as a result, current protocols have attempted to minimize such tragic events.

While there is a great deal of excitement about the potential benefit of transplantation therapy for adults and children with severe arthritis, the use of ASCT raises several important ethical issues (in addition to many scientific and medical ones) that must be considered before this treatment is offered to patients and families. The processes of decision making and informed consent are confounded by the lack of good evidence in this patient group, making risk-benefit calculations difficult. These issues apply both to adults and children with rheumatic diseases but they are more profound in children for

See Report on the NIH Workshop on Autologous Stem Cell Transplantation for Pediatric Rheumatic Diseases, *page 2337 and* Special IBMTR/ABMTR Workshop on the Role of Hematopoietic Stem Cell Transplantation for RA, *Supplement 64*

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several reasons. These relate primarily to their inability to make decisions (although they must participate in decision making) and the potential longterm complications. The ethical imperative to act in the best interests of the child — a generally accepted standard of decision making — may be threatened by competing interests, including those of other patients requiring scarce resources, caregivers who are also researchers, and even members of the child's family. Finally, potential side effects such as infertility beg the question whether decisions should be deferred until the child is able to participate.

The complexities and challenges inherent in the decision making process are enormous. ASCT under these circumstances might be considered to be "innovative" treatment, i.e., treatment that is routinely used in one group of patients, but is non-validated in another[27]. ASCT has a role to play in a number of malignant diseases and is considered to be an accepted mode of therapy. However, when used in patients with autoimmune disease, it must be considered innovative until there is a solid body of evidence that proves its benefits. Patients and families must therefore make decisions that may lead to devastating consequences under conditions of considerable uncertainty.

While for some children the benefits of this treatment may be significant, it may be difficult to assess these benefits in light of the potential for significant harm. Although the mortality of the ASCT in malignant or hematologic disease is as low as 3–5%, the EBMT (European Group for Blood and Marrow Transplantation) data have shown a mortality of close to 15% in children with arthritis. While death may be preventable with a more thorough evaluation for underlying infection and maintenance of corticosteroid treatment for a longer period after the transplant itself, it is currently not possible to provide "true" risk figures to patients undergoing this procedure and their families. This is ethically problematic for the communication and informed consent processes[28]. One group has recommended that in trials where there is more than minimal risk involved, and the subjects are vulnerable and incompetent, that some form of consent monitoring be considered[29].

It may be ethically acceptable to offer treatments posing significantly greater than minimal risk to mature patients who are living with illness and are capable of deciding for themselves, and to accept from them a decision to risk death. We might question, however, a parent's "right" to place a young child at risk of death when the child's condition is not life threatening and the potential for benefit is uncertain. Parents and guardians of vulnerable children have an ethical obligation to act in the child's best interests, and would only under exceptional circumstances be permitted to authorize research that carries such risk[30-32].

In order to provide the best possible outcomes for children, ASCT should only be performed in centers with transplantation expertise. This may limit the ability of individual centers to offer such a procedure to their patients. Since most institutions have limited resources and expertise to do ASCT, offering this procedure to patients with JRA may restrict others who require it as part of their care (e.g., children with leukemia or aplastic anemia) from receiving it in a timely way.

The transplantation procedure and the process of immunologic reconstitution provide valuable opportunities to further the basic understanding of the pathophysiology of inflammatory arthritis. The patients who serve as "human subjects" thus become important resources for researchers. These research opportunities must not become the driving force to offer and perform transplants. Patients and families must be informed that in addition to ASCT being an unproven treatment, it may also be considered as a "laboratory experiment." Approvals by a research ethics board must be obtained, including approval of consent and assent forms. Clinicians should be aware of the potential conflict between their role as caregiver and that of researcher[30], and always mindful of the trust families place in them to protect the welfare of the patient[33].

Severe disease has a major impact on the quality of life of the entire family. There are tremendous indirect costs associated with the disease that fall upon the parents and family. The patient and family may be required to travel a significant distance, removing the child from his/her home life and daily routine. One or both parents may have to take a leave of absence from work, which can create a significant financial burden. Quite naturally, these factors may have a significant influence on decision making, with the potential for conflicts of interest in parents requesting the ASCT procedure[34]. While this is understandable, the team should ensure that the best interests of the child remain the focus of decision making. Significant psychosocial and financial support and assistance with decision making should be available for families if it is needed.

While the risk of death is most significant, the pretransplant regimen has significant potential toxicity, including malignancy and infertility. The dosages of cyclophosphamide used may be associated with infertility in both females and males. These risks are increased in patients who have previously received cyclophosphamide to control the underlying disease process[35]. Infertility is a life affecting condition that has implications for the whole family. Knowledge of the powerful negative effects that infertility has on some individuals strongly supports the argument that when possible, the choice of treatment that is likely to cause infertility should be made by the individual herself or himself, when they are sufficiently mature to grasp the implications of such a decision. This would be true of any decision that is made by substitute decision makers for an incapable person, when it involves an "elective" procedure that is likely to have significant, lifelong side effect(s).

On the other hand, while infertility for some individuals may be unexpected and unexplained, if one knows from an

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early age that one will not have the ability to conceive a biologically related child there may be less of a sense of loss and lack of control. If parents feel very strongly that the treatment must be provided *now*, and there are either medical reasons to support this decision, or at least no medical grounds to reject it, then it would be reasonable to require — or at least strongly recommend — that counseling be provided to parents about the infertility issues so that they will be able to build this into the child's developing sense of self, and his or her sense of the future.

This is an exciting time in rheumatology. Improved understanding of the immunopathogenesis of inflammatory arthritis has led to many new treatments and treatment approaches. Transplantation offers the potential for longterm remissions with much improved quality of life for these patients. As additional clinical and scientific evidence to support this form of treatment is accumulating, we must not lose sight of the many ethical issues that should be considered as we embark down these new therapeutic paths.

RONALD M. LAXER, MD, FRCPC;
Professor of Paediatrics and Medicine,
Member, Joint Centre for Bioethics,
University of Toronto,
Associate Pediatrician in Chief,
Pediatric Rheumatologist, Department of Pediatrics,
The Hospital for Sick Children,
555 University Avenue, Suite 8253,
Toronto, Canada M5G 1X8;
CHRISTINE HARRISON, PhD,
Assistant Professor of Paediatrics,
Member, Joint Centre for Bioethics,
University of Toronto,
Director of Bioethics,
The Hospital for Sick Children.

Address reprint requests to Dr. Laxer.

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