Programming a hematopoietic stem cell donor: the evolution of a project over time

Giuseppe Roberto Burgio, Franco Locatelli*
Dipartimento di Scienze Pediatriche, Università di Pavia, IRCCS Policlinico San Matteo, Pavia, Italy;
**Oncoematologia Pediatrica, IRCCS Policlinico San Matteo, Università di Pavia, Italy. E-mail: f.locatelli@smatteo.pv.it*

Allogeneic hematopoietic stem cell transplantation (HSCT) is a treatment largely employed for a number of hereditary and/or hematologic conditions, both malignant and non-malignant.[1] Nearly 40 years have elapsed since the first successful bone marrow transplantation;[2,3] since then, significant improvements have been reported, also in connection with the use of cord blood as a source of stem cells. The availability of an HLA-compatible family donor still remains of such paramount importance in terms of the possibility of success of HSCT[4] that, sometimes, the parents of an affected child resort to programming the birth of a child with the aim of taking advantage of his/her cord blood as a source of stem cells capable of saving the life of a sibling in danger.

In 1987, for the first time, we reported on a bone marrow transplant performed from a donor conceived with the hope that he would be HLA-compatible with his sister.[5] The patient was 7 years old and had Philadelphia-positive chronic myelogenous leukemia in first chronic phase, a disease that was invariably fatal within a few years at that period. In January 1985, the girl's parents had decided to initiate another pregnancy, with the hope, based on a 25% statistical probability, that the newborn might be HLA-identical with the patient, so that he could become a donor of bone marrow-derived stem cells capable of saving his sister's life. Prenatal testing of HLA compatibility between the fetus and his sister was not performed. Following an uneventful pregnancy, the child was born and found to be HLA-compatible, thus allowing him to act as a bone marrow donor, 20 months after his birth.

The most relevant ethical issue raised by this particular case was the decision to conceive a child *also* with the hope that he/she would be suitable as a donor of hematopoietic stem cells.[5] The issue was further addressed in both the medical and ethical literature,[6-8] as well as commented upon in newspapers and periodicals of various European countries.

Today, almost 18 years after the bone marrow transplant, the patient remains in remission with full donor chimerism, without chronic graft-versus-host disease and has graduated from a prestigious Fine Arts Academy in Milan. Her 20-year old brother has recently started stable employment, following completion of high school. They are both in perfect physical, mental and socio-relational health.

Eighteen years have elapsed since this paradigmatic case, but not without important advances in the field of childhood HSCT. In particular, as already mentioned, the safety of the collection of placental blood for the newborn,[9] as well as the demonstration of efficacy of cord blood transplantation in several disorders,[4,10,11] have provided the clinical basis for starting large programs of collection, characterization, cryopreservation and storage of hematopoietic stem cells from umbilical cord to be used for transplantation. Likewise, registries of volunteer bone marrow donors are now well established in most developed countries; these registries are advantageously integrated with umbilical cord blood banks and it can be now estimated that a significant proportion of patients in need of HSCT and lacking an HLA-identical sibling have the possibility of finding a suitable, non-consanguineous donor.[11] The refinement of HLA typing from serological methods to high-resolution (i.e. allelic) molecular techniques has allowed, in many cases, the selection of the most suitable and most compatible unrelated donor. The advance offered by high-resolution HLA molecular typing is clearly documented by the comparable results obtained in patients transplanted from either an HLA-identical sibling or a non-consanguineous donor, identical at the allelic level with the recipient.[12,13]

Although the progress of unrelated donor HSCT has been noteworthy, it does not mean that sibling donors, and therefore HSCT from a *programmed* newborn donor, have become obsolete. In fact, an allelic-matched unrelated volunteer can be located for only approximately 40% of Caucasian patients who start a search to find a suitable, non-consanguineous donor.[13] Moreover, the value of HSCT from an HLA-identical sibling, and in particular of cord blood transplantation from an HLA-compatible relative, is best documented by studies demonstrating negligible or even no transplant-related mortality.[4] Thus, especially for patients who cannot find a suitable unrelated volunteer as a hematopoietic stem cell donor, the programming of an HLA-compatible sibling donor remains an attractive option. This strategy can now take advantage of a new technique, which, if successful, increases the chances of obtaining a stem cell donor from 25% for an unselected pregnancy to 100%. This technique is *assisted fertilization with pre-implantation genetic diagnosis (PGD)* for selecting HLA-compatible embryos; it produces a donor who, besides being HLA-compatible with the candidate recipient, in the case of a genetic disorder, is also non-affected.[14]

However, the selection of the *HLA-compatible and non-affected* embryo entails discarding other (equally non-affected) embryos just because they are not suitable as donors for HSCT. The use of PGD does, therefore, raise a bioethical problem, made more complex by conflicting

opinions, directly related to individual viewpoints, which are more philosophical than scientific, regarding when cells derived from a zygote attain the status and the dignity of a human being. One line of thought (and action) suggested by supporters of this technique claims that it has life-saving ethical merit.[14,15] One might also find support in an ethical perspective privileging the vision that *desperate ills call for desperate remedies*.[16] Of course, some would argue against this position with an equally respectable notion, according to which sometimes *the cure can be worse than the disease*. However, in the specific problem described here, the choice of giving priority to this latter position over the former would entail the decision to renounce a life-saving remedy or, in any case, the remedy associated with the best possibility of curing the sick recipient.

Reduced to its essential ethical-bioethical issues, PGD *for HLA-compatibility* with selection, on this basis, of an embryo suitable as a donor entails weighing the desirable option of saving of a life against that of discarding a number of other embryos, *useless* as far as transplantation is concerned. However, before even beginning to weigh these options it is obviously essential to impose, as a starting point, the condition that the parents must not desire the donor child *solely* as a donor and therefore potentially a *life-saver* for a sick sibling, but rather because the new child is truly desired and consequently will be fully loved and cared for[16-18] Indeed, we feel that the single inescapable premise of any planned birth must be, first and foremost, the desire for this child for its own sake, so that it will be loved for itself, protected and nurtured, to ensuring that its rights are always respected in order to grant the child the highest possible quality of life.

To conceive a child with the exclusive goal of using him or her as a donor would render such a project ethically aberrant. The fear that such a highly questionable perspective could be realized has recently been expressed, and prefigured by extremely disturbing scenarios, such as those of giving up the new baby for adoption after having used its cord blood or bone marrow or, even worse, of aborting the fetus with the purpose of employing the stem cells present in its liver.[18] Undoubtedly, such fears and threatening predictions testify to a degree of human perversity, capable of transforming a project, originally conceived with the purpose of saving lives, into a deplorable intention.

The brief history of programming the birth of a child to become (*although not exclusively*) a hematopoetic stem cell donor for a sibling with a disease amenable to treatment with HSCT shows all the hallmarks of a genuine project evolving over time. Until 2001,[14] the project was based only on the hope that the *programmed child* was HLA-compatible, with a 25% chance of success. However, since 2001, besides this widely accepted (without limits or legal constraints) uncertain hope, in some countries of the world, a near certainty that an HLA-compatible child can be obtained for couples choosing to avail themselves of assisted fertilization with PGD has become an available option. In both options an ethical or bioethical limit still exists and is represented by the unethical use of a person purely as a means to achieve a goal.

Funding: this work was partly supported by grants from AIRC (Associazione Italiana Ricerca sul Cancro), MURST (Ministero dell'Università e della Ricerca Scientifica), European Union (Allostem Project) and IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) Policlinico S. Matteo to FL.

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