Post-transplant cyclophosphamide prevents graft-versus-host disease in Haploidentical stem-cell transplanted children with inborn errors of immunity: a single-center experience

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Abstract

INTRODUCTION: For many patients with Primary immune deficiency (PID), stem-cell transplantation (SCT) may be lifesaving. OBJECTIVE: To review our experience of 11 years transplanting children with PID in Mexico. METHODS: Chart review of patients who underwent SCT from 2008 to 2018, to describe their diagnoses, time to transplant, conditioning regime, survival rate and outcomes. All patients received post-transplant cyclophosphamide as graft-versus-host-disease (GVHD) prophylaxis. RESULTS: 19 patients with combined, phagocytic or syndromic PID from 5 states. Twelve of them were male (58%) and 14 survive (79%). Mean age at HSCT was 41.9 months; mean time from diagnosis, 31.2 months. Seven grafts were umbilical cord and 12 haploidentical. The conditioning regime was myeloablative, with seven primary graft failures. Two patients had partial and 10 full chimerism. Five patients died within 2 months after transplant. Immune reconstitution was complete in 11 of 19 patients. We found a prevalence of 21% GVHD. DISCUSSION: We describe 19 patients from Mexico with 8 PID diagnoses who underwent allogenic HSCT over a period of 11 years. Survival rate and other outcomes compare well with industrialized countries. We recommend the use of post-transplant cyclophosphamide to prevent GVHD in scenarios of resource scarcity and a lack of HLA-identical donors.

HIGHLIGHTS

We describe the experience of our hospital, UMAE 25 IMSS in Monterrey NL, Mexico, of 11 years performing hematopoietic stem-cell transplantation (HSCT) in pediatric patients with primary immune deficiencies.

We report the clinical features, origin, diagnoses, treatment and outcome of 19 patients with 8 PID diagnoses who underwent HSCT, with a 79% survival rate, 21% GVHD prevalence, 47% stable chimerism, and 58% of complete immune reconstitution.

Post-transplant cyclophosphamide has been proven effective as anti-GVHD prophylaxis. Despite all our grafts coming from umbilical cord and haploidentical donors, we were able to prevent GVHD by using post-transplant cyclophosphamide.

In Mexico and Latin America, we need better local and regional donor registries. We can achieve encouraging positive results despite resource scarcity and other regional limitations.

INTRODUCTION:

Primary immune deficiencies (PID) are a group of over 400 rare congenital diseases with increased susceptibility to infection, autoimmunity, inflammation, cancer and atopy (1); some of which are amenable to hematopoietic stem-cell transplantation (HSCT). Since 1968 (2), those PID patients with genetic variants that affect T cell function, or with a strong hematopoietic component (3) that confer a long-life risk for overwhelming infection, autoimmunity and cancer (4), are recognized as good candidates for allogeneic HSCT.

During the last couple of decades, the prognosis for patients with PID who undergo HSCT has greatly improved, thanks to the shared experience of multiple centers around the globe, leading the way in the generation of insights and implementing advances that have become the standard of care (5,6). Early age, identical matched donor, and active infection-free status are three main protective factors that impact survival (7). The rates of graft-versus-host disease (GVHD) in the first 12 months of transplantation with mobilized blood stem-cells from peripheral blood can be as high as 35-50% with conventional chemotherapy regimens. Ideally, T cell-depleted grafts from HLA-identical donors are preferred.

For many patients, HSCT may be lifesaving and curative. However, on the road to transplant there is a series of obstacles and hurdles for providers and patients to overcome, starting with the search for a compatible donor, getting to day zero without an active infection, achieving engraftment, sustaining donor chimerism, preventing complications like rejection, viral reactivation, GVHD, post-transplant lymphoproliferative disease (PTLD), or fatal infection before immune reconstitution. Successful transplant, uneventful recovery or even survival are never assured. Nevertheless, every hospital must start at some point and endure their own lengthy learning curve before reaching optimal results.

OBJECTIVE:

We aimed to review our experience of 11 years transplanting children with PID, with their features and outcomes.

METHODS:

We retrospectively reviewed the charts of patients who underwent HSCT at our hospital from 2008 to 2018, to report their demographic data, diagnoses, age at diagnosis, diagnostic delay, time to transplant, type of HSCT, donors, conditioning regime, engraftment, complications, chimerism, survival rate and outcomes.

We used descriptive statistics, including proportions and measures of central tendency. Tables were built on MS Excel. This retrospective study is exempt from institutional review board approval. All authors endorse the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects. We kept the identities of patients confidential, and we have no conflict of interests.

RESULTS

From 2008 to 2018 we transplanted and followed 19 patients with PID. Twelve of them were male (58%), and 14 survive (79%). **Table 1**summarizes some of their demographic and clinical features.

Their phenotypic diagnoses were: Wiskott-Aldrich Syndrome (WAS), 7 patients; Severe-combined immune deficiency (SCID), 6 patients; and, Chediak-Higashi syndrome (CHS), Severe congenital neutropenia (SCN), X-linked Chronic granulomatous disease (CGD), Cartilage-hair hypoplasia (CHH), STAT1 deficiency, and Omenn syndrome (RAG1 deficiency), one patient each. Genetic diagnosis was achieved for only 3 patients, usually after the transplant. Eight patients (42%) were undernourished.

Mean age at HSCT was 41.9 months (range 3 to 156 months). Mean age at diagnosis of PIDD was 10.68 months (range 1 through 40); mean diagnostic delay (age at diagnosis – age at onset) was 7.95 months. Time elapsed from diagnosis to transplant was, on average, 31.2 months. Only two patients (one with SCID and one with STAT1-LOF) had a history of inbreeding (consanguinity or endogamy), and two patients (one with CGD and one with T-B+NK+ SCID) had adverse reactions to the BCG vaccine (10%). Nine of the patients (47%) had a family history suggestive of PID, or a similarly affected sibling. Regarding treatment, most patients received monthly human intravenous gammaglobulin (IVIG) until HSCT, and beyond (see

below), as well as ambulatory prophylactic antibiotics. Other treatments before HSCT included transfer factor (leukocyte dialysate), prednisone, rituximab and valganciclovir.

By type, the first six grafts were obtained from umbilical cord (a total of 7, or 37%), and the last 8 were haploidentical (a total of 12, or 63%). The donors of the latter were the patients' parents (11 of 12), and one sibling. Two patients had undergone a previous, unsuccessful HSCT. The conditioning regime was myeloablative in all cases, consisting of Busulfan, anti-thymocyte globulin (ATG), and Cyclophosphamide. Anti-Graft-versus-host disease (GVHD) included cyclosporin, tacrolimus (TAC), mophetil mycophenolate (MMF), cyclophosphamide, and deflazacort, alone or in different combinations (see **Table 2**).

All patients received post-transplant cyclophosphamide, with TAC and MMF, within the first three days. Engraftment was typically achieved around day +14, as measured by increasing counts of neutrophils, platelets and erythrocytes, in that order. There were seven primary graft failures. Of these, two patients received a second rescue transplant, one of them successful. Four patients developed GVHD, for a prevalence of 21% (2 skin, 1 kidney, 1 lung) all of them grade I or II. Two patients had partial or mixed chimerism (60-88%) that became stable, and seven had a stable 100% chimerism. Immune reconstitution was complete in 11 of 19 patients (58%). Most patients under gammaglobulin replacement treatment were able to leave it 12 months after HSCT (9/14); one after 24 months, and 4 still need it.

As for complications and deaths, one patient developed post-transplantation lymphoproliferative disorder (PTLD) but recovered. Three patients died of septic shock, one had severe pulmonary edema, and one died of disseminated intravascular coagulation, for a total of 5 deaths, all within the first two months after transplant (days +22 to +54, mean 34.2 days).

DISCUSSION:

We describe a series of 19 patients from Mexico with 8 PID diagnoses who underwent allogenic HSCT at a single center in Monterrey, NL over a period of 11 years. 58% of them were male, and 79% survived. Their age at transplantation ranged from 3 months to 13 years old. The mean time from diagnosis was 31.2 months. Only 21% developed GVHD, and one patient suffered from PTLD.

To our knowledge, this is the first report of its kind in our country. Although the sample size is small, we want to share our experience to encourage other hospitals to perform HSCT in their patients with severe PID. Our figures in survival and GVHD prevalence compare well to what has been reported with centers in industrialized countries, which is no small feat when we consider that all our stem cells came from umbilical cord or haploidentical donors, in a country with limited therapeutic options and a very small donor registry.

Patiroglu *et al* in Turkey 2017 (8), reported the outcomes of 20 transplanted PID patients (of which 6 were also SCID), with a median age at transplant of 21 months, 11 related HLA-matched, 6 haploidentical; they found a 65% survival rate, and a prevalence of 30% for GVHD. In Seoul, Yi *et al* . described in 2018 their experience of 26 patients in 11 years (9), most of which had WAS, CGD, or SCID; they found a 73.1% survival rate, and 85% of patients with complete chimerism after 1 year. In India, Uppuluri et al (10) transplanted 16 children with PID, and used post-transplant cyclophosphamide on days 3-4; they found a 50% prevalence for GVHD.

The Paris group at Necker Hospital recently reported their experience with post-transplant cyclophosphamide to reduce the risk of graft failure and GVHD in children with PID or osteopetrosis without an HLA-identical donor (11). They found a 77.7% survival rate after two years, with a cumulative incidence of 45.8% and 24.2% for acute and chronic GVHD. In the rest of North America and Europe, nearly four decades of experience and research have allowed for excellent survival rates. From their large cohorts we have learned that the outcome is largely dependent on active infection-free status at the moment of transplant (5,6).

HSCT remains the only curative treatment for many children with PIDD. The guidelines for HSCT in children with PID are accepted and known internationally; they are considered standard practice pretty much everywhere in the world (3). The determinants of the differences in outcomes are therefore fourfold: 1) early diagnosis, 2) the availability of HLA-matched donors, 3) the availability of effective therapeutic agents,

and 4) each center's learning curve. Mexico and Latin America are lagging in all those four determinants, and yet we need to respond to our newly diagnosed PID patients with the best care and ingenuity that we can summon. The need for local and regional donor registries is especially felt, as the chances of finding an unrelated HLA-matched donor are lower for patients from under-represented ethnic groups, and also because having to import cells or donors from abroad prolongs waiting times and makes the final cost far more expensive.

In Mexico and Latin America, we need multicenter collaboration and regional donor registries. We have found that we can achieve encouraging results in the outcome of our patients despite resource scarcity and other limitations we share with developing countries and small centers elsewhere.

We would like to repeat this analysis when we reach 100 patients transplanted for PID. In the meantime, the best we can do is to keep learning from other centers' experiences, continue teaming up with other specialists, and collaborate with researchers in other hospitals and countries. The British Cycling Olympic team famously focused their efforts on making small improvements in every aspect of their craft (12). As we deal with scarcity, unpredictability and the many obstacles of transplanting children with PID in our country, we subscribe to this philosophy of "marginal gains" in every aspect that can be improved, in order to better the chances of survival for our next patient.

To conclude, after 11 years performing allogeneic HSCT in 19 children with PID, we can recommend the use of post-transplant cyclophosphamide to prevent GVHD. A courageous attitude, stoic patience, and a philosophy of "marginal gains" for improvement cannot hurt, and these may all be learned from our patients as they journey through their illnesses enduring frightening procedures.

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TABLES

TABLE 1 Demographic and clinical features of 19 patients with PID who underwent HSCT at our center from 2008 to 2018.

Abbreviations: Pat., patient; M, male; F, female; Dx, diagnosis; BCG, Bacile Calmette-Guérin vaccine; SCID, Severe-combined immune deficiency; WAS, Wiskott-Aldrich Syndrome; SCN, Severe congenital neutropenia; X-CGD, X-linked Chronic granulomatous disease; CHH, Cartilage-hair hypoplasia; LOF, loss of function. All ages are in months.

TABLE 2 Features and outcomes of 19 patients with PID who underwent HSCT at our center from 2008 to 2018.

Abbreviations: PID, primary immune deficiency; HSCT, hematopoietic stem-cell transplantation; M, male; F, female; SCID, Severe-combined immune deficiency; WAS, Wiskott-Aldrich Syndrome; SCN, Severe congenital neutropenia; X-CGD, X-linked Chronic granulomatous disease; CHH, Cartilage-hair hypoplasia; Myeloabl, myeloablative; Defla, deflazacort; cyclospor, cyclosporin; tacro, tacrolimus; MMF, mophetil mycophenolate; cyclophos, cyclophosphamide; AIHA, autoimmune hemolytic anemia; PTLD, post-transplant lymphoproliferative disease.

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`Tables HSCTMTY.pdf` available at https://authorea.com/users/365035/articles/485296-post-transplant-cyclophosphamide-prevents-graft-versus-host-disease-in-haploidentical-stem-cell-transplanted-children-with-inborn-errors-of-immunity-a-single-center-experience