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ORIGINAL ARTICLE

Haploidentical stem cell transplantation in a boy with chronic granulomatous disease

A. Regueiro-García[a,*], S. Fariña-Nogueira[a], J.Á. Porto-Arceo[b], J.M. Couselo-Sánchez[a]

[a] *Pediatric Hematology & Oncology Department, Hospital Clínico Universitario de Santiago, Spain*
[b] *Pediatric Allergy Unit, Hospital Clínico Universitario de Santiago, Spain*

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Abstract Chronic granulomatous disease is a primary immunodeficiency caused by mutations in any one of the five components of the NADPH oxidase in phagocytic leucocytes. This causes impaired microbial killing, which leads to severe life-threatening bacterial and fungal infections. Currently, allogenic hematopoietic stem cell transplantation (HSCT) is the only curative treatment for chronic granulomatous disease, although gene therapy may provide a new therapeutic option for the treatment of patients with CGD. Haploidentical HSCT provides a potentially curative treatment option for patients who lack a suitably HLA-matched donor, but only a few cases have been reported in the literature. Herein, we report a boy with X-linked chronic granulomatous disease treated successfully by haploidentical HSCT with post-transplant cyclophosphamide using a treosulfan-based conditioning regimen.

Introduction

Chronic granulomatous disease (CGD) is an uncommon inherited immunodeficiency, occurring in about one in 250,000 individuals. It is a genetically heterogeneous condition characterized by recurrent, life-threatening bacterial and fungal infections and granuloma formation. CGD is caused by defects in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which constitutes the phagocyte oxidase (phox). CGD results from constitutional inactivating mutations in the *CYBB*, *CYBA*, *NCF1*, *NCF2* or *NCF4* genes that encode subunits of phagocytic NADPH oxidase. X-linked CGD (with mutation of *CYBB* gene encoding the gp91^{phox} subunit) is the most frequent form of the disease accounting for 65% of cases. These genetic defects result in the inability of phagocytes (neutrophils, monocytes and macrophages) to destroy certain microbes.

The cornerstones of CGD management are antimicrobial and immunomodulatory prophylaxis, early diagnosis of infections, and aggressive management of infectious complications. Currently, allogenic hematopoietic stem cell

* Corresponding author.
E-mail address: alexandra.regueiro.garcia@sergas.es (A. Regueiro-García).

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transplantation (HSCT) is the only established curative therapy for CGD, although gene therapy may provide a new therapeutic option for the treatment of patients with CGD.

Reports on haploidentical HSCT for CGD are scarce, however, haploidentical HSCT could be an option in some CGD patients for whom HLA-matched related or unrelated donors are not available. We report the case of a pediatric patient who had CGD complicated by severe pulmonary disease and chronic inflammatory bowel disease and was successfully treated by haploidentical HSCT with high-dose post-transplant cyclophophamide.

Case report

We report an 11-year-old boy with X-linked CGD who underwent haploidentical HSCT with high-dose post-transplant cyclophophamide.

He was the younger of two children of non-consanguineous parents. He lived with his uncle and aunt on his father's side who had the legal custody of the patient. There was no family history of immunodeficiency. He was vaccinated with Bacillus Calmette-Guérin (BCG) in infancy, which was complicated by a BCGitis at the injection site on his arm. At 12 months of life, he was admitted with a bronchopneumonia that responded well to antibiotic treatment. At three years old he was diagnosed of pulmonary tuberculosis and he was on anti-tuberculosis treatment.

At seven years old he was admitted to our hospital because of a two-month history of asthenia, failure to thrive, loss of weight and respiratory symptoms, with the initial suspicion of disseminated tuberculosis, which was ruled out after relevant studies, including a lung biopsy that showed necrotizing granulomatous inflammation. The patient had no detectable NADPH-oxidase activity in the dihydrorhodamine (DHR) and the nitroblue terazolium (NBT) test. Subsequently, mutation analysis detected a mutation in exon 2 of the *CYBB* gene encoding the $gp91^{phox}$ protein in the boy (X-linked disease).

In spite of continued antimicrobial prophylaxis (cotrimoxazole, itraconazole) and immunomodulatory treatment (interferon-γ), the patient developed severe complications including restrictive lung disease, consisting of dyspnea and hypoxemia, diffuse interstitial infiltrates in chest radiographs and a restrictive pattern in pulmonary function tests.

He progressively developed chronic inflammatory bowel disease with intermittent abdominal pain, diarrheic stools, decrease appetite and moderate malnutrition. At nine years old he underwent an esophagogastroduodenoscopy and colonoscopy, which showed pancolitis with gross pathologic features, resembling Crohn's disease. Colonic biopsies showed extensive granulomatous inflammation. Laboratory tests were significant for anemia, hypoalbuminemia, iron deficiency, elevated inflammatory markers and markedly elevated stool calprotectin. Treatment was initiated with prednisone and mesalazine, and a few months later, also with azathioprine as maintenance therapy because he had symptomatic relapse when tapered to low-dose prednisone.

Throughout the following months, he presented a torpid evolution of chronic inflammatory bowel disease and no improvement of pulmonary disease.

At diagnosis, human leukocyte antigen (HLA) typing of the patient, his biological parents, and his sister was performed, and a rare HLA-haplotype was detected in the patient. He did not have a matched sibling donor and a search for an unrelated donor was initiated, although no unrelated matched donor was found either within an appropriate time frame since the diagnosis. Thus, given the torpid clinical evolution, we proposed to perform a haploidentical HSCT. The father was preferred as the haploidentical donor because his biological mother had hepatitis C viral infection.

The patient underwent HSCT with peripheral blood stem cells (PBSC). The conditioning regimen consisted of treosulfan (14 g/m^2 on day -7, -6 and -5) and fludarabine (30 mg/m^2 over five days). In addition, rabbit anti-thymocyte globulin was given at a total dose of 7 mg/kg. He received high doses of cyclophosphamide post-HSCT (50 mg/kg days 3 and 4). Graft versus host disease (GvHD) prophylaxis consisted of tacrolimus and mycophenolate mofetil. Supportive care was given according to the protocol of our center.

The patient received $10.018 \times 10^8\ kg^{-1}$ of total nucleated cells (CD34+ cells, $4.007 \times 10^6\ kg^{-1}$; CD3+ cells, $2.053 \times 10^8\ kg^{-1}$). Neutrophil and platelet engraftments were achieved at 17 and 14 days after HSCT, respectively. Febrile neutropenia developed seven days after HSCT and no cytomegalovirus or Epstein–Barr virus infections have been detected at routine check-ups. No granulocyte infusions were performed. His superoxide production normalized two months after transplantation. Chimerism analysis revealed that 0.06% of myeloid cells were receipt cells at 30 days, and chimerism status has been sustained without important fluctuation. The most recent chimerism test was performed nine months after HSCT.

Inflammatory bowel disease was resolved completely after transplantation, although the patient has not yet crossed the percentiles for height and weight. Otherwise, improvement of respiratory symptoms was observed throughout the follow-up period after transplantation. It was possible to discontinue antibiotic and antifungal prophylaxis, as well as all medication for inflammatory bowel disease.

This case has been followed for 15 months. The patient does not have clinical manifestations of chronic GvHD.

Discussion

CGD is a rare, primary immunodeficiency disorder of phagocytes. It is characterized by repeated bacterial and fungal infections with excessive inflammation and granuloma formation.[1] HSTC is a potentially curative therapy for CGD leading resolution of infections and inflammatory complications.[2] Moreover, published data demonstrate that children with CGD who had undergone HSCT have better quality of life compared with those managed conservatively.[3] It has been demonstrated that there are fewer infections and admissions to the hospital and improved growth in patients after transplantation compared with those who had not undergone transplantation.[4] Acceptable rates of engraftment without transplant related mortality or GvHD are the goals of transplantation. Good results achieved with matched related donors have justified the extension to alternative donors, especially matched

unrelated donors.[5,6] Unfortunately, a substantial number of patients remain without an available HLA-matched related or unrelated donor. As other immunodeficiencies or malignant hematological diseases,[7] the use of alternative donors as haploidentical donors has increased the possibilities of cure in CGD, although haploidentical transplantation in CGD has been poorly reported.

Some successful haploidentical HSCT in CGD using ex vivo T-cell depletion with anti-CD3 antibodies have been reported.[8,9] Furthermore, some authors have reported haploidentical HSCT with high-dose of cyclophophamide post-HSCT. Parta et al. reported a single case report of an haploidentical HSCT following conditioning regimen with targeted busulfan, fludarabine, cyclophosphamide and total body irradiation in a patient with CGD with refractory infection as indication for transplantation.[10] Our patient had a progressive pulmonary insufficiency as well as a refractory inflammatory bowel disease and secondary malnutrition that could not be controlled with medical treatment and nutritional support. Reduced intensity conditioning using a treosulfan-based conditioning regimen was preferred because of the high-risk pre-HSCT clinical features. Currently, treosulfan has been increasingly used as one of the main conditioning drugs for allogenic HSCT for children with malignant and non-malignant disorders, including CGD, with reduced incidence of transplant-related mortality.[11]

Besides that, our patient underwent HSCT with PBSC. The concept for haploidentical HSCT in our institution is utilization of PBSC as stem cell source. One of the reasons is the low failure rate for single apheresis with single-agent G-CSF. Moreover, donors prefer HSC collection from peripheral blood as it spares them general anesthesia and cells can be harvested in the outpatient setting. Besides benefits for the donors, faster hematopoietic engraftment and immune reconstitution have been observed in patients receiving PBSC compared to those given bone marrow grafts.[12] In our patient PBSC-HSCT was preferred in order to achieve a rapid myeloid engraftment.

Conversely, randomized studies of bone marrow (BM) vs. peripheral blood (PB) as the allograft source in transplantation from HLA-matched related donors or unrelated donors showed comparable outcomes with the exception of an absolute increase of 6–15% in the incidence of chronic GvHD after transplantation of PB.[13] However, in the setting of non-ablative conditioning, a recent retrospective study from the Center for International Blood and Marrow Transplant Research showed that rates of acute GvHD, chronic GvHD and overall survival were similar after transplantation of BM compared with PB.[14] Further, O'Donell et al. compared data from a multi-center phase II trial of haplo-BM conducted in the US with published and unpublished data from phase II trials of haplo-PB transplants in the US, Europe and Australia by means of a matched-pair analysis and they did not find significant differences in the rate or global severity of chronic GvHD after haplo-BM or haplo-PB transplantation.

Combining the use of PBSC with in vivo T-cell depletion of the graft was the approach in our patient with the aim of benefiting from the faster engraftment associated with the use of PBSC without exposing him to high risks of severe GvHD. Rabbit ATG was administered from day -8 to -6 (total dose 7 mg/kg). It is known that after in vivo infusion, all forms of ATG induce depletion of both T and antigen-presenting cells by complement-dependent lysis or antibody-dependent cellular cytotoxicity, apoptosis of activated T cells, and maintenance of dendritic cells in a tolerogeneic state. Furthermore, rabbit ATG induces the generation of regulatory T cells (Treg), both in vitro and in vivo. This is clinically relevant, given accumulating evidence showing an important role for Treg in GvHD prevention after allogeneic HCT.[15] Tacrolimus and mycophenolate mofetil were administered as post-grafting immunosuppression.

Finally, it is worth mentioning that gene therapy is providing exciting new treatment options for patients with primary immune deficiency diseases, including GCD, and advances are sure to continue. Currently, three US sites (NIH, Boston and Los Angeles) are recruiting patients with CGD for a trial with a third generation lentivirus (ClinicalTrials.gov Identifier: NCT02234934). Similar studies using lentivirus are being conducted in Frankfurt, London and Zurich (ClinicalTrials.gov Identifier: NCT01855685), while the site in Paris is also accepting younger children (ClinicalTrials.gov Identifier: NCT02757911).[16]

This report shows that haploidentical HSCT using a treosulfan-based conditioning regimen could be a safe treatment option in those pediatric patients with CGD who HLA-matched related or unrelated donors are not available, especially in those with high-risk pre-HSCT clinical features, leading to an improvement in the quality of life.

Conflict of interest

The authors have no conflicts of interest to disclose.

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