Published in final edited form as:

Pediatr Diabetes. 2017 December ; 18(8): 832–834. doi:10.1111/pedi.12430.

Curative Potential of Allogeneic Hematopoietic Stem Cell Transplant in Type 1 Diabetes

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Abstract

The mainstay of treatment for type 1 diabetes (T1D) is exogenous insulin. Here, we report a case in which exogenous insulin requirements were eliminated after allogeneic hematopoietic stem cell transplant for aplastic anemia in a pediatric patient recently diagnosed with T1D, and explore the validity of this approach compared to current treatments.

Keywords

Autoimmune; aplastic anemia; type 1 diabetes; transplant

Introduction

Type 1 diabetes (T1D) is a chronic autoimmune disease in which pancreatic β -cell destruction results in loss of endogenous insulin production. Already one of the most prevalent chronic childhood diseases, the incidence of T1D in children and young adults is projected to continue to increase over the next several decades (1). Though advances in technology have allowed for improved glucose monitoring and insulin delivery, no curative therapy is currently available for this growing patient population. Moreover, patients continue to experience long-term complications such as blindness and kidney failure, even with the most intensive insulin regimens (2). Consequently, the direct and indirect medical costs of this disease are substantial. When considering the 1.1 million patients with T1D identified in 2005, the estimated lifetime direct medical cost and cost due to lost income are \$133.7 billion and \$289 billion, respectively (3).

Case Report

A previously healthy 17-year-old male presented to his primary care physician with an eight-day history of petechiae, epistaxis and frank hematuria. A CBC revealed a WBC of $2.6 \times 10^3/\mu\text{l}$ (59% neutrophils, 19% lymphocytes, 20% monocytes, 1% eosinophils), hemoglobin of 10.3 g/dL, platelet count of $1000/\mu\text{l}$, and $0.3 \times 10^6/\mu\text{l}$ reticulocytes (0.77%). Serum

chemistries were remarkable for hyperglycemia (blood glucose of 599 mg/dL). Bone marrow biopsy was markedly hypocellular without neoplastic infiltration, fibrosis, or evidence of dysplasia. Bone marrow cytogenetic studies were normal. Testing for Fanconi anemia and paroxysmal nocturnal hemoglobinuria were negative. Hemoglobin A1c (HbA1c) was 7.8%. Three of the four pancreatic antibodies associated with T1D were positive (Table 1). The patient was diagnosed with idiopathic aplastic anemia and T1D. Primary treatment of aplastic anemia was allogeneic HSCT from an HLA-matched sibling donor, after conditioning with cyclophosphamide (200 mg/kg) and anti-thymocyte globulin (90 mg/kg). Red blood cell, platelet, and neutrophil engraftment occurred on days 11, 16, and 31 post-transplant, respectively. Peripheral blood chimerism studies performed 97 days post-transplant showed greater than 95% donor CD3⁺ and CD33⁺ cells. Primary treatment of T1D was exogenous insulin. All four pancreatic antibodies were monitored for the first year, followed by monitoring of islet cell and GAD-65 antibodies prospectively to the present. Interestingly, two months post-transplant, exogenous insulin needs were significantly decreased and insulin therapy was safely discontinued. One year post-transplant, all four pancreatic antibody levels decreased and three of the four completely normalized, reflecting significant reduction in autoimmunity (Table 1). At 24 months post-transplant, the patient remained euglycemic without insulin therapy, HbA1c was 5.3% (Figure 1), and antibodies remained stable: GAD-65 of 0.04 and islet cell antibody of <1:4. This case illustrates the possibility of using allogeneic transplant to cure T1D.

Discussion

To our knowledge, the question of whether HSCT from a matched sibling donor could be considered as a curative treatment option for children with early onset T1D has not been formally studied. Virtually all research on the role of HSCT for T1D has focused on autologous transplantation.

The goal of autologous HSCT is to reset the immune system by treating patients with lymphoablative chemotherapy. The patient's own stem cells are then infused to facilitate hematopoietic recovery and generate a naïve, and more tolerant, immune system. However, results from studies investigating this approach for T1D have been varied. In one study from Brazil, autologous HSCT for new onset T1D resulted in a cessation of insulin therapy for a mean of 16.2 months, with normalization of HbA1c and variable increases in c-peptide levels during time of follow-up (4). In contrast, a Chinese pediatric study comparing autologous HSCT recipients with matched standard insulin treatment controls found similarly elevated HbA1c levels, and no significant difference in c-peptide or insulin dose requirements between groups at 1, 3, and 5-year follow-up (5).

Unlike autologous HSCT, allogeneic transplant does not rely on the patient's own immune system to reconstruct itself in a favorable manner, but rather it depends on the successful introduction a new immune system from HLA-matched donor stem cells. Factors limiting the exploration of allogeneic HSCT in this setting include the early risk of mortality from a transplant-related complication, and the late risks of chronic graft *versus* host disease (GVHD) and infertility. However, allogeneic HSCT is commonly used to treat a wide variety of non-malignant conditions including Wiskott-Aldrich syndrome, Diamond-Blackfan

anemia, beta thalassemia, and sickle cell disease (6–8). Despite no *immediate* risk of death for the majority of patients suffering from these other non-malignant conditions, the benefits of transplant are felt to outweigh the long-term physiologic consequences of these chronic diseases. Additionally, reduced-intensity conditioning regimens, introduced over 20 years ago, have been gaining favor among clinicians. Recent studies have shown that oncology patients undergoing allogeneic HSCT who receive reduced intensity conditioning had similar rates of transplant success, but with lower risk of transplant-related mortality and GVHD, compared to patients treated with fully myeloablative regimens (9). Similar observations have been made in pediatric patients undergoing allogeneic HSCT for non-malignant conditions (10).

When using an HLA matched allogeneic transplant donor to treat an autoimmune condition, there is an additional concern that the intolerant immune system will re-develop post-transplant. Specific combinations at the DQA1, DQB1, and DRB1 HLA loci (e.g. DR3, DR4) determine the extent of haplotypic risk of T1D, though HLA is not the only predictor of risk (11). Thus, identically matching HLA haplotypes to optimize transplant outcomes, may also confer risk for the return of autoimmunity. However, this concern may be lessened by looking for other markers of T1D risk. The presence of islet autoantibodies (GAD-65, IA-2, ZnT8, and islet cell antibodies) in relatives of patients with diabetes has been shown to be a risk factor for the development of T1D (12). One study revealed that in a group of high-risk HLA-typed siblings of T1D patients, 70% of those with positive islet cell antibodies went on to develop T1D by 8 years of follow-up, compared to only 5% of siblings with negative islet cell antibodies (13). Thus, the identification of pancreatic autoantibodies (e.g. islet cell antibodies) could be a valuable screening tool in unaffected HLA identical siblings to reduce the risk of post-transplant disease recurrence.

Conclusion

Given the rising costs and burden of T1D, continued investigation for innovative treatments is a timely and worthwhile pursuit. This case illustrates the curative potential for allogeneic HSCT and posits that further discussion and perhaps evaluation of this approach for early intervention in certain patients with T1D should be considered. There have been no clinical studies to date evaluating the efficacy of allogeneic HSCT in adult or pediatric T1D patients. Initial studies exploring this approach should focus on risk stratification and techniques to identify candidate patients and donors with the highest likelihood of success and lowest risk of complications, and early intervention to protect remaining beta-cell function. Reduced-intensity conditioning regimens can minimize transplant-related risks while maintaining a reasonable probability of donor engraftment. Given the current success of allogeneic HSCT in curing other non-malignant conditions in pediatric patients, a prospective clinical trial comparing standard insulin therapy and allogeneic HSCT from an HLA identical sibling donor lacking islet cell antibodies may be warranted to evaluate the merits of this approach.

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Figure 1. HbA1c values from presentation to most recent follow-up 24 months post sibling HLA-matched allogeneic HSCT

Month -1 is month of presentation; 0 is the month of transplant identified by the arrow.

HbA1c ranges, Normal range: 4–6%, Goal for T1D: <7.5%. Dotted line indicates when exogenous insulin was discontinued.

Table 1

Pancreatic antibodies associated with T1D, pre- and post- allogeneic HSCT

Antibody	Reference Range	Pre-transplant	1 Year Post-transplant
GAD-65	<0.02 nmol/L	0.3 nmol/L	0.05 nmol/L
IA-2	<0.8 U/mL	4.9 U/mL	< 0.8 U/mL
ZnT8	<10 U/mL	107.9 U/mL	< 10 U/mL
ICA	<1:4	<1:4	<1:4

GAD-65, Glutamic acid decarboxylase 65; *IA-2*, Insulinoma-associated antigen, *ZnT8*, zinc transporter 8; *ICA*, Islet cell antibody.