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Bone marrow transplantation in Schimke immuno-osseous dysplasia

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Abstract

Schimke immuno-osseous dysplasia (SIOD, OMIM 242900) is a rare autosomal recessive multisystem childhood disorder characterized by short stature, renal failure, T-cell immunodeficiency, and hypersensitivity to genotoxic agents. SIOD is associated with biallelic mutations in *SMARCA1* (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin, subfamily a-like 1), which encodes a DNA stress response enzyme with annealing helicase activity. Two features of SIOD causing much morbidity and mortality are bone marrow failure and T-cell deficiency with the consequent opportunistic infections. To address the safety and efficacy of bone marrow transplantation (BMT) in SIOD we reviewed the outcomes of the only five SIOD patients known to us in whom bone marrow or hematopoietic stem cell transplantation has been attempted. We find that only one patient survived the transplantation procedure and that the existing indicators of a good prognosis for bone marrow transplantation were not predictive in this small cohort. Given these observations, we also discuss some considerations for the poor outcomes.

Keywords

Schimke immuno-osseous dysplasia; bone marrow transplantation; genotoxic agents

INTRODUCTION

Individuals with Schimke immuno-osseous dysplasia (SIOD, OMIM 242900), a disorder caused by biallelic mutations of *SMARCA1*, frequently have T-cell immunodeficiency and consequently opportunistic infections, autoimmune diseases and non-Hodgkin lymphoma [Baradaran-Heravi et al., 2012b; Boerkoel et al., 2000; Zieg et al., 2011]. The question arises

therefore as to the efficacy of bone marrow transplantation (BMT). Although one boy has been successfully transplanted, the conundrum is that cells and organisms deficient for *SMARCAL1* orthologs are hypersensitive to genotoxic and cytotoxic agents [Bansbach et al., 2009; Baradaran-Heravi et al., 2012b; Ciccio et al., 2009; Petty et al., 2000]. To address the safety and efficacy of BMT for individuals with SIOD, we review the treatment and outcomes of the five individuals with SIOD in whom BMT has been attempted.

Individuals affected with SIOD usually die within the first two decades of life from infections (23%), stroke (17%), renal failure (15%), pulmonary hypertension and congestive heart failure (15%), complications of organ transplantation (9%), complications of lymphoproliferative disease (9%), gastrointestinal bleeding (6%), bone marrow failure (3%), and unspecified acute restrictive lung disease (3%) [Baradaran-Heravi et al., 1993 (updated 2011)]. *SMARCAL1* encodes an annealing helicase [Yusufzai and Kadonaga, 2008] that contributes to DNA replication, recombination, transcription and stress responses [Bansbach et al., 2009; Baradaran-Heravi et al., 2012a; Betous et al., 2012; Ciccio et al., 2009].

Since immunodeficiency and the consequent opportunistic infections are the leading cause of death among SIOD patients, BMT is a potential life-saving treatment. To assess this, we report the outcome of BMT for five SIOD patients (Table I).

PATIENTS AND METHODS

Human Subjects

Patients gave informed consent approved by the Institutional Review Board of Baylor College of Medicine (Houston, TX, USA), the Hospital for Sick Children (Toronto, ON, Canada), or the University of British Columbia (Vancouver, BC, Canada). Referring physicians provided clinical data.

DNA Sequencing

We identified mutations in the coding exons and intronic splice junctions of the *SMARCAL1* gene as previously described [Boerkoel et al., 2002]. Briefly, we amplified the cDNA or coding exons and intronic splice junctions from genomic DNA by PCR amplification, purified the PCR products using the Qiagen PCR purification kit (Qiagen), and sequenced them with dye-terminator chemistry (Applied Biosystems).

RESULTS

Clinical Reports

Patient 1 (SD38)—The proband was born at 34 gestational weeks with intra-uterine growth restriction. His growth restriction continued postnatally and by age 2 years, he developed recurrent respiratory infections, otitis media, enteritis, and herpes zoster. By 6.5 years, he had spondyloepiphyseal dysplasia, pancytopenia, transient ischemic attacks and nephrotic syndrome. He was diagnosed with SIOD and found to have biallelic *SMARCAL1* mutations p.[M288_D366del]+[M288_D366del]. By 9.5 years his disease progressed to end stage renal failure and bone marrow insufficiency unresponsive to transfusions and erythropoietin. Consequently, at age 10.5 years, he received sequential kidney and bone marrow stem cell transplants from his father. The renal graft was successful and six weeks later, he received a bone marrow stem cell infusion. Pulmonary function testing prior to BMT revealed a mild reduction of vital capacity with no obstruction; this was ascribed to an antecedent pneumonia. His BMT conditioning therapy regimen included busulfan (16 mg/kg/day from day -10 to -7), thiothepa (10 mg/kg on day -6), cyclophosphamide (50mg/kg/day from day -5 to -2), and rabbit anti-thymocyte globulin (ATG, 20 mg/kg on day -3) and

(30 mg/kg/day from day -2 to -1). Sixteen days following stem cell infusion, he had 100% donor chimerism in his peripheral blood. Six days later, he developed grade I-II skin graft versus host disease (GVHD) that resolved with cyclosporine A and dexamethasone. Sixty-three days after transplantation he contracted an adenovirus infection and gram-negative sepsis. He recovered from his sepsis with antibiotic treatment; however, despite cidofovir therapy his adenoviral infection progressed. Ninety-two days after BMT, he was diagnosed with pulmonary aspergillosis, and despite treatment with ambisome, his disease progressed. He died 100 days after transplantation due to an acute cardiopulmonary arrest.

Patient 2 (SD47)—The transplantation history of the propositus, the only individual with SIOD who survived BMT, has been previously described [Petty et al., 200]. In brief, at the age six years he received a BMT from his father. His conditioning regimen included busulfan (4 mg/kg/day from day -9 to -6) and cyclophosphamide (50 mg/kg/day from day -5 to -2). Despite prophylaxis against GVHD with tacrolimus and methotrexate he developed acute GVHD (grade III skin, grade IV GI) 26 days following BMT. The GI-GVHD did not respond to methylprednisolone, mycophenolate mofetil, anti-thymocyte globulin, and octreotide therapies but did resolve after administration of anti-CD2 monoclonal antibody. Seven months after BMT he required hemodialysis for declining renal function and 13 months after starting hemodialysis he received a kidney transplant from his father. Beginning at 13 years, 7 years after BMT, he developed transient complicated migraine-like attacks or encephalopathic events. These attacks, which are preceded by an aura and cause garbled speech or aphasia, are precipitated by stress or fatigue and have a frequency of 2-3 times per year; magnetic resonance imaging and angiography have not identified a vascular cause and full recovery follows within three days. Currently, he is a 21 year-old university student with good bone marrow and renal function.

Patient 3 (SD79)—The proposita was born at 36 weeks gestation with a weight and length below the 3rd centile. She had postnatal growth restriction and, by 4 years of age, developed spondyloepiphyseal dysplasia, T-cell deficiency and nephrotic syndrome with focal segmental glomerulosclerosis. The diagnosis of SIOD was confirmed by detection of a p.R820H *SMARCAL1* mutation in her paternal allele and absence of expression of her maternal allele [Clewing et al., 2007]. On account of her worsening cellular immunodeficiency, she received stem cell transplantation at age 9.5 years from an unrelated donor matched for blood group and 7 of 8 HLA loci. The conditioning therapy consisted of fludarabine (30 mg/m²/day from day -7 to -3), melphalan (70 mg/m²/day from day -4 to -3), and rabbit ATG (2.5 mg/kg/day from day -2 to +2). Prophylaxis against GVHD was tacrolimus and mycophenolate mofetil. During stem cell infusion, she developed hypertension, seizures and posterior reversible encephalopathy syndrome. Her bone marrow aspirate showed chimerism for the donor marrow 14 days following infusion, although she still needed frequent red blood cell and platelet transfusions. Forty-four days after infusion, she developed grade I skin GVHD and an increased Epstein-Barr virus (EBV) titer. Although her GVHD was controlled with tacrolimus and mycophenolate mofetil, she developed severe emesis, emaciation, abdominal pain, increased C-reactive protein level and elevated serum amylase suggestive of pancreatitis. She subsequently developed seizures, bradycardia, pulmonary edema and cardiac effusion with tamponade, and despite hemodialysis, she died 105 days following transplantation.

Patient 4 (SD86)—The proposita was the third child of healthy nonconsanguineous French parents. Her birth weight was below the 3rd centile. By age one year, she manifested decreased linear growth, T-cell deficiency and mild delay of motor, language, and social development. At 2 years, she developed nephrotic syndrome with focal segmental glomerulosclerosis. She was diagnosed with SIOD and had biallelic *SMARCAL1* mutations

(p.[E377Q]+[I755fsX2]). At age 5.5 years, her T-cell deficiency was treated with an HLA identical (10/10) allogeneic BMT. Her conditioning regimen was busulfan (total dose 16 mg/kg over 4 days), cyclophosphamide (200 mg/kg total dose) and rabbit anti-T lymphocyte globulin (10 mg/kg). Cyclosporine was added as GVHD prophylaxis. At the end of the conditioning regimen, she had severe hypoproteinemia (38 g/l) and hypoalbuminemia (14 g/l). A day after bone marrow infusion, she developed pneumococcal septicemia that was controlled with antibiotic treatment. Despite preventive anticoagulation, she died 9 days after infusion from a pulmonary embolism.

Patient 5 (SD131)—The propositus was delivered at 30 weeks gestation due to intra-uterine growth restriction. He had poor postnatal growth and mild to moderate delay in motor, language and social development. By 3 years, he developed pancytopenia, recurrent infections, nephrotic syndrome, and sensorimotor polyneuropathy. He started hemodialysis at 3.6 years and shortly thereafter developed transient ischemic attacks and seizures; cerebral magnetic resonance imaging showed diffuse cortical atrophy. His diagnosis of SIOD was confirmed by detection of biallelic *SMARCAL1* mutations (p.[Y342X]+[I755S]). At age 4 years, he received a BMT from his mother. He received radiation therapy (200 cGy on day -7), fludarabine (100 mg/m² total dose from day -7 to -4), cyclophosphamide (235 mg/m²/day from day -6 to -3) and rabbit ATG (5 mg/kg/day from day -5 to -3) as conditioning therapy and rituximab (375 mg/m² on day -1) for GVHD prophylaxis. By day 11, he had complete chimerism denoting engraftment. Thirty days after stem cell infusion, he developed cytomegalovirus (CMV) infection and was treated with gancyclovir. The following day he developed enterococcus faecium sepsis and diarrhea without evidence of GVHD as well as leucopenia, thrombocytopenia and coagulopathy. He was treated with vancomycin, teicoplanin, bicarbonate infusion, intensive dialysis, platelet and plasma infusions and G-CSF. Forty-nine days after BMT he manifested bilateral nystagmus, hypotension, severe oxygen desaturation and epistaxis and by computed tomography, his brain had multiple hemorrhagic-ischemic areas. He died 55 days following transplantation.

DISCUSSION

BMT or hematopoietic stem cell transplantation effectively treats many primary immunodeficiencies. Approximately 70% of patients with common primary immunodeficiency syndromes survive BMT [Griffith et al., 2008]. In contrast, four of five SIOD patients died from complications of BMT or stem cell transplantation.

Factors adversely affecting overall survival after BMT include mismatched HLA, increased donor age, older patient age, advanced disease, myeloablative conditioning, GVHD, infections, and bleeding [Finke et al., 2012; Labrador et al., 2012; Magauran and Salgado, 2011; Satwani et al., 2008; Szabolcs et al., 2010]. Regarding their health at the time of BMT, patients SD38 and SD131 had a hematopoietic cell transplant-comorbidity index (HCT-CI) of > 3 and developed pancytopenia and end stage renal failure prior to BMT [Sorrer, 2010]. On the other hand, patients SD47, SD79 and SD86 had HCT-CI scores of 1 and their nephrotic syndrome did not progress to end stage renal failure prior to BMT. Despite this indicator of a good prognosis for individuals SD47, SD79 and SD86, only patient SD47 survived. Based on the medical records, we are unable to identify the factors contributing to patient SD47's survival compared to the other two.

Besides a debilitated state, another factor possibly contributing to the poor outcome is the hypersensitivity of *SMARCAL1* deficient tissues to genotoxic agents [Bansbach et al., 2009; Ciccia et al., 2009]. Conventional myeloablative conditioning includes genotoxic agents such as cyclophosphamide, busulfan, fludarabine, melphalan, alemtuzumab, treosulfan and total body irradiation. These cause systemic toxicity and tissue injury that is worse on the

background of defective DNA repair [de la Fuente and Dokal, 2007; Wagner et al., 2007]. Also, SIOD patients are prone to restrictive lung disease due to their skeletal dysplasia [Morimoto et al., 2012]; therefore, since busulfan and cyclophosphamide are associated with interstitial pneumonitis and pulmonary fibrosis [Cooper et al., 1986], the pulmonary side effects of these drugs should be considered for SIOD patients.

An alternative to myeloablative conditioning is reduced-intensity conditioning (RIC), which relies on immunosuppression rather than profound myeloablation. RIC decreases morbidity and mortality among patients with primary immune deficiency but does not change the incidence of acute GVHD. Also, since RIC selectively depletes T lymphocytes, this approach increases the chance of viral infections, particularly EBV, after transplantation [Cohen et al., 2005; Satwani et al., 2008]. In this study individual SD79 received RIC; however, despite this and a HCT-CI of 1, she did not survive. We conclude therefore that the efficacy of RIC and the consequences of the genotoxicity of conventional myeloablative conditioning remain unclear for SIOD patients.

In summary, the one of five SIOD patients who survived BMT had conventional myeloablative conditioning but a difficult and prolonged recovery [Petty et al., 2000]. No specific conclusions can be drawn from this cohort regarding predictors of outcome. Nonetheless, consistent with observations in other studies, considerations include performing BMT before SIOD patients become debilitated and using HLA identical grafts. Additionally, the hypersensitivity of *SMARCAL1* deficient tissues to genotoxic agents might suggest benefit from a modified reduced-intensity conditioning regimen similar to that recommended for dyskeratosis congenita [Dietz et al., 2011].

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Table 1

Summary of the clinical course of the bone marrow transplantation in SIOD patients.

Pedigree number	SMARCA1 mutation	Disease severity score [Clewling et al., 2007]	Age at BM T	Age at onset of renal dysfunction/dialysis	Current age	HLA/Graft modification	Prophylactic antibiotics	Conditioning therapy	GVHD prophylaxis/control	Outcome (days after BMT)
SD38	p.[M288_D366del][M288_D366del]	5	10.5y	6.8y/9.7y	dec.	Haplo type matched/Ex vivo T-cell depletion	Valaciclovir, Aciclovir, Fluconazole, Penicillin, Ciprofloxacin	Busulfan, Thiotepa, Cyclophosphamide, and Rabbit ATG	Cyclosporine A, Dexamethasone	- Day 22: acute skin GVHD - Day 63: adenovirus infection further complicated by rotavirus infection, gram negative sepsis - Day 92: Pulmonary aspergillosis - Day 100: passed away due to cardiopulmonary arrest.
SD47 [Pety et al., 2000]	p.[R820H][+][?] ¹	4	6y	4y/7.5y	21y	Haplo type matched/NR	NR	Busulfan, Cyclophosphamide	Tacrolimus, Methotrexate, Methylprednisolone, Mycophenolate mofetil, ATG and Anti-CD2 monoclonal antibody	- Day 26: acute skin and GI-GVHD - Day 210: hemodialysis - Day 600: renal transplantation - Patient is now 21 years old with good bone marrow and renal functions.
SD79	p.[R820H][+][?] ²	3	9.5y	4y/NA	dec.	Matched in 7/8 HLA loci/NR	Bactrim	Fludarabine, Melphalan, Rabbit ATG	Tacrolimus, Mycophenolate mofetil	- Day 0: hypertension, seizures, posterior reversible encephalopathy syndrome - Day 44: acute GVHD and increased EBV titer - Day 84: abdominal pain, increased CRP and serum amylase - Day 105: passed away due to pulmonary edema and tamponade

Pedigree number	SMARCAL1 mutation	Disability score [Clewning et al., 2007]	Age at BMT	Age at onset of renal dysfunction/dialysis	Current age	HLA/Gratification	Prophylactic antibiotics	Conditioning therapy	GVHD prophylaxis/control	Outcome (days after BMT)
SD86	p.[E377Q] + [I755fsX2]	3	5.5 y	2y/NA	dec.	Matched in 10/10 HLA loci/NR	Corrimoxazole, Amphotericin B, Acyclovir	Busulfan Cyclophosphamide	Anti-thymocyte globulin, Cyclosporine A	- Day 1: pneumococcal septicemia - Day 9: passed away due to pulmonary embolism. - Day 30: reactivation of CMV infection - Day 31: systemic sepsis with enterococcus faecium and severe lactic acidosis - Day 49: bilateral nystagmus, hypotension, severe oxygen desaturation and epistaxis - Day 55: Passed away due to complications of cerebral hemorrhagic-ischemic regions
SD131	p.[Y342X] + [I755S]	5	4.5 y	3y/3.8y	dec.	Haplo type matched/Ex vivo T-cell depletion	Gancyclovir, Acyclovir, Amphotericin B, Bactrim, Cefazidime	Radiation therapy, Fludarabine, Cyclophosphamide, Rabbit ATG	Rituximab	

Abbreviations: dec., deceased; BMT, bone marrow transplantation; ATG, anti-thymocyte globulin; GVHD, graft versus host disease; GI, gastrointestinal; EBV, Epstein-Barr virus; CMV, cytomegalovirus; NR, not reported

¹No *SMARCAL1* coding mutation was found in the paternal allele, however, by qRT-PCR and cDNA sequencing there was no expression of the paternal allele. Quantitative RT-PCR showed expression of *SMARCAL1* mRNA approximately half that observed in control cells [Clewning et al., 2007].

²No *SMARCAL1* coding mutation was found in the maternal allele, however, by qRT-PCR and cDNA sequencing there was no expression of the maternal allele. Quantitative RT-PCR showed expression of *SMARCAL1* mRNA approximately half that observed in control cells [Clewning et al., 2007].