HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2015 December 01.

Published in final edited form as:

Pediatr Blood Cancer. 2014 December ; 61(12): 2307–2309. doi:10.1002/pbc.25102.

Autoimmune Thyroid Disease Following Alemtuzumab Therapy and Hematopoietic Cell Transplantation in Pediatric Patients with Sickle Cell Disease

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Abstract

Allogenic hematopoietic cell transplantation (alloHCT) is currently the only curative treatment option for patients with sickle cell disease. Alemtuzumab is a monoclonal antibody directed against CD52 positive cells used in myeloablative conditioning regimens for alloHCT. Its use has been associated with development of autoimmune disease in adult patients with rheumatologic conditions. We report on three cases of new onset autoimmune thyroid disease after alloHCT treatment with alemtuzumab in pediatric patients with sickle cell disease.

Keywords

alemtuzumab; sickle cell disease; autoimmunity; thyroid dysfunction; stem cell transplant

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy with a median life expectancy of 45 years [1]. Despite the development of disease-modifying treatments such as hydroxyurea leading to decreased mortality rates [2], allogenic hematopoietic cell transplantation (alloHCT) remains the only curative treatment.

Studies have demonstrated the effectiveness of alloHCT in this patient population using myeloablative conditioning regimens, such as busulfan and cyclophosphamide [3,4]. Limitations of this procedure include graft failure, which has been significantly lowered by use of immune ablative T-cell depleting agents such as rabbit anti-thymocyte globulin(rATG) or alemtuzumab. [3,5].

Alemtuzumab is a monoclonal antibody directed against CD52, a cell surface marker found predominantly on lymphocytes and macrophages [5]. It is used in alloHCT and recently has been found to be effective in the treatment of relapsing-remitting multiple sclerosis(MS)

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Disclosure statement: The authors have nothing to disclose. The authors have no known or perceived conflicts of interest.

[6,7]. However, approximately 20% of patients who received alemtuzumab for MS developed thyroid dysfunction, particularly Graves' disease, upon recovery of lymphocyte counts [6,7].

We prospectively studied 26 patients with symptomatic SCD who received a busulfan, fludarabine, and alemtuzumab conditioning regimen followed by alloHCT [8,9]. Of these 26 patients, three (12%) developed autoimmune thyroid disease after alloHCT. To our knowledge, no reports of autoimmune thyroid disease have been reported in pediatric patients after the use of alemtuzumab in the setting of alloHCT.

CASE 1

Patient 1 was diagnosed with Hemoglobin S/Beta Thalassemia at six months of age and started on hydroxyurea at the age of 11 years. Five years later, he underwent a 6/6 human leukocyte antigen (HLA) matched sibling alloHCT (Table I) and achieved stable donor chimerism.

At 10 months post-alloHCT, he was admitted for respiratory distress and started on prednisone for pneumonia. During the prednisone taper, he reported myalgias, weakness, fatigue, anorexia, weight gain, constipation, dry skin, and cold intolerance. Thyroid function tests(TFTs) (Table II) were obtained and he was found to have an elevated thyroid stimulating hormone(TSH) level of 209.08mIU/mL (normal 0.32–4.05mIU/mL) and undetectable free and total thyroxine (T4) levels(<0.4ng/dL, <1.05ug/dL respectively). Upon referral to our pediatric endocrinology division, he was diagnosed with Hashimoto's thyroiditis as anti-thyroid peroxidase(anti-TPO) and anti-thyroglobulin(anti-TG) antibodies were both elevated(anti-TPO 382 IU/mL, normal <20 IU/mL, and anti-TG 1722 IU/mL, normal <1 IU/mL). He has been maintained on levothyroxine with normalized laboratory tests and resolution of symptoms.

CASE 2

Patient 2 was diagnosed with Hemoglobin S/Beta Thalassemia at birth. He was started on hydroxyurea and later referred for alloHCT due to lack of response to hydroxyurea. He received a 5/6 HLA matched unrelated alloHCT and achieved full donor chimerism.

At three years post-alloHCT, he reported increased appetite without weight gain, persistent headaches, and exophthalmos was found on examination. TFTs revealed a suppressed TSH (<0.03 mIU/L) in the setting of elevated T4(14.67 ug/dL, normal 5.41–11.66 ng/dL), free T4(2.14 ng/dL, normal 0.7–1.24 ng/dL) and triiodothyronine levels(342 ng/dL, normal 94–170 ng/dL). Coupled with positive anti-TPO(10096 IU/mL) and anti-TG antibodies (56 IU/mL), but a negative TSH receptor antibody, the patient was diagnosed with Hashimoto's hyperthyroidism and has been treated with methimazole without complications. There has been normalization of T4 levels with continued suppression of TSH levels. He has remained asymptomatic on treatment.

CASE 3

Patient 3 was diagnosed with Hemoglobin SC disease at birth and at 18 years of age, underwent a 6/6 HLA matched sibling alloHCT and achieved full donor chimerism.

Three years post-alloHCT, he presented with fever, leukocytosis and multi-focal pain. He was admitted for an infectious work-up and TFTs were done suggesting hyperthyroidism. TFTs repeated during that admission were: TSH <0.03mIU/L, T4 13.89ug/dL, free T4 2.39ng/dL, and triiodothyronine 207ng/dL. Review of systems was significant only for diarrhea. Physical exam was negative for thyromegaly, exophthalmos, or lid lag. Further laboratory evaluation confirmed a diagnosis of Graves' disease as the patient had multiple positive thyroid antibodies, including anti-TPO(72IU/mL), anti-TG(>3000IU/mL), TSH receptor antibody(10.55 IU/L, normal<1.75 IU/L) and thyroid stimulating immunoglobulin(207%, normal<122%). He was started on methimazole with improving TFTs.

DISCUSSION

The overall and event free survival after alloHCT for SCD has been reported at greater than 85% [3,4,8]. In this case series we report the development of autoimmune thyroid disease in 3/26 patients with SCD after alloHCT. The incidence of thyroid dysfunction in pediatric patients after alloHCT is reported at ~30% [10,11]. Subclinical compensated and overt non-autoimmune primary hypothyroidism are more frequently seen in long-term survivors of alloHCT [11,12], likely due to the effects of chemotherapy [13] or radiation [10].

All of the 26 patients in our series received busulfan based conditioning regimens, with 3 developing thyroid disease. In a recent study by Sanders et al, 30% of patients receiving busulfan developed thyroid dysfunction, primarily non-autoimmune hypothyroidism [10]. Our patients were found to have antibody-mediated disease, possibly implicating an alternative cause. One proposed mechanism of the development of autoimmune thyroid disease after alloHCT is adoptive immunity, or the transfer of thyroid antibodies from donor to recipient [14]. For the two patients receiving matched sibling alloHCT, there was no known family history of thyroid disease.

Alemtuzumab allows for the use of lower dose maintenance immunosuppression and decreases rejection risk [15] and has been used in the management of MS [6]. In patients receiving alemtuzumab for MS, the incidence of autoimmune thyroid dysfunction is reported at 15–30% [6,16]. This is in comparison to a baseline incidence of 1–2% in patients with MS not receiving immunotherapy [17]. Immune reconstitution has been implicated in the pathogenesis of thyroid autoimmunity after use of alemtuzumab [18,19]. Recovery of CD8+T-cells and slower production of memory CD4+T-cells, which suppress autoimmunity, follow alemtuzumab-induced lymphopenia [18,19]. The disordered expansion of T-cells seen early in the immune reconstitution process is thought to increase the likelihood of self-reactive T-cell proliferation leading to autoimmunity [17,20]. On further evaluation of T-cell markers in these 3 patients, we were unable to find an association between onset of thyroid disease and CD8+ or CD4+T-cell count recovery

during the 3–5 years post-alloHCT. Autoimmune disease can occur due to immune recovery dysregulation as seen in chronic graft versus host disease (cGVHD). We further reviewed all patients for history of cGHVD. Patient 2 was successfully treated for cGVHD three years prior to his diagnosis of thyroid disease, making this an unlikely etiology.

In our review to date, there have been no published cases of autoimmune thyroid disease after treatment with alemtuzumab and alloHCT in pediatric patients. It is plausible that these patients developed thyroid disease as a result of the use of busulfan, but these patients typically develop thyroid disease as a result of damage to the thyroid gland. The presence of multiple thyroid-related antibodies found in all three patients suggests an alternate cause for thyroid disease in this population, possibly alemtuzumab induced autoimmunity. Given the increased use of alemtuzumab in alloHCT in patients not only with SCD, but other malignant and non-malignant conditions, evaluation for thyroid disease is of increased importance as symptoms may be non-specific or masked by other transplant complications. The greatest risk of autoimmune disease appears to be in the 12–36 month period following the initial alemtuzumab infusion [16] with some reporting an increased incidence up to 5 years after treatment [17]. While this is a small cohort of patients, the results highlight the importance of incorporating yearly screening of thyroid disease in patients with both hemoglobinopathies as well as other diagnoses post-alloHCT.

Acknowledgments

Sources of support: none

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Table I

Clinical characteristics of patients with new onset autoimmune thyroid disease

Case	Diagnosis	Age at transplant (yrs)	Transplant type	Neutrophil Engraftment
1	Hg S/beta thalassemia	16	6/6 matched sibling bone marrow	Day +13
2	Hg S/beta thalassemia	9	5/6 matched unrelated cord blood	Day +28
3	Hg SC	18	6/6 matched sibling bone marrow	Day +14

Table II

Thyroid profile at time of diagnosis of thyroid disease

Case	FT4 (ng/dL)	T4 (ug/dL)	T3 (ng/dL)	TSH (mIU/L)	Anti-TG (IU/mL)	Anti-TPO (IU/mL)	TBII (IU/L)	TSI (%)	Thyroid Ultrasound
1	<0.4	< 1.05	<30	209.08	1722	382	-	-	Enlarged heterogeneous gland, no nodules
2	2.14	14.67	342	< 0.03	56	10096	<0.3	-	Heterogeneous gland with increased vascularity
3	2.39	13.89	207	< 0.03	>3000	72	10.55	207	-

Reference values for FT4 (free thyroxine) are 0.7–1.24 ng/dL, T4 (thyroxine) 5.41–11.66 ng/dL, T3 (triiodothyronine) 94–170 ng/dL, TSH (thyroid stimulating hormone) 0.32–4.05 mIU/mL, Anti-TG (anti-thyroglobulin antibody) <1 IU/mL, Anti-TPO (anti-thyroid peroxidase antibody) <20 IU/mL, TBII (TSH receptor antibody) <1.75 IU/L, and TSI (thyroid stimulating immunoglobulin) <122%.