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Incidence and Predicting Factors for Abnormal Thyroid Function Test in Adult Patients Post Hematopoietic Stem Cell Transplantation at King Hussein Cancer Center

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Abstract

Introduction: The risk of abnormal thyroid function after hematopoietic stem cell transplantation (HSCT) is well-known especially in pediatric patients. There are few studies about adult patients that showed 3-year cumulative incidence ranges between 8-23%. In this study we studied the incidence of abnormal thyroid function in patients older than 18 years, and reviewed its predicting factors.

Patients and Method: This is a retrospective study for all adult patients who underwent HSCT at KHCC from 2004-2010.Our cohort consisted of 108 patients who had normal thyroid function before transplant, and at least one Thyroid Function Test (TFT) done after transplant. From the group 54.8% had autologous transplant, 45.2% had allogenic transplant from which 94.6% had myeloablative transplant. Total Body Irradiation (TBI) was used in the conditioning regimen in 29% of the patients.

Results: At a median follow up of 1.1 year (0.1-6.1 years), 34 patients (31%) developed abnormal thyroid function tests, high TSH accounted for 40.7%, low TSH for 38.9%, low T4 for 11.1%, and high TSH with low T4 for 3.7%. The factors that showed significant correlation with Abnormal Thyroid Function (ATF) were: Female gender, allogenic transplant, and TBI-based conditioning. From the 34 patients who developed abnormal test after transplant, 61.7% of them developed thyroid dysfunction in the first year post transplant, and 20.5% in the second year.

Conclusion: The incidence of abnormal thyroid function for adult patients after HSCT is around 30%. Most of the abnormalities happened in the first 2 years after transplant. Female gender, allogenic transplant, and TBI-based conditioning were associated with more occurrences of thyroid function abnormalities.

Keywords: Thyroid function; Incidence and predicting factors; Hematopoietic stem cell transplantation

Introduction

The occurrence of Abnormal Thyroid Function (ATF) as a late complication of hematopoietic stem cell transplantation (HSCT) and the factors associated with it have been described primarily in pediatric recipients of allogeneic HSCT [1-3]. However, fewer studies have analyzed the incidence of this complication in adults [4-6], in particular after autologous HSCT [4], these studies showed 3-year cumulative incidence of ATF ranges between 8-23%. The risk factors for ATF after HSCT is not consistent in all studies, some studies showed TBI as a significant predictor [1], other studies showed the only significant predictor is the type of transplant, with higher incidence in autologus transplant compared to allogenic transplant [7]. We aimed in this study to find the incidence of ATF after HSCT at our center, and to study the significance of different factors for its occurrence.

Patients and methods

We retrospectively analyzed the incidence of ATF in all consecutive adult HSCT recipients who underwent HSCT at our center between June 2004 and June 2010. After reviewing the files, we included patients who had normal thyroid function before transplant, and they had at least one reading of thyroid function following transplant. We had 293 patients who underwent transplant during that period. From this group, there were 155 patients who did not have pre transplant and or follow up Thyroid Function Test (TFT) after transplant, so they were excluded. From the remaining 138 patients, there were 30 patients who had abnormal TFT before transplant, so they were excluded too. So, our cohort consisted of 108 patients in spite that it is a routinely done test regardless of presence or absence of symptoms. We collected data about age, gender, underlying disease, type of transplant (autologous, allogenic), type of conditioning regimen (myeloablative versus nonmyeloablative,

and Total Body Irradiation (TBI) versus non-TBI based conditioning), and number of transplants.

Definitions

Normal thyroid function was defined as a TSH level between (0.5 - 4.7) mIU/ L, free T4 between (10 - 23) pmol/ L, T3 between (3.5 - 6.5) pmol/ L.

We considered any level above or below the normal range as abnormal. Subclinical hypothyroidism defined as high TSH and normal T4. Overt hypothyroidism defined as high TSH and low T4, subclinical hyperthyroidism defined as low TSH and normal T4 and overt hyperthyroidism was defined as low TSH and high T4.

Statistics

Descriptive statistics was used to present patients demographics and Clinical information. Categorical factors such as: gender and disease type were described using counts and percentages, while continuous factors such as Age and duration between BMT and last follow up date were described using Mean and Range. A comparison between patients with Normal and abnormal thyroid function test following HSCT according to patients demographics and clinical information was done using Chi square test, fisher exact, and t-test, depending on the assumption required for each test. A significance criterion of $p \leq 0.05$ was used in the analysis. All analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

At a median follow up of 1.1 year (0.1-6.1 years) 75% of the patients were alive. The median age at the time of transplant was 37.5 years (18.2-69), and 66% were males. Pre transplant diagnoses were; Lymphoma & myeloma which constituted 57.4%, acute leukemia accounted for 24%, and aplastic anemia for 5.6%.

From the group 54.8% had autologous transplant, 45.2% had allogenic transplant from which 94.6% were myeloablative transplants. The conditioning regimen was TBI-based in 29%, and 13.9% had more than one transplant (Table 1).

Regimens used for autologous transplant were all non TBI based myeloablative conditioning. These include: BEAM (BiCNU, Etoposide, Ara-C, Melphalan), Melphaln, and Carboplatin plus Etoposide. Rigemens used for allogeneic translpant were either Reduced Intensity Conditioning (RIC), or Myeloablative Conditioning (MAC), and both included TBI vs non-TBI regimens. RIC regimens include Fludarabine plus TBI, Fludarabine plus Melphaln. MAC regimens included TBI plus Cyclophophamide, Busulphan plus Cyclophophamide with median follow up of 1.1 year (0.1-6.1 years), 34 patients (31%) developed abnormal thyroid function tests, as shown in table 2.

The predicting factors which showed significant p value for the development of abnormal TFT are shown in table 3. The disease category, number of transplants, and myeloablative versus non myeloablative were not predictors of the occurrence of abnormal thyroid function test (not shown in the table).

From the 34 patients who developed abnormal test after transplant, 61.7% of them developed this in the first year post transplant, 20.5% in the second year, and the remaining 17.8% after that with 2.9% occurred after 4 years.

From the 34 patients 19 (56%) had allogenic transplantation, and 11 out of the 19 (58%) had chronic graft versus host disease. Six patients out of the 19 (31%) required treatment with Thyroxin.

Out of the 34 patients, 15 (44%) had autologous transplantation, from whom 7 patients required treatment with Thyroxin.

In our cohort, there were 15 patients who underwent more than one transplantation.Ten patients had second autologous transplantation and 5 had allogenic transplantation. In this group 7 out of 15 (47%) patients developed ATF. While in the one transplantation group 27 out of 93 (29%) patients developed ATF (P value: 0.172).

Table 1: Patients' characteristics

Total number of patients	**108**
Median age (years)	37.5 years
Male gender%	66%
Diagnosis & %	Lymphoma &MM: 57.4% Acute leukemia: 24% Aplastic anemia: 5.6%
Number of transplants & %	1: 85.1% >1: 13.9%
Type of transplant & %	Autologus: 54.8% Allogenic: 45.2%
Intensity of conditioning & %	Myeloablative: 94.6% Non-myeloablative: 5.4%
TBI-based %	29%

Note: Abbreviations, TBI: Total Body Irradiation

Table 2: the most common subtypes of abnormal TFT

Abnormal result	**percentage**
High TSH, isolated	40.7%
Low TSH, isolated	38.9%
Low T4, isolated	11.1%
High TSH & Low T4	3.7%

Note: Normal values for TFT: TSH level between (0.5 - 4.7) mIU/ L, freeT4 between (10 - 23) pmol/ L, T3 between (3.5 - 6.5) pmol/ L.

Table3: predicting factors with significant P value

Variable	**Sub variable & % of ATF**	**Odds ratio (95% CI), P value**
Gender	Male: 24.2% Female: 42.9%	2.34 (1.021-5.379), 0.042
Type of transplant	Autologous: 19.6% Allogenic: 40.5%	2.05 (0.572-7.35), 0.027
TBI-based	TBI: 44.4% Non-TBI: 22.7%	1.6(0.43-5.958), 0.036

Note: Abbreviations, TBI: Total Body Irradiation

Discussion

Thyroid dysfunction is a well known adverse effect of autologous and allogeneic HSCT. This effect was extensively studied in pediatric age groups [1-3]. Several researchers have reported a prevalence of thyroid dysfunction ranging between 10% to 50% both in children and in adult HSCT long-term survivors having been conditioned with chemotherapy combined with TBI [1,3,5,8-10].

The increasing interest in the late effect of HSCT on the thyroid function prompted us to study this in adult patients. The incidence of early or late complications is influenced by the antineoplastic agents used, total dose of the preparative chemotherapy, initial diagnosis, age at time of HSCT and development of Graft-Versus-Host Disease (GVHD) [5,11,12]. Cyclophosphamide in combination with busulphan (BUCY2) is one of the most commonly used combinations. Other regimens that might be used include etoposide, cytosine arabinoside and melphalan (BECYM, BEAM) [2,4]. The adverse effect of these agents in combination with immunosuppressive drugs such as glucocorticoids and cyclosporine used after HSCT for the prevention and treatment of GVHD on the endocrine system is yet to be evaluated. In more recent literature, the incidence of thyroid dysfunction in adult recipients of HSCT after BUCY2 conditioning without TBI ranges from 10% to 47% [11,12].

An incidence of 1.16% for overt primary hypothyroidism and 12.8% for subclinical primary hypothyroidism was observed in our study population; with overall incidence for thyroid dysfunction amounted to 31%. The incidence of hypothyroidism in the general population from the area of Jordan that these patients came from is not known. We have used as a reference the incidence encountered in endocrinology texts referring to the general population, that is, prevalence rates for overt hypothyroidism in women varying from 0.5 to 1.5 %, and as low as a tenth of these rates in men, and the rates for subclinical hypothyroidism varying from 8 to 10% in women and 1 to 2% in men [13,14]. Overall overt or subclinical hypothyroidism occurred more frequently in female than male patients (42.9% vs. 24.2%), with statistical significance, and odds ratio of 2.34. So, in our study female gender was a predictor for the occurrence of ATF after HSCT, which was not the case in two previous studies [4,7]. The incidence of ATF in our study was more in allogenic group with odds ratio of 2.05 and significant P value, which is contradicting the result of the study by Sanchez-O, et al. (7). This might be due to shorter follow up time in our study, since in Sanchez-O study the median follow up was 39 months, with 25% developing it between 7-14 years. The third factor which predicted the occurrence in our study was TBI with odds ratio of 1.6 and significant P value, and this is consistent with pediatric data [1]. In conclusion our study showed an increased risk of ATF after HSCT, female gender, allogenic transplantation and the use of TBI were predictors of this risk. So a high index of suspicion for ATF is needed in survivors after HSCT. Thyroid function testing is recommended by international guidelines for all Blood And Marrow Transplant (BMT) survivors yearly after the procedure or if new relevant symptoms develop [8] in our study about 53% of patients did not have follow up TFT after HSCT, so the current recommendations for sustained long-term monitoring of thyroid function tests in adult BMT recipients should be reinforced particularly in patients who have factors predicting higher risk of ATF.

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Nothing to declare

References

1. Sanders JE, Hoffmeister PA, Woolfrey AE, Carpenter PA, Storer BE, Storb RF, et al. Thyroid function following hematopoietic cell transplantation in children: 30 years' experience. Blood. 2009;113(2):306-8. doi: 10.1182/blood-2008-08-173005.
2. Berger C, Le-Gallo B, Donadieu J, Richard O, Devergie A, Galambrun C, et al. Late thyroid toxicity in 153 long-term survivors of allogeneic bone marrow transplantation for acute lymphoblastic leukaemia. Bone Marrow Transplant. 2005;35(10):991-5.
3. Jung MH, Cho KS, Lee JW, Chung NG, Cho B, Suh BK, et al. Endocrine complications after hematopoietic stem cell transplantation during childhood and adolescence. J Korean Med Sci. 2009;24(6):1071-7. doi: 10.3346/jkms.2009.24.6.1071.
4. Somali M, Mpatakoias V, Avramides A, Sakellari I, Smias Ch, Anagnostopoulos A, et al. Thyroid dysfunction in adult long term survivors after hematopoietic stem-cell transplantation (HSCT). Horm Metab Res. 2005;37(8):494-9.
5. Tauchmanovà L, Selleri C, Rosa GD, Pagano L, Orio F, Lombardi G, et al. High prevalence of endocrine dysfunction in long-term survivors after allogeneic bone marrow transplantation for hematologic diseases. Cancer. 2002;95(5):1076-84.
6. Savani BN, Koklanaris EK, Le Q, Shenoy A, Goodman S, Barrett AJ. Prolonged chronic graft-versus-host disease is a risk factor for thyroid failure in long-term survivors after matched sibling donor stem cell transplantation for hematologic malignancies. Biol Blood Marrow Transplant. 2009;15(3):377-81. doi: 10.1016/j.bbmt.2008.11.032.
7. Sánchez-Ortega I, Canals C, Peralta T, Parody R, Clapés V, de Sevilla AF, et al. Thyroid dysfunction in adult patients late after autologus and allogenic blood and marrow transplantation. Bone Marrow Transplant. 2012;47(2):296-8. doi: 10.1038/bmt.2011.54.
8. Rizzo JD, Wingard JR, Tichelli A, Lee SJ, Van Lint MT, Burns LJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2006;12(2):138-51.
9. Kauppila M, Koskinen P, Irjala K, Remes K, Viikari J. Long–term effects of allogenic bone marrow transplantation (BMT) on pituitary, gonad, thyroid and adrenal function in adults. Bone Marrow Transplant. 1998;22(4):331-7.
10. Kolb HJ, Bender-Götze C. Late complications after allogenic bone marrow transplantation for leukaemia. Bone Marrow Transplant. 1990;6(2):61-72.
11. Al-Fiar FZ, Colwill R, Lipton JH, Fyles G, Spaner D, Messner H. Abnormal thyroid stimulating hormone (TSH) levels in adults following allogenic bone marrow transplants. Bone Marrow Transplant. 1997;19(10):1019-22.
12. Brennan B, Shalet SM. Endocrine late effects after bone marrow transplant. Oncol Res. 2010;18(11-12):607-15.
13. Larsen PR, Davies TF, Hay ID. The Thyroid Gland. In: Jean D, Wilson JD. Foster DW, Kronenberg HM, Larsen PR (eds). Williams Textbook of Endocrinology, 9th edition. Philadelphia: W. B. Saunders Company; 1998. p. 389-517.
14. Utiger RD. Hypothyroidism. In: De Groot LJ (ed). Endocrinology, Philadelphia: W. B. Saunders Company; 1989. p. 702-722.