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ORIGINAL ARTICLE

Impact of allogeneic stem cell transplantation on thyroid function

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Abstract

Purpose Primary hypothyroidism is a main endocrine complication after allogeneic stem cells transplantation (allo-SCT) in children, but in adults data on post-SCT hypothyroidism are limited. The aims of this observational, cross-sectional study were to assess the prevalence of hypothyroidism in adult allo-SCT recipients according to time from transplantation, and to identify risk factors.

Methods One hundred and eighty-six patients (M 104; F 82; median age 53.4 years) who underwent allo-SCT between January 2010 and December 2017 were enrolled and divided into three groups, according to time from allo-SCT (1–3 years; 3–5 years; > 5 years). Pre-transplant TSH and fT4 levels were available for all patients. After transplantation, TSH, fT4 and anti-thyroperoxidase antibodies (TPO-Ab) were evaluated.

Results After a follow-up of 3.7 years, 34 (18.3%) patients developed hypothyroidism, with higher prevalence in females ($p < 0.001$) and in patients who received matched unrelated donor grafts ($p < 0.05$). No difference in prevalence was found at different time points. Patients who developed hypothyroidism showed higher rate of TPO-Ab positivity ($p < 0.05$) and higher pre-transplant TSH levels (median 2.34 μU/ml) compared to those with preserved thyroid function (median 1.53 μU/ml; $p < 0.001$). Multivariable analysis identified higher pre-transplant TSH levels as a positive predictor of hypothyroidism ($p < 0.005$). The ROC curve analysis identified a pre-SCT TSH cutoff of 1.84 μU/ml, which can predict hypothyroidism with sensitivity 74.1% and specificity 67.2%.

Conclusions About one out of four patients developed hypothyroidism after allo-SCT, with a greater incidence in females. Pre-transplant TSH levels seem to predict the onset of post-SCT hypothyroidism.

Keywords Cancer survivorship · Allogeneic stem cell transplantation · Hypothyroidism · Adults

Introduction

Allogeneic stem cell transplantation (allo-SCT) represents a potentially curative treatment for a variety of hematologic diseases. Over the past two decades, advances in conditioning regimens and in post-transplant supportive care, along with the availability of alternative graft sources, decreased the morbidity/mortality of allo-SCT, resulting in more than half a million allo-SCT survivors worldwide [1]

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and in a growing interest in the long-term complication of allo-SCT [2–4].

Endocrine dysfunction is one of the main complications of allogeneic hematopoietic SCT, specifically, diabetes, dyslipidemia, hypogonadism, and thyroid dysfunction [5–13].

Involvement of the thyroid gland can present as early- or late-onset dysregulation. The international blood and marrow transplant recommendations [14] suggest testing thyroid function yearly after allo-SCT, even in the absence of suggestive symptoms. This guidance mainly relies on data from childhood cancer survivors [8]. Nonetheless, data on the incidence and risk factors of thyroid dysfunction following allo-SCT in adults are still limited. The risk of hypothyroidism in adult allo-SCT recipients reported in available studies is highly variable, due to inhomogeneity in composition and duration of follow-up among the considered cohorts [10, 12, 13, 15–17]. Predictive factors of hypothyroidism following allo-SCT in the adult population include advanced age, multiple allo-SCTs, chronic graft versus host disease (GVHD), prolonged immunosuppressive therapy for GVHD, and high-dose total body irradiation (TBI) [10, 12, 13, 15, 18].

The present study aims to determine the prevalence of thyroid dysfunction in adult allo-SCT recipients with respect to time from transplantation and, additionally, to identify potential risk factors for developing post-SCT hypothyroidism.

Materials and methods

An observational, cross-sectional, single-center study was conducted. The study protocol was approved by the Ethical Committee of our Institution (protocol number 00179/2020) and a written informed consent was obtained from enrolled patients. Adult patients who underwent allo-SCT between 1st January 2010 and 31st December 2017 at the Stem Cell Transplant Center of the "Città della Salute e della Scienza Hospital" of Turin were consecutively recruited from 1st January 2018 until 30th June 2019, after at least 1 year of regular follow-up.

Inclusion criteria were: (a) allo-SCT performed for hematological diseases; (b) age at allo-SCT ≥ 18 years; (c) at least 1 year of regular follow-up after allo-SCT. Patients who underwent two or more allo-SCT, those with recurrent disease after allo-SCT, or those with thyroid dysfunction diagnosed prior to allo-SCT were excluded from the study.

Patients were divided into three subgroups according to time elapsed since allo-SCT (group 1: 1–3 years; group 2: 3–5 years; group 3: > 5 years).

Data on TSH and fT_4 levels before allo-SCT were available for all patients as a part of routine pre-transplant workup. At the time of the study, blood samples measuring levels of TSH, fT4, and anti-thyroperoxidase antibodies (TPO-Ab) were collected. At that time, clinical data on hematological disease, medical treatments, as well as on thyroid dysfunction and other complications occurred after allo-SCT (e.g. acute/chronic GVHD) [19], were also collected from the original medical records.

For subgroup analysis, patients with hypothyroidism diagnosed after the SCT, but prior to the study were assigned to the appropriate subgroup, depending on time elapsed between allo-SCT and the study.

Patients who had discontinued systemic immunosuppressive therapy for less than 6 months were considered as being on "active therapy".

Laboratory measurements were carried out at our hospital laboratory by electrochemiluminescence immunoassay (ECLIA) system with sandwich technique for TSH and with competitive technique for fT_4 and TPO-Ab.

Overt primary hypothyroidism was defined as increased serum TSH and reduced serum fT_4 levels (> 4.2 μU/ml and < 9.3 pg/ml, respectively, according to reference ranges provided from our laboratory), while subclinical hypothyroidism was defined as increased TSH despite fT_4 serum levels within normal range.

Statistical analysis

Data are expressed as median and interquartile ranges or absolute numbers and percentages. Distributions of continuous variables were analyzed using the Shapiro–Wilk test. Data were evaluated by Chi square test, parametric (Student;s *t* test for independent or paired samples, ANOVA) or non-parametric (Mann–Whitney, Wilcoxon signed-rank, Kruskal–Wallis) tests, as appropriate. The receiver operating curves (ROC) analysis were used to assess the predictivity for hypothyroidism of pre-SCT TSH levels (Fig. 2). Correlation analysis calculating Spearman coefficient was performed to assess the strength of the association between demographic and clinical variables and hypothyroidism. The factors that were significantly associated with hypothyroidism at the univariate analysis were included in multiple regression. Statistical significance was assumed at $p < 0.05$. All analyses were performed using MedCalc™ for Windows, version 18.11.3.

Results

Among the initial cohort of 462 patients, 186 (104 males and 82 females) met the inclusion criteria and agreed to participate in the study. The selection process is described in Fig. 1.

Enrolled patients had a median age of 49.3 (range 40.1–58.3) years at the time of allo-SCT and 53.4 (range 44.4–62.4) years at the time of the study (Table 1). Almost

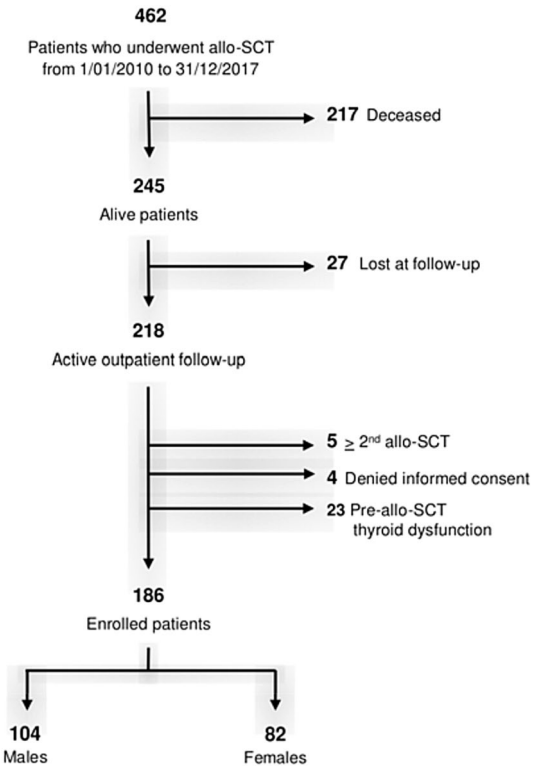

Fig. 1 Flowchart of screening and enrollment process

all patients (97.3%) were transplanted for hematological malignancies, mainly acute myeloid ($n = 84$; 45.2%) or lymphoid ($n = 30$; 16.1%) leukemia or non-Hodgkin lymphoma ($n = 25$; 13.4%), whereas five (2.7%) received allo-SCT for severe aplastic anemia (SAA). Prior to allo-SCT, all subjects underwent chemotherapy with high-dose alkylating agents and nine of them (4.8%) were also treated with radiotherapy to the neck. Myeloablative conditioning (MAC) was performed in 160 subjects (86%) using either busulfan (70.4%) or high-dose TBI (14.5%) (Table 1).

Post-transplant immunosuppressive regimen consisted of calcineurin inhibitors (CNIs) and methotrexate in all but four (treated with CNIs and mycophenolate mofetil, MMF) patients with a sibling donor, post-transplant cyclophosphamide (PTCY) followed by CNIs and MMF in all patients with a haploidentical donor and with antithymocyte globulin (ATG), CNIs and MTX in 94/99 patients receiving allo-SCT from matched unrelated donors (MUD), of which 5 of them received CNIs and MMF instead.

Acute and chronic GVHD were diagnosed in 81 (43.5%) and 113 (60.8%) patients, respectively. In 90 cases (48.4%), chronic GVHD was moderate or severe and 68 patients (36.6%) were on active treatment for GVHD at the time of evaluation (Table 1). First-line treatment of GVHD was according to guidelines [20]; for refractory diseases ruxolitinib was used in ten patients, ibrutinib and imatinib in eight patients each and rituximab in five.

After a median follow-up of 44 months (range 8–113 months) from allo-SCT, 34 (18.3%) patients showed hypothyroidism which was subclinical in 24 (12.9%) and overt in 10 (5.4%) of them.

No difference was found between patients evaluated at the three different time points (prevalence: 23.3% at 1–3 years from SCT; 16.3% at 3–5 years from SCT; 14% at > 5 years from SCT; $P = 0.318$) (Table 2). No patients developed hyperthyroidism after allo-SCT.

TPO-Ab were detected in 4 out of 10 (40.0%) patients with overt hypothyroidism, in 5 out of 23 (21.7%) patients with subclinical hypothyroidism and in 14 out of 122 (11.5%) patients without thyroid abnormalities following allo-SCT ($p < 0.05$). The prevalence of hypothyroidism was higher in patients showing TPO-Ab positivity at the time of the study ($p < 0.05$) (Table 1). Moreover, the prevalence of hypothyroidism was higher in females ($p < 0.05$) (Table 3) and in patients transplanted from MUD (25.3%) compared to those who received HLA-haploidentical (11.1%) or HLA-identical sibling donors (10%) ($p < 0.05$) (Table 1).

Considering the entire population, no difference was found in hypothyroidism prevalence between patients who received TBI (19.1%) and those who did not (18.1%; $p = 0.936$). However, restricting the analysis to patients belonging to subgroup 3, the prevalence of hypothyroidism was significantly higher in patients who underwent TBI (40%) than in those who did not (6.1%; $p < 0.005$). Patients who had received cervical RT showed a higher prevalence of hypothyroidism, even in the absence of statistical significance. There was no difference in post-SCT hypothyroidism prevalence in patients receiving busulfan, in patients on active immunosuppressive therapy, in patients who had received a previous auto-SCT or in those receiving myeloablative conditioning regimen than reduced-intensity conditioning regimen (Table 1). Prior to allo-SCT, patients who developed hypothyroidism showed significantly higher TSH levels (median 2.34 µU/ml; range 1.79–2.66) than those who retained normal thyroid function (median 1.53 µU/ml; range 1.07–2.03; $p < 0.001$) (Table 1). Moreover, among patients who did not develop hypothyroidism, TSH levels were significantly lower before than after allo-SCT (median pre-SCT TSH 2.34 µU/ml; range 1.07–2.03; median post-SCT TSH 2.02 µU/ml; range 1.4–2.7; $p < 0.0001$), whereas no significant difference was found between fT4 levels before (median 11 pg/ml; range 9.9–12.2) and after allo-SCT (median 11.4 pg/ml; range 10–12.6; $p = 0.131$).

The ROC curve analysis identified a TSH value of 1.84 µU/ml, above which it is possible to predict the onset of post-SCT hypothyroidism with a sensitivity of 74.1% and specificity of 67.2% (AUC 0.735; $p < 0.0001$) (Fig. 2). In detail, at the workup evaluation, 59 (31.7%) patients

Table 1 Clinical and hormonal features according to thyroid function

	Population ($n=186$)	Euthyroidism ($n=152$)	Hypothyroidism ($n=34$)	p value
Median age				
At evaluation (years)	53.4 (44.4 – 62.4)	53.4 (44.8 – 62.4)	53.1 (41.7 – 61.9)	0.46
At allo-SCT (years)	49.3 (40.1 – 58.3)	49.3 (40.4 – 58)	49.8 (37.9 – 59.7)	0.70
Gender				
Male	104 (55.9%)	92 (86.5%)	12 (11.5%)	*0.01*
Female	82 (44.4%)	60 (73.2%)	22 (26.8%)	
Underlying disease				
Myeloid disorders	115 (61.8%)	95 (82.6%)	20 (17.4%)	0.5
Lymphoid disorders	66 (35.5%)	54 (81.8%)	12 (18.2%)	
SAA	5 (2.7%)	3 (60%)	2 (40%)	
Previous auto-SCT	38 (20.4%)	31 (81.6%)	7 (18.4%)	0.8
Donor source				
HLA-identical sibling donor	60 (32.3%)	54 (90%)	6 (10%)	*0.03*
HLA-haploidentical donor	27 (14.5%)	24 (88.9%)	3 (11.1%)	
Matched unrelated donor	99 (53.2%)	74 (74.8%)	25 (25.2%)	
Stem cells source				
PBSC	154 (82.8%)	128 (83.1%)	26 (16.9%)	0.41
BM	32 (17.2%)	24 (75%)	8 (25%)	
Cervical RT				
Yes	9 (4.8%)	6 (66.7%)	3 (33.3%)	0.45
No	177 (95.2%)	146 (82.5%)	31 (17.5%)	
Conditioning				
MAC	160 (86%)	130 (81.3%)	30 (18.7%)	0.89
RIC	26 (14%)	22 (84.6%)	4 (15.4%)	
TBI				
No TBI	144 (77.4%)	118 (81.9%)	26 (18.1%)	0.77
Low-dose TBI (200 cGy)	15 (8.1%)	13 (86.7%)	2 (13.3%)	
High-dose TBI (12 Gy)	27 (14.5%)	21 (77.8%)	6 (22.2%)	
Busulfan	131 (70.4%)	108 (82.4%)	23 (17.6%)	0.85
Acute GvHD	81 (43.5%)	62 (76.5%)	19 (23.5%)	0.16
Chronic GvHD				
No cGvHD	73 (39.2%)	62 (84.9%)	11 (15.1%)	0.25
Mild cGvHD	23 (12.4%)	16 (69.6%)	7 (30.4%)	
Moderate-severe cGvHD	90 (48.4%)	74 (82.2%)	16 (17.8%)	
Active therapy for cGvHD	68 (36.6%)	56 (82.4%)	12 (17.6%)	0.98
TSH pre-allo-SCT (μU/ml)	1.63 (1.15–2.25)	1.53 (1.07–2.03)	2.34 (1.79–2.66)	*< 0.001*
fT4 pre-allo-SCT (pg/ml)	11 (9.9–12.05)	11.1 (9.98–12.10)	10.4 (9.23–11.78)	0.27
AbTPO positivity	23 (14.8%)	14 (60.9%)	9 (39.1%)	*0.04*

Data expressed as "median (interquartile range)" or "absolute number (percentage)"

p-values ≤ 0.05 are italicised

Allo-SCT allogeneic stem cell transplantation, *TSH* thyroid-stimulating hormone, fT_4 free tetra-iodothyroxine, *AbTPO* anti-thyroperoxidase antibodies, *auto-SCT* autologous stem cell transplantation, *SAA* severe aplastic anemia, *PBSC* peripheral blood stem cells, *BM* bone marrow, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *RT* radiotherapy, *TBI* total body irradiation, *GvHD* graft versus host disease, *n* number

showed TSH > 1.84 μU/ml. Thirteen of them (22%) developed subclinical hypothyroidism, while 7 (11.9%) developed overt hypothyroidism. The prevalence of post-SCT hypothyroidism was 33.9% in patients with TSH > 1.84 μU/ml and 11% in patients with TSH < 1.84 μU/ml at the workup evaluation ($p < 0.001$). No differences were detected in gender, age at transplantation, previous auto-SCT, donor type, previous cervical RT, TBI and GVHD between patients with pre-SCT TSH levels above or below 1.84 μU/ml (Table 4).

Table 2 Clinical and hormonal features of the whole population and subgroups based on the time since transplantation

	Population ($n=186$)	1–3 years ($n=73$)	3–5 years ($n=49$)	> 5 years ($n=64$)	p value
Median follow-up time (years)	3.7 (1.8–5.9)	1.5 (1.2–2.1)	3.9 (3.2–4.4)	6.5 (5.8–7.5)	
Thyroid function					
Euthyroidism	152 (81.7%)	56 (76.7%)	41 (83.7%)	55 (86%)	0.32
Subclinical hypothyroidism	24 (12.9%)	10 (13.7%)	7 (14.3%)	7 (10.9%)	
Overt hypothyroidism	10 (5.4%)	7 (9.6%)	1 (2%)	2 (3.1%)	
Median age					
At evaluation (years)	53.4 (44.4–62.4)	53.7 (45.8–62.1)	53.4 (42.5–61.6)	53.2 (44.8–64.5)	0.83
At allo-SCT (years)	49.3 (40.1–58.3)	51.5 (43.4–59.7)	49.1 (38.7–57.5)	46.8 (38.7–57.4)	0.11
Gender					
Male	104 (55.9%)	44 (60.3%)	27 (55.1%)	33 (51.6%)	0.59
Female	82 (44.1%)	29 (39.7%)	22 (44.9%)	31 (48.4%)	
Underlying disease					
Myeloid	115 (61.8%)	49 (67.1%)	32 (65.3%)	34 (53.1%)	0.41
Lymphoid	66 (35.5%)	23 (31.5%)	16 (32.7%)	27 (42.2%)	
SAA	5 (2.7%)	1 (1.4%)	1 (2%)	3 (4.7%)	
Previous auto-SCT	38 (20.4%)	8 (11%)	10 (20.4%)	20 (31.3%)	*0.01*
Donor source					
MRD	87 (46.8%)	24 (32.9%)	29 (59.2%)	34 (53.1%)	*0.01*
MUD	99 (53.2%)	49 (67.1%)	20 (40.8%)	30 (46.9%)	
Stem cell source					
PBSC	154 (82.8%)	65 (89%)	37 (75.5%)	52 (81.3%)	0.14
BM	32 (17.2%)	8 (11%)	12 (24.5%)	12 (18.7%)	
Cervical RT	9 (4.8%)	0 (0%)	2 (4.1%)	7 (10.9%)	*0.01*
Conditioning					
MAC	160 (86%)	59 (80.8%)	44 (89.8%)	57 (89.1%)	0.26
RIC	26 (14%)	14 (19.2%)	5 (10.2%)	7 (10.9%)	
TBI					
No TBI	144 (77.4%)	53 (72.6%)	42 (85.7%)	49 (76.6%)	0.23
Low-dose TBI (200 cGy)	15 (8.1%)	9 (12.3%)	3 (6.1%)	3 (4.7%)	
High-dose TBI (12 Gy)	27 (14.5%)	11 (15.1%)	4 (8.2%)	12 (18.7%)	
Busulfan	131 (70.4%)	53 (72.6%)	37 (75.5%)	41 (64.1%)	*0.36*
Acute GvHD	81 (43.5%)	39 (53.4%)	18 (36.7%)	24 (37.5%)	0.09
Chronic GvHD					
No cGvHD	73 (39.2%)	25 (34.3%)	22 (44.9%)	26 (40.6%)	0.50
Mild cGvHD	23 (12.4%)	9 (12.3%)	8 (16.3%)	6 (9.4%)	
Moderate-severe cGvHD	90 (48.4%)	39 (53.4%)	19 (38.8%)	32 (50%)	
Active therapy for cGvHD	68 (36.6%)	45 (61.6%)	8 (16.3%)	15 (23.4%)	*< 0.001*
TSH pre-allo-SCT (μU/ml)	1.63 (1.15–2.25)	1.72 (1.09–2.42)	1.58 (1.17–2.12)	1.54 (1.12–1.99)	0.66
fT4 pre-allo-SCT (pg/ml)	11 (9.9–12.05)	11.25 (9.95–12.35)	11.1 (10–11.95)	10.4 (9.63–11.95)	0.42
AbTPO positivity	23 (14.8%)	7 (9.6%)	8 (16.3%)	8 (12.5%)	0.19

Data expressed as "median (interquartile range)" or "absolute number (percentage)"

p value refers to differences between groups: "1–3 years", "3–5 years" and "> 5 years"

p-values ≤ 0.05 are italicised

Allo-SCT allogeneic stem cell transplantation, *TSH* thyroid-stimulating hormone, fT_4 free tetra-iodothyroxine, *AbTPO* anti-thyroperoxidase antibodies, *auto-SCT* autologous stem cell transplantation, *SAA* severe aplastic anemia, *MRD* matched related donor, *MUD* matched unrelated donor, *PBSC* peripheral blood stem cells, *BM* bone marrow, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *RT* radiotherapy, *TBI* total body irradiation, *GvHD* graft versus host disease, *n* number

Table 3 Clinical and hormonal features according to gender

	Females ($n=82$)	Males ($n=104$)	p value
Thyroid function			
Euthyroidism	60 (73.1%)	92 (88.5%)	*0.01*
Subclinical Hypothyroidism	14 (17.1%)	10 (9.6%)	
Overt hypothyroidism	8 (9.8%)	2 (1.9%)	
Median age			
At evaluation (years)	53.2 (44.3–62)	53.6 (44.4–62.4)	0.76
At allo-SCT (years)	49.9 (40.3–58.3)	49.2 (40.1–58.2)	0.80
Underlying disease			
Myeloid disorders	57 (69.5%)	58 (55.8%)	0.16
Lymphoid disorders	23 (28.1%)	43 (41.3%)	
SAA	2 (2.4%)	3 (2.9%)	
Previous auto-SCT	15 (18.3%)	23 (22.1%)	0.65
Donor source			
MRD	38 (46.3%)	49 (47.1%)	0.97
MUD	44 (53.7%)	55 (52.9%)	
Stem cell source			
PBSC	65 (79.3%)	89 (85.6%)	0.35
BM	17 (20.7%)	15 (14.4%)	
Cervical RT			
Yes	4 (4.9%)	5 (4.8%)	0.75
No	78 (95.1%)	99 (95.2%)	
Conditioning			
MAC	74 (90.2%)	86 (82.7%)	0.21
RIC	8 (9.8%)	18 (17.3%)	
TBI			
No TBI	65 (79.3%)	79 (76%)	0.87
Low-dose TBI (200 cGy)	6 (7.3%)	9 (8.7%)	
High-dose TBI (12 Gy)	11 (13.4%)	16 (15.3%)	
Busulfan	61 (74.4%)	70 (67.3%)	0.37
Acute GvHD	37 (45.1%)	44 (42.3%)	0.81
Chronic GvHD			
No cGvHD	40 (48.8%)	33 (31.7%)	0.05
Mild cGvHD	10 (12.2%)	13 (12.5%)	
Moderate-severe cGvHD	32 (39%)	58 (55.8%)	
Active therapy for cGvHD	25 (30.5%)	43 (41.4%)	0.17
TSH pre-allo-SCT (μU/ml)	1.67 (1.15–2.34)	1.59 (1.1–2.13)	0.48
fT4 pre-allo-SCT (pg/ml)	10.9 (9.5–11.8)	11.3 (10.1–12.6)	0.10
AbTPO positivity	12 (14.6%)	11 (10.6%)	0.36

Data expressed as "median (interquartile range)" or "absolute number (percentage)"

p-values ≤ 0.05 are italicised

Allo-SCT allogeneic stem cell transplantation, *TSH* thyroid-stimulating hormone, fT_4 free tetra-iodothyroxine, *AbTPO* anti-thyroperoxidase antibodies, *auto-SCT* autologous stem cell transplantation, *SAA* severe aplastic anemia, *MRD* matched related donor, *MUD* matched unrelated donor, *PBSC* peripheral blood stem cells, *BM* bone marrow, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *RT* radiotherapy, *TBI* total body irradiation, *GvHD* graft versus host disease, *n* number

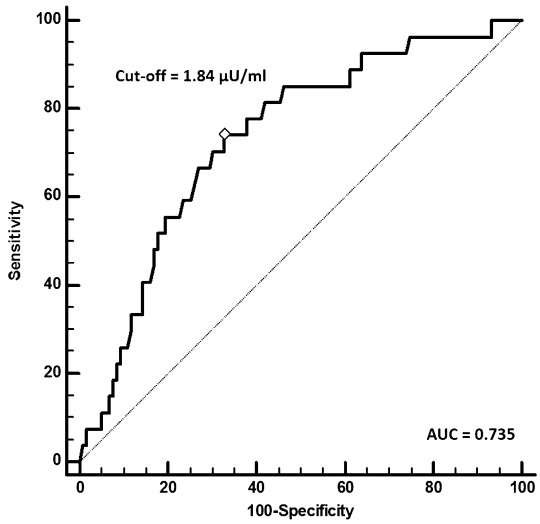

Fig. 2 Receiving operator curve (ROC) analysis for pre-transplant TSH level predictivity of hypothyroidism

Multiple regression analyses identified male gender (OR 0.341; CI95% 0.132 – 0.880; $p<0.05$) as a negative predictor of hypothyroidism and pre-SCT TSH levels (OR 2.249; CI95% 1.343–3.767; $p<0.005$) as a positive one (Table 5).

Discussion

In our cohort of 186 adult patients who underwent allo-SCT, 24 (12.9%) developed subclinical hypothyroidism, while 10 (5.4%) developed overt hypothyroidism, reaching an overall prevalence of 18.3%. Our results are in line with previous studies, reporting a frequency of hypothyroidism in adult SCT recipients ranging between 9.0 and 23.0% [9, 12, 15, 21]. In 2009, Savani et al. [13] reported a post-SCT hypothyroidism incidence of 37%, probably due to the longer duration of follow-up (median 84 months; range 25–166 months) and the presence of both children and adults within the cohort. Moreover, in that study, the great majority of patients (90%) received TBI (which was delivered only to the 22.6% of our patients). Finally, there is a different distribution of underlying diseases (about 60% of patients of their cohort were affected by chronic myelogenous leukemia). More recently, Farhadfar et al. [10], in a retrospective longitudinal study on 259 adult allo-SCT recipients, found a 5-year cumulative incidence of hypothyroidism of about 30%. Again, the follow-up (median 55 months; range 28–185 months) was longer than in our study and, also in this case, a larger number of patients underwent TBI (58.3%), at full doses in the majority of subjects. Furthermore, most patients were diagnosed with subclinical hypothyroidism, while the prevalence of overt hypothyroidism (3.1%) was similar to that found in our cohort. The prevalence of post-SCT hypothyroidism

Table 4 Clinical features of patients with pre-transplant TSH levels below and above 1.84 µU/ml

	TSH ≤ 1.84 µU/ml (*n* = 127)	TSH > 1.84 µU/ml (*n* = 59)	*p* value
Thyroid function			
Euthyroidism	113 (88.9%)	39 (66.1%)	*< 0.001*
Subclinical hypothyroidism	11 (8.7%)	13 (22%)	
Overt hypothyroidism	3 (2.4%)	7 (11.9%)	
Median age at the allo-SCT (years)	50.3 (40.7–58.4)	48.6 (39.8–57.8)	0.57
Gender			
Male	73 (57.5%)	31 (52.5%)	0.64
Female	54 (42.5%)	28 (47.5%)	
Underlying disease			
Myeloid	78 (61.4%)	37 (62.7%)	0.30
Lymphoid	44 (34.7%)	22 (37.3%)	
SAA	5 (3.9%)	0 (0%)	
Previous auto-SCT	26 (20.5%)	12 (20.3%)	0.86
Donor source			
MRD	58 (45.7%)	29 (49.2%)	0.78
MUD	69 (54.3%)	30 (50.8%)	
Cervical RT	6 (4.7%)	3 (5.1%)	0.79
TBI	30 (23.6%)	12 (20.3%)	0.76
Acute GvHD	51 (40.2%)	30 (50.9%)	0.23
Chronic GvHD	78 (61.4%)	35 (59.3%)	0.91

Data expressed as "median (interquartile range)" or "absolute number (percentage)"

p value refers to differences between patients with pre-transplant TSH ≤ and > 1.84 µU/ml

p -values ≤ 0.05 are italicised

Allo-SCT allogeneic stem cell transplantation, *TSH* thyroid-stimulating hormone, *auto-SCT* autologous stem cell transplantation, *SAA* severe aplastic anemia, *MRD* matched related donor, *MUD* matched unrelated donor, *RT* radiotherapy, *TBI* total body irradiation, *GvHD* graft versus host disease, *n* number

Table 5 Multiple regression analysis

Risk of hypothyroidism	*P = 0.0002*			*p*
	B	Odd ratio	CI 95%	
TSH pre-allo-SCT	0.816	2.249	1.343–3.767	*0.002*
Male gender	− 1.076	0.341	0.132–0.880	*0.026*

Dependent variable: hypothyroidism. Independent variables: TSH pre-allo-SCT, male gender, AbTPO positivity, donor source (MRD–MUD)

p-values ≤ 0.05 are italicised

Allo-SCT allogeneic stem cell transplantation, *TSH* thyroid-stimulating hormone, *AbTPO* anti-thyroperoxidase antibodies, *MRD* matched related donor, *MUD* matched unrelated donor

in our cohort was similar to that found in 2020 by Atilla et al. in a cohort of 259 patients who underwent allo-SCT between 2006 and 2016 (22%) [22]. Post-SCT hypothyroidism was finally found in 23% by Medinger et al. in 2017, but the cohort study was composed of acute myeloid leukemia survivors only [12].

Female patients had a higher risk of post-allo-SCT hypothyroidism. This is not surprising considering the gender difference in thyroid disorder within the general population [23]. However, the female:male ratio (about 3:1) is lower than those in the general population (roughly 10:1) [24], suggesting a causative role of allo-SCT even more remarkable than gender in the onset of hypothyroidism.

Patients who developed post-SCT hypothyroidism showed a higher percentage of TPO-Ab positivity, suggesting a possible pathophysiological role of autoimmunity in post-STC hypothyroidism. Even if the correlation between hypothyroidism and TPO-Ab was not confirmed at the multivariate analysis, this finding does not exclude the possible role of autoimmunity. It has been demonstrated a possible transfer of abnormal B- and T-lymphocyte from the donor to the SCT-recipient [25]. Moreover, it is also important to note that a minority of patients may develop autoimmune thyroiditis without evidence of TPO-Ab assessment [23], while in the general Italian population the prevalence of thyroid antibodies positivity without thyroid dysfunction can reach 5% [26]. Unfortunately, in our cohort, TPO-Ab were not measured at the baseline and in donors, hampering the possibility to explore a causal relationship between allo-SCT and the development of thyroid autoimmunity.

In patients with post-allo-SCT hypothyroidism, we also observed a higher percentage of transplants from MUD than from haploidentical or sibling donors. In our center, patients treated with allo-SCT from haploidentical donor received PTCY as GVHD prophylaxis, whereas those transplanted from MUD received ATG. Given the dysimmune origin of hypothyroidism, we might speculate a role of ATG in long-term immune control in the setting of HLA disparity. PTCY could give an advantage in immune reconstitution, as suggested by recent reports comparing PTCY vs ATG [27]; however, these results need to be confirmed.

Several studies reported the detrimental effect of ionizing radiation on thyroid function, mediated by direct damage to thyroid follicles, their supporting stroma and to endothelial vascular cells [28]. In our study, considering the whole cohort, the exposure to TBI seems not to impact on thyroid function. Nevertheless, considering only patients with more than 5 years of follow-up after allo-SCT (subgroup 3) hypothyroidism is more frequent in patients who underwent TBI-based conditioning regimen. Despite the small number of patients with hypothyroidism in the subgroup 3, this result likely reflects the relatively long time required for the development of radiation-induced hypothyroidism [29]. We also did not find significant association between cervical RT and post-SCT hypothyroidism, but this result reflects the very low number of subjects who received this treatment. Patients developing hypothyroidism after allo-SCT showed significantly higher pre-transplant TSH levels than patients with preserved thyroid function. Moreover, the ROC curve analysis showed that pre-transplant TSH levels > 1.84 μU/ml may be predictive of hypothyroidism after allo-SCT, with moderate sensitivity (74.1%) and specificity (67.2%). Beyond the exact cutoff found in our population and from a clinical perspective, patients showing higher pre-transplant levels of TSH, but still within the normal range, may have a reduced thyroid functional reserve, resulting in a higher risk of developing hypothyroidism after transplantation and suggesting the usefulness of a closer monitoring of thyroid function after allo-SCT in these subjects. The impact of allo-SCT on thyroid function is also suggested by the higher, even if normal, TSH levels observed in patients who did not developed hypothyroidism when compared with their pre-SCT TSH levels. This observation agrees with the phenomenon described by Somali et al. who documented an abnormal TSH response after thyroid stimulation in about 40% of transplanted patients [9], indicating a compensated impairment of thyroid function.

Our study has some limitations due to its cross-sectional nature that hampers the possibility to exactly define the time when hypothyroidism occurred. Moreover, the relatively short duration of follow-up after allo-SCT likely led to underestimation of total cases of post-transplant hypothyroidism. Finally, it should be noted that one third of our patients were taking immunosuppressive therapy at the time of the study, with possible influence on thyroid function (especially when corticosteroids are administered).

In conclusion, the current study substantiates prior data and highlights hypothyroidism as a major complication of allogeneic stem cell transplantation, with an estimated prevalence of 18%, which seems not to vary with time after allo-SCT. Moreover, our data seem to indicate female gender and higher pre-SCT TSH levels as potential risk factors. Therefore, pre-transplant TSH levels may be a useful biomarker to identify patients who are at risk of developing post-allo-SCT hypothyroidism. Additional multicenter prospective trials are necessary to confirm these data and recommend practice changing guideline.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Research involving human participants and/or animals The Authors confirm that the study was approved by the Ethics Committee of Città della Salute e della Scienza Hospital of Turin (number 179/2020) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Gratwohl A, Pasquini MC, Aljurf M, Atsuta Y, Baldomero H, Foeken L, Gratwohl M, Bouzas LF, Confer D, Frauendorfer K, Gluckman E, Greinix H, Horowitz M, Iida M, Lipton J, Madrigal A, Mohty M, Noel L, Novitzky N, Nunez J, Oudshoorn M, Passweg J, van Rood J, Szer J, Blume K, Appelbaum FR, Kodera Y, Niederwieser D, Worldwide Network for Blood and Marrow Transplantation (WBMT) (2015) One million haemopoietic stem-cell transplants: a retrospective observational study. Lancet Haematol 2(3):e91–100. https://doi.org/10.1016/S2352-3026(15)00028-9. [Erratum in: Lancet Haematol. 2015 May;2(5):e184. PMID: 26687803.Duell, T. Health and Functional Status of Long-Term Survivors of Bone Marrow Transplantation. Ann. Intern. Med. 126, 184 (1997)]
2. Duell T, van Lint MT, Ljungman P et al (1997) Health and functional status of long-term survivors of bone marrow transplantation. EBMT Working Party on Late Effects and EULEP Study Group on Late Effects. European Group for Blood and Marrow Transplantation. Ann Intern Med 126(3):184–192. https://doi.org/10.7326/0003-4819-126-3-199702010-00002
3. Chiodi S, Spinelli S, Ravera G, Petti AR, Van Lint MT, Lamparelli T, Gualandi F, Occhini D, Mordini N, Berisso G, Bregante S, Frassoni F, Bacigalupo A (2000) Quality of life in

244 recipients of allogeneic bone marrow transplantation. Br J Haematol 110(3):614–619. https://doi.org/10.1046/j.1365-2141.2000.02053.x
4. Lee SJ, Logan B, Westervelt P, Cutler C, Woolfrey A, Khan SP, Waller EK, Maziarz RT, Wu J, Shaw BE, Confer D, Horowitz MM, Anasetti C (2016) Comparison of patient-reported outcomes in 5-year survivors who received bone marrow vs peripheral blood unrelated donor transplantation: long-term follow-up of a randomized clinical trial. JAMA Oncol 2(12):1583–1589. https://doi.org/10.1001/jamaoncol.2016.2520.PMID:27532508;PMCID:PMC5145732
5. Khera N, Storer B, Flowers ME, Carpenter PA, Inamoto Y, Sandmaier BM, Martin PJ, Lee SJ (2012) Nonmalignant late effects and compromised functional status in survivors of hematopoietic cell transplantation. J Clin Oncol 30(1):71–77. https://doi.org/10.1200/JCO.2011.38.4594
6. Giaccone L, Felicetti F, Butera S, Faraci D, Cerrano M, Dionisi Vici M, Brunello L, Fortunati N, Brignardello E, Bruno B (2020) Optimal delivery of follow-up care after allogeneic hematopoietic stem-cell transplant: improving patient outcomes with a multidisciplinary approach. J Blood Med 15(11):141–162. https://doi.org/10.2147/JBM.S206027
7. Zavattaro M, Felicetti F, Faraci D, Scaldaferri M, Dellacasa C, Busca A, Dionisi-Vici M, Cattel F, Motta G, Giaccone L, Ghigo E, Arvat E, Lanfranco F, Bruno B, Brignardello E (2021) Impact of allogeneic stem cell transplantation on testicular and sexual function. Transplant Cell Ther 27(2):182.e1-182.e8. https://doi.org/10.1016/j.jtct.2020.10.020
8. Sanders JE, Hoffmeister PA, Woolfrey AE, Carpenter PA, Storer BE, Storb RF, Appelbaum FR (2009) Thyroid function following hematopoietic cell transplantation in children: 30 years' experience. Blood 113(2):306–308. https://doi.org/10.1182/blood-2008-08-173005
9. Somali M, Mpatakoias V, Avramides A, Sakellari I, Smias Ch, Anagnostopoulos A, Papachristou A, Antoniadou A (2005) Thyroid dysfunction in adult long-term survivors after hemapoeitic stem-cell transplantation (HSCT). Horm Metab Res 37(8):494–499. https://doi.org/10.1055/s-2005-870308
10. Farhadfar N, Stan MN, Shah P, Sonawane V, Hefazi MT, Murthy HS, Zou F, Sican X, Hashmi SK (2018) Thyroid dysfunction in adult hematopoietic cell transplant survivors: risks and outcomes. Bone Marrow Transpl 53(8):977–982. https://doi.org/10.1038/s41409-018-0109-5
11. Berger C, Le-Gallo B, Donadieu J, Richard O, Devergie A, Galambrun C, Bordigoni P, Vilmer E, Plouvier E, Perel Y, Michel G, Stephan JL (2005) Late thyroid toxicity in 153 long-term survivors of allogeneic bone marrow transplantation for acute lymphoblastic leukaemia. Bone Marrow Transpl 35(10):991–995. https://doi.org/10.1038/sj.bmt.1704945
12. Medinger M, Zeiter D, Heim D, Halter J, Gerull S, Tichelli A, Passweg J, Nigro N (2017) Hypothyroidism following allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia. Leuk Res 58:43–47. https://doi.org/10.1016/j.leukres.2017.04.003
13. Savani BN, Koklanaris EK, Le Q, Shenoy A, Goodman S, Barrett AJ (2009) 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 Transpl 15(3):377–381. https://doi.org/10.1016/j.bbmt.2008.11.032
14. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C, Burns LJ, Chaudhri N, Davies S, Okamoto S, Seber A, Socie G, Szer J, Lint MT, Wingard JR, Tichelli A (2012) Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Rev Bras Hematol Hemoter 34(2):109–133. https://doi.org/10.5581/1516-8484.20120032
15. Al-Fiar FZ, Colwill R, Lipton JH, Fyles G, Spaner D, Messner H (1997) Abnormal thyroid stimulating hormone (TSH) levels in adults following allogeneic bone marrow transplants. Bone Marrow Transpl 19(10):1019–1022. https://doi.org/10.1038/sj.bmt.1700771
16. Sánchez-Ortega I, Canals C, Peralta T, Parody R, Clapés V, de Sevilla AF, Duarte RF (2012) Thyroid dysfunction in adult patients late after autologous and allogeneic blood and marrow transplantation. Bone Marrow Transpl 47(2):296–298. https://doi.org/10.1038/bmt.2011.54
17. Tauchmanova L, Colao A, Selleri C, De Rosa G, Rotoli B (2006) Thyroid dysfunction after autologous hematopoietic stem cell transplant. Am J Med 119(6):e5-6. https://doi.org/10.1016/j.amjmed.2005.09.017
18. Akirov A, Sawka AM, Ben-Barouch S, Lipton J, Ezzat S (2019) Endocrine complications in patients with GVHD. Endocr Pract 25(5):485–490. https://doi.org/10.4158/EP-2018-0529
19. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datiles MB, Jacobsohn D, Heller T, Kitko CL, Mitchell SA, Martin PJ, Shulman H, Wu RS, Cutler CS, Vogelsang GB, Lee SJ, Pavletic SZ, Flowers ME (2015) National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transpl 21(3):389-401.e1. https://doi.org/10.1016/j.bbmt.2014.12.001
20. Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F, Ciceri F, Cornelissen J, Malladi R, Duarte RF, Giebel S, Greinix H, Holler E, Lawitschka A, Mielke S, Mohty M, Arat M, Nagler A, Passweg J, Schoemans H, Socié G, Solano C, Vrhovac R, Zeiser R, Kröger N, Basak GW (2020) Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. Lancet Haematol 7(2):e157–e167. https://doi.org/10.1016/S2352-3026(19)30256-X
21. Isshiki Y, Ono K, Shono K, Onoda M, Yokota A (2016) Autoimmune thyroid dysfunction after allogeneic hematopoietic stem cell transplant. Leuk Lymphoma 57(5):1227–1229. https://doi.org/10.3109/10428194.2015.1085532
22. Ataca Atilla P, Akkus E, Atilla E, Gokmen N, Civriz Bozdag S, Kurt Yuksel M, Toprak SK, Baskal N, Akan H, Demirer T, Topcuoglu P, Arslan O, Ilhan O, Ozcan M, Beksac M, Gurman G (2020) Thyroid dysfunctions in adult patients after allogeneic hematopoietic stem cell transplantation. Clin Transpl 34(10):e14049. https://doi.org/10.1111/ctr.14049
23. Caturegli P, De Remigis A, Rose NR (2014) Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev 13(4–5):391–397. https://doi.org/10.1016/j.autrev.2014.01.007
24. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE (2018) Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 14(5):301–316. https://doi.org/10.1038/nrendo.2018.18
25. Au WY, Lie AK, Kung AW, Liang R, Hawkins BR, Kwong YL (2005) Autoimmune thyroid dysfunction after hematopoietic stem cell transplantation. Bone Marrow Transpl 35(4):383–388. https://doi.org/10.1038/sj.bmt.1704766
26. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P (2015) Autoimmune thyroid disorders. Autoimmun Rev 14(2):174–180. https://doi.org/10.1016/j.autrev.2014.10.016
27. Battipaglia G, Labopin M, Kröger N, Vitek A, Afanasyev B, Hilgendorf I, Schetelig J, Ganser A, Blaise D, Itälä-Remes M, Passweg JR, Bonifazi F, Finke J, Ruggeri A, Nagler A, Mohty M (2019) Posttransplant cyclophosphamide vs antithymocyte

globulin in HLA-mismatched unrelated donor transplantation. Blood 134(11):892–899. https://doi.org/10.1182/blood.2019000487

28. Jereczek-Fossa BA, Alterio D, Jassem J, Gibelli B, Tradati N, Orecchia R (2004) Radiotherapy-induced thyroid disorders. Cancer Treat Rev 30(4):369–384. https://doi.org/10.1016/j.ctrv.2003.12.003
29. Inskip PD, Veiga LHS, Brenner AV, Sigurdson AJ, Ostroumova E, Chow EJ, Stovall M, Smith SA, Weathers RE, Leisenring W, Robison LL, Armstrong GT, Sklar CA, Lubin JH (2018) Hypothyroidism after radiation therapy for childhood cancer: a report from the childhood cancer survivor study. Radiat Res 190(2):117–132. https://doi.org/10.1667/RR14888.1