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Original article

Hypothyroidism following allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia

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ABSTRACT

Background: Hypothyroidism may complicate allogeneic hematopoietic stem cell transplantation (allo-HSCT); we therefore analyzed risk factors in this study.
Patients and methods: We studied 229 patients with acute myeloid leukemia (AML) who underwent an allo-HSCT between 2003 and 2013 with different conditioning regimens (myeloablative, reduced-intensity, chemotherapy-based, or total body irradiation-based). Thyroid-stimulating hormone (TSH) and free thyroxine levels (fT4) were available in 104 patients before and after allo-HSCT.
Results: The median age at transplantation (n = 104) was 47 (IQR 40–59)], 37 (35.6%) patients were female, and the overall mortality was 34.6% (n = 36). After a median follow-up period of 47 (IQR 25–84) months, overt hypothyroidism (basal TSH > 4.49 mIU/l, FT4 < 11.6 pmol/l) was observed in 4 patients (3.8%) and subclinical hypothyroidism (basal TSH > 4.49 mIU/l, normal fT4) was observed in 20 patients (19.2%). Positive thyroperoxidase (TPO) antibodies were found in 5 (4.8%) patients. A total of 13 patients (12.5%) were treated with thyroid hormone replacement. Acute graft-versus-host disease (aGvHD) ≥grade 2 occurred in 55 (52.9%) and chronic GvHD (cGvHD) in 74 (71.2%) of the patients. The risk of developing hypothyroidism was higher in the patients with repeated allo-HSCTs ($P = 0.024$) and with positive TPO antibodies ($P = 0.045$). Furthermore, the development of overt hypothyroidism was inversely proportional to age ($P = 0.043$). No correlation was found with GvHD, HLA-mismatch, total body irradiation, and gender.
Conclusion: After allo-HSCT, a significant number of patients experience thyroid dysfunction, including subclinical and overt hypothyroidism. Long-term and continuous follow-up for thyroid function after HSCT is important to provide timely and appropriate treatment.

1. Introduction

Acute myeloid leukemia (AML) is one the most common myeloid malignancies, with an overall incidence of 2.5–3.7 per 100,000 inhabitants/year [1–3]. Over the years, hematopoietic stem cell transplantation (HSCT) has been developed as an established treatment for AML [4,5]. The life expectancy of post-HSCT-patients is still low, with the leading causes of HSCT-related deaths being infections, chronic graft-versus-host-disease (cGvHD), secondary malignancies, and respiratory and cardiovascular diseases [6–8]. However, because of the continuous development of HSCT and the decrease in transplant-related mortality, long-term survival has risen significantly. With the improvement in the AML cure rate, the surveillance of long-term survivors has become an important concern [6,9,10].

Previous studies showed that frequent, not disease-related complications after HSCT included cGvHD, mitral and tricuspid regurgitation, cataracts, symptomatic pulmonary changes, sicca syndrome, psychological disorders, and endocrinopathies [11–13]. Overall, the endocrine system is one of the most frequent targeted after HSCT, involving ovarian insufficiency, an increase in follicle-stimulating hormone in men indicating spermatogenesis damage, and thyroid dysfunction. Mostly, thyroid dysfunction is due to low T3 syndrome reflecting the

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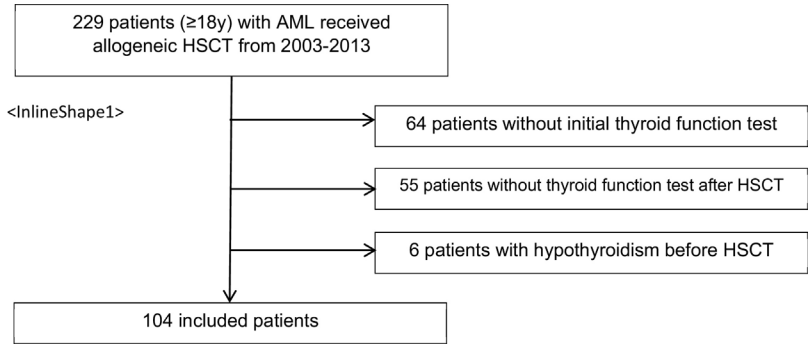
Table 1
Study flow diagram.



general health of the patients; however, the development of chronic thyroiditis, hyper-, and hypothyroidism is frequent [14,15]. Hypothyroidism is one of the most common endocrinopathies occurring after HSCT with a prevalence of 13–25% for subclinical hypothyroidism and 4–11% for overt hypothyroidism [16–18]. Several risk factors, including cGvHD, prolonged immunosuppressive therapy, HLA B35 of the donor, and female donors to male recipients has been described in different patient cohorts [14,16,17], but large long-term studies about hypothyroidism after allo-HSCT for AML are still lacking.

Therefore, we conducted a large retrospective study including patients with AML after receiving an allo-HSCT at the University Hospital Basel with the aim to describe the prevalence and the underlying cause of hypothyroidism and to identify possible risk factors.

2. Patients and methods

This retrospective single-center cohort study was performed according to the regulations of the local ethics committee. Our cohorts met the following inclusion criteria: all patients (1) had AML; (2) had undergone allo-HSCT at our institution between 2003 and 2013; (3) had different conditioning regimens; (4) underwent available thyroid function tests before and after HSCT; and (5) had available data for acute and chronic GvHD. We decided to include only patients with AML in the study and not other hematological malignancies. The reason was to obtain a more homogenous patient population with about the same therapy regimen before HSCT (induction chemotherapy). AML was diagnosed according to the World Health Organization (WHO) 2008 criteria and remission status was defined according to the guidelines of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in AML [19,20]. Acute and chronic GvHD were diagnosed based on clinical symptoms and/or skin, oral mucosa, liver, or gut biopsies and were graded using consensus criteria for acute and chronic GvHD [21,22]. GvHD prophylaxis administered along with the myeloablative conditioning regimens—busulfan (Bu), cyclophosphamide (Cy); cyclophosphamide; total body irradiation (TBI); cyclophosphamide, etoposide, and TBI—was cyclosporine A and methotrexate as well as anti-T-cell globulins (ATGs) in the case of an unrelated donor. In patients with reduced-intensity conditioning (RIC), the GvHD prophylaxis consisted of cyclosporine A, methotrexate, and ATGs in the case of an unrelated donor and in matched related donors ≥40 years old, according to institutional standards (if RIC was fludarabine/busulfan) or cyclosporine A and mycophenolate mofetil (MMF) (if RIC was fludarabine/2 Gy low-dose total body irradiation). Clinical, laboratory (peripheral blood counts), and follow-up data were obtained by reviewing the charts. Thyroid hormones such as TSH and fT4 were measured before and then on a regular basis at least annually after HSCT. Subclinical hypothyroidism was defined as increased TSH (TSH > 4.49 mIU/l) with normal serum fT4 and free triiodothyronine (fT3), while overt hypothyroidism included high TSH and decreased fT4 and fT3 (basal TSH > 4.49 mIU/l, FT4 < 11.6 pmol/l) [23,24]. Thyroid antibodies such as TPO antibodies and thyroglobulin (TG) antibodies were measured only in patients with a thyroid dysfunction.

2.1. Statistical analysis

Discrete variables are expressed as frequency (percentage), continuous Gaussian variables as means with standard deviation (SD), and non-Gaussian variables as medians with interquartile ranges (IQR). Comparisons between groups were made using the chi-squared test, the Mann-Whitney *U* test, and the Kruskal-Wallis test as appropriate. In the multivariate analyses, the following risk factors for thyroid dysfunction were considered: age at transplantation, gender, HLA-mismatch, GvHD, and TBI in the conditioning regimen. Analyses were performed using STATA 12.1, SPSS (SPSS 22.0, Chicago, IL, USA) and GraphPad Prism (Version 6, La Jolla, CA, USA). *P* values less than 0.05 were considered statistically significant.

3. Results

Overall, 229 patients received allo-HSCT after AML from 2003 to 2013 at the University Hospital Basel. In total, 64 patients were excluded due to a lack of initial thyroid function tests and 55 patients had no thyroid function test after the HSCT, mostly due to early mortality after HSCT (survival time 3 (1–4.25) months). Furthermore, 6 patients were diagnosed with hypothyroidism before the allo-HSCT. For the final analysis, 104 patients were included in this study (Table 1).

3.1. Patients' characteristics

The patients' baseline characteristics are shown in Table 2. The median age of all patients (n = 104) at AML diagnosis was 46 years (IQR 39–58) and the age at transplantation was 47 years (39.75–59). Thirty-seven (35.6%) of our patients were female, the average follow-up time was 47 (25–84) months, and the mortality rate was 34.6% (n = 36). Overall, 61 (58.7%) donors were male and 43 (41.3%) were female. Some 13/104 patients had more than 1 allo-HSCT due to AML relapse after the first HSCT.

3.2. Prevalence and cumulative incidence of hypothyroidism

During follow-up, 24 (23.1%) patients developed subclinical (19.2%, n = 20) or overt hypothyroidism (3.8%, n = 4). The median age at diagnosis was 44.5 (39–57.25) years, and 15 patients (62.5%)