Brief report

Thyroid function following hematopoietic cell transplantation in children: 30 years’ experience

Jean E. Sanders,1 Paul A. Hoffmeister,1 Ann E. Woolfrey,1 Paul A. Carpenter,1 Barry E. Storer,1 Rainer F. Storb,1 and Frederick R. Appelbaum1

1Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA

Thyroid dysfunction is a known complication after hematopoietic cell transplantation (HCT) in children with reports involving relatively short follow-up and small patient numbers. This study involves 791 patients less than 18 years of age at HCT at the Fred Hutchinson Cancer Research Center with follow-up from 1969 through 2007. Thyroid dysfunction continued for 28 years after transplantation. Hypothyroidism was the most common abnormality with other abnormalities of hyperthyroidism and thyroiditis. Multivariate analysis showed that thyroid dysfunction was more likely if patients were less than 10 years of age (P < .001), but there was no difference between receiving a total body irradiation or busulfan based regimens (P = .48) compared with cyclophosphamide conditioning alone (P = .008). Thyroid tumors occurred at a median of 9.9 (4.5-22.3) years after HCT and included 13 with papillary carcinoma and 5 with benign adenomas. Children who receive a HCT should be monitored for thyroid abnormalities throughout life.

Introduction

Thyroid dysfunction has been reported after hematopoietic cell transplantation (HCT).1-5 Radiation has been considered the main cause for this and for thyroid malignancies, but in the context of HCT total body irradiation (TBI) has been considered to be the major cause. Relatively little to no thyroid dysfunction has been reported after chemotherapy only preparative regimens for malignancies or severe aplastic anemia.6-8 We have previously described hypothyroidism and compensated hypothyroidism after HCT.1,6 Most studies of thyroid dysfunction after HCT have had relatively short follow-up of 1 to 6 years, but none have shown the various types of thyroid dysfunction that may occur nor described the trajectory of dysfunction over long periods of time. Here we report our experience with thyroid dysfunction and thyroid malignancies over a 30-year period. Results showed that thyroid dysfunction continued to develop for up to 28 years after HCT and that patients receiving busulfan-based regimens have thyroid dysfunction not significantly different from those given TBI-based regimens and significantly greater than regimens containing only cyclophosphamide.

Methods

Patients

We investigated 791 patients who underwent their HCT at the Fred Hutchinson Cancer Research Center (FHCRC) between 1969 and December 31, 2006, were less than 18 years old at HCT, and survived for more than 1 year after HCT. Thyroid function was one of the endocrine systems evaluated in the study of the endocrine function of all pediatric patients. Data collected prospectively according to FHCRC Institutional Review Board–approved protocols 245 and 999 were reviewed. Patients were considered evaluable if they had either thyroid-stimulating hormone (TSH) and T4 or T3 or free T4 testing performed. The study was approved by the Institutional Review Board and informed consent was obtained from the patients’ parents in accordance with the Declaration of Helsinki. Patients included were a median of 9.5 years of age (range, 0.3-17.9) at HCT. A total of 631 received transplants for hematologic malignancies and 160 for nonmalignant hematologic disorders. Sources of hematopoietic cells were bone marrow (n = 714), peripheral blood (n = 49), cord blood (n = 19), and bone marrow and peripheral blood (n = 9). Data were obtained from the FHCRC clinical information database, pretransplantation medical records, transplant flow sheets, long-term follow-up records, and annual contact with referring physicians. Study data were collected through December 31, 2007, and analyzed in April 2008.

Transplantation procedures

The preparative regimens, chosen depending upon diagnosis and the protocols active at the time of transplantation, included full-dose TBI regimens (10.0 Gy single exposure, 12-15.75 Gy fractionated exposure; n = 573), busulfan-based regimens (n = 109), cyclophosphamide only (200 mg/kg; n = 84), and reduced-dose TBI (200-450 cGy; n = 25). TBI was administered from dual Co60 sources from 1969 to June 1999, and after that from 6 megavoltage (MeV) linear accelerator. The transplant donors were either human leukocyte antigen (HLA)–matched or –mismatched family members (n = 547), unrelated marrow, peripheral blood or cord blood donors (n = 196), or autologous donors (n = 48).

Definitions

Primary hypothyroidism was present if TSH was elevated concomitant with normal or low T4 or T3 or free T4. Hyperthyroidism was defined as low or normal TSH and elevated T4 or T3. Central hypothyroidism was considered when TSH was normal and T4 or free T4 was low.
Regimen

What to expect long term.1-6,8,9 Types of abnormalities seen after transplantation, but no studies to date have given a picture of Thyroid dysfunction has been reported during the first several years after transplant was estimated by standard methods. Thyroid dysfunction was defined as the first occurrence of a thyroid function abnormality based on laboratory studies. Patients were censored when they developed thyroid malignancy or goiter. All others were censored as of the date of last contact. Analysis of risk factors

Cox regression analysis was used to evaluate univariate and multivariate associations of pretransplantation risk factors with development of thyroid dysfunction. The cumulative incidence of thyroid function abnormalities after transplant was estimated by standard methods. Thyroid dysfunction was defined as the first occurrence of a thyroid function abnormality based on laboratory studies. Patients were censored when they developed thyroid malignancy or goiter. All others were censored as of the date of last contact.

Results and discussion

Thyroid dysfunction has been reported during the first several years after transplantation, but no studies to date have given a picture of what to expect long term.1-6,8,9 Types of abnormalities seen after HCT in the present study included primary hypothyroidism (compensated, n = 125 and uncompensated, n = 11), central hypothyroidism (n = 74), unclassifiable hypothyroidism due to lack of complete data (n = 28), hyperthyroidism (n = 23), and Hashimoto thyroiditis (n = 4). Hypothyroidism is the most common type of thyroid dysfunction as 30% developed some type of hypothyroidism at various times after HCT, and among these 20% were treated with thyroid hormone. Other studies have reported hypothyroidism occurring in 0% to 58% of patients. The wide variability among studies likely reflects the relatively short follow-up period and the relatively small number of patients included in the separate investigations available for evaluation.

Multivariate analysis in the present study showed that the preparative regimen (P = .008), patient age (P < .001), and disease type were the most significant factors associated with developing abnormal thyroid function after transplant (Table 1). Specifically, regimens using only cyclophosphamide appeared to have a lower risk of thyroid dysfunction, whereas regimens containing busulfan and TBI appear to increase risk. These results are similar to results reported by the Japanese and the French groups with smaller numbers of patients.10,11 Patient diagnosis of a hematologic malignancy also was significant, with Hodgkin lymphoma carrying the greatest significance (P < .001). The lower risk among patients who received transplants for aplastic anemia likely reflects the use of cyclophosphamide in the preparative regimen. Patients receiving busulfan-based chemotherapy preparative regimen had risk factors that were not significantly different from those who received a TBI-based preparative regimen (P = .48; Figure 1A). Younger patients had a higher risk of subsequent development of thyroid dysfunction (Figure 1B). The observation of impact of patient age is not different from what has been observed previously among a smaller number of patients.11 The observation of approximately 30% probability of thyroid dysfunction at 10 years after transplantation is lower than that observed by Berger et al, who reported a higher probability of thyroid dysfunction at 10 years.10 In the present study, we observed that thyroid dysfunction continues to occur as long as 28 years after HCT after TBI and as long as 10 years after busulfan-cyclophosphamide (BUCY) preparative regimens.

Thyroid malignancies have been previously reported after TBI-based regimens for long-term survivors of HCT.12,13 In the present study a total of 18 patients (0.02%) developed thyroid tumors, not all of which were malignant. Eleven patients with normal thyroid function developed

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. patients</th>
<th>Percentage abnormal*</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Overall P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CY + TBI†</td>
<td>538</td>
<td>32</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUCY/BU MELTT</td>
<td>108</td>
<td>23</td>
<td>0.84 (0.5-1.4)</td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>BU + TBI‡</td>
<td>61</td>
<td>56</td>
<td>1.7 (1.1-2.5)</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>CY</td>
<td>84</td>
<td>7</td>
<td>0.32 (0.1-0.9)</td>
<td>.03</td>
<td>.008</td>
</tr>
<tr>
<td>Local radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>761</td>
<td>29</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes§</td>
<td>30</td>
<td>57</td>
<td>1.82 (1.0-3.2)</td>
<td>.05</td>
<td>.05</td>
</tr>
<tr>
<td>Age at HCT, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 or more</td>
<td>372</td>
<td>25</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td>419</td>
<td>35</td>
<td>1.7 (1.3-2.2)</td>
<td>.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmalignant</td>
<td>160</td>
<td>11</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloid</td>
<td>314</td>
<td>35</td>
<td>2.92 (1.5-5.8)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Lymphoid</td>
<td>302</td>
<td>33</td>
<td>2.86 (1.4-5.8)</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Hodgkin</td>
<td>15</td>
<td>73</td>
<td>15 (5.8-38)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; TBI, total body irradiation; BU, busulfan; CY, cyclophosphamide; MEL, melphan; TT, thiopeta; and HCT, hematopoietic cell transplantation.

*Percent of patients with abnormal thyroid function.
†Cyclophosphamide with or without other chemotherapy agents.
‡Includes 18 BUCY + TBI patients, 3 BU + TBI, 40 BUCY for HCT no. 1, and CY/TBI for HCT no. 2.
§Local radiotherapy included spinal, mantle, and total lymphoid irradiation.

Figure 1. Cumulative incidence of developing thyroid dysfunction after HCT in childhood. (A) Cumulative incidence of developing thyroid dysfunction after hematopoietic cell transplantation divided by type of preparative regimen received: TBI, busulfan, busulfan + TBI, or cyclophosphamide only. (B) Cumulative incidence of developing thyroid dysfunction after hematopoietic cell transplantation divided by patient age. The bottom curve represents patients who received transplants between 10 and 17 years of age and the top curve represents patients who received transplants between 0 and 9 years of age.

Table 1. Multivariate analysis: thyroid dysfunction
thyroid tumors (9 papillary carcinoma and 2 benign adenoma). 7 patients with abnormal thyroid function developed thyroid tumors (4 papillary carcinoma and 3 benign adenoma). All 18 thyroid tumors occurred after TBI-based regimens at a median of 9.9 years (range, 4.5-22.3 years). All thyroid tumors were treated with thyroidectomy and replacement thyroid hormone. All of these patients survive. These data demonstrate that patients who have received a hematopoietic cell transplant must be followed for life for the development of thyroid function abnormalities and the development of thyroid tumors. We recommend that thyroid function studies be performed annually and consideration be given to incorporation of thyroid ultrasound in annual evaluations beginning several years after HCT.

Acknowledgment

This work was supported by the National Cancer Institute (CA 018029, HL 36444, CA15704, and CA78902).

Authorship

Contribution: J.E.S. designed research, saw patients in the study, and wrote the paper; P.A.H. collected research data and assisted with data analysis; A.E.W. and P.A.C. assisted in seeing patients entered into the study; B.E.S. performed the multivariate and univariate analyses; R.F.S. designed the preparative regimens used for some of the patients with nonmalignant diseases and F.R.A. designed the preparative regimens used for some of the patients with leukemia.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Jean E. Sanders, MD, Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Suite D5-280, Seattle, WA 98109; e-mail: jsanders@fhcrc.org.

References

Thyroid function following hematopoietic cell transplantation in children: 30 years' experience

Jean E. Sanders, Paul A. Hoffmeister, Ann E. Woolfrey, Paul A. Carpenter, Barry E. Storer, Rainer F. Storb and Frederick R. Appelbaum

Updated information and services can be found at:
http://www.bloodjournal.org/content/113/2/306.full.html

Articles on similar topics can be found in the following Blood collections
- Brief Reports (1928 articles)
- Clinical Trials and Observations (4509 articles)
- Free Research Articles (4400 articles)
- Transplantation (2210 articles)

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml