

## ENDOCRINE COMPLICATIONS OF PEDIATRIC STEM CELL TRANSPLANTATION

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### 1 ABSTRACT

Abnormalities of endocrine function and growth are common following stem cell transplantation in the pediatric/adolescent population. Impaired linear growth and adult short stature are associated with younger age at transplant, use of TBI and prior cranial irradiation, and development of chronic GvHD. Primary hypothyroidism is the most common abnormality of the thyroid and is observed in 10-28% of cases following fractionated TBI. Autoimmune hyperthyroidism has also been described post-stem cell transplant and most often results from adoptive transfer of abnormal clones of T or B cells from donor to recipient. Gonadal dysfunction is extremely prevalent and includes oligo-azoospermia in the majority of males treated with TBI, and primary ovarian failure in most women treated with TBI or Busulfan/Cyclophosphamide. Leydig cell function, however, is retained in most males treated with standard forms of cytoreduction. Many patients demonstrate reduced bone mineral density and are at risk of developing osteoporosis in the future.

### 2 INTRODUCTION

Recent advances in bone marrow/stem cell transplantation (eg, use of unrelated and mismatched donors, utilization of mobilized stem cells from peripheral blood and stem cells from placental cord blood) have resulted in broadened indications for stem cell transplantation, while improvements in supportive care have reduced the risk of peritransplant mortality (1). Thus, there is a steadily increasing pool of children who will become long-term survivors of pediatric stem cell transplantation. These individuals are at risk of developing

a variety of delayed toxicities owing both to their treatment exposures and as a consequence of graft versus host disease (GvHD).

The endocrine organs are especially prone to injury from radiotherapy and chemotherapy. Endocrine abnormalities are, in fact, the most prevalent late effects observed in survivors of stem cell transplantation; approximately 50% of survivors followed long-term will develop one of several endocrinopathies. This overview focuses on the late endocrine disturbances that are most commonly observed following successful stem cell transplantation for the treatment of childhood acute leukemias and aplastic anemia.

#### 2.1. Growth and hypothalamic-pituitary function

Impaired linear growth following bone marrow/stem cell transplantation is likely due to the interaction of a multitude of factors. The most important of these factors include patient characteristics (eg, young age), treatment variables (eg, prior cranial irradiation, total body irradiation (TBI)), and post-treatment complications such as chronic GvHD (2).

Children treated with high-dose chemotherapy alone appear to grow normally and most continue to grow along their pre-transplant height centile. Thus, children treated with cyclophosphamide for aplastic anemia (3) as well as those treated with a busulfan-containing regimen for a hematologic malignancy (4-6) appear to grow normally, so long as they do not develop a significant complication (eg, GvHD, liver dysfunction) post-transplant.

**Table 1.** Risk Factors for Impaired Growth

<b>Patient Factors</b>	Young Age		
<b>Treatment Factors</b>	Prior Cranial RT Preparative Regimen	TBI vs. Chemotherapy Single Fraction vs. Fractionated TBI	
<b>Complications</b>	GH Deficiency		

Although the data are limited, recent findings suggest that final height is unaffected in children who receive busulfan/cyclophosphamide as their pre-transplant conditioning (7).

Treatment of aplastic anemia with cyclophosphamide plus total lymphoid irradiation (TLI) is associated with some decrease in growth. One study that examined growth after single dose TLI (750 cGy) demonstrated a small loss in height which was statistically significant only at year three post-bone marrow transplant (8).

In contrast, severe growth impairment and reduced final height are common following bone marrow/stem cell transplant for hematologic and solid malignancies. Interpretation of the available data has been difficult due to the different preparative regimens employed at different centers, the heterogeneity of diagnostic groups, and the relatively small number of subjects studied at most centers. Nonetheless, certain risk factors for poor linear growth and adult short stature have been noted consistently by most investigators (1, 7, 9) (Table 1).

In a large series reported from Seattle, Sanders *et al* noted that following TBI for leukemia or lymphoma all subjects experienced a decrease in their growth rate (3). Growth was more impaired in those with chronic GvHD and in those treated with single dose (920-1000 cGy) TBI compared to those who received fractionated irradiation (200 cGy to 225 cGy once daily for 6-7 days). Most subsequent reports on the growth of children after stem cell transplant indicate smaller losses in height in those treated with fractionated TBI compared to those treated with single dose irradiation (10, 11), despite the fact that the total dose of irradiation is higher in patients treated with fractionated TBI. Interestingly, some (11, 12), but not all (13), workers have observed disproportionate growth following both single fraction and fractionated TBI, with spinal growth being more impaired than growth of the legs.

Additionally, prior cranial irradiation (CRT) has emerged as an extremely important determinant of poor growth after transplantation, regardless of the type of preparative regimen administered (11, 12, 14-16). In an analysis of 72 children treated at Memorial Sloan-Kettering Cancer Center for acute leukemia after conditioning with hyperfractionated TBI (125 cGy repeated 3 times per day for 4 days), we observed that patients treated with previous cranial irradiation experienced more than twice the decrease in height as those who had not received CRT prior

to transplantation (16). Similarly, Cohen *et al* (7) found the mean final height z-score of children treated with both CRT and fractionated TBI to be -1.69, compared to a z-score of -0.98 for those treated with fractionated TBI but no prior CRT.

The growth retardation that can occur after stem cell transplant would appear to result from a variety of insults. A variable but high incidence of growth hormone (GH) deficiency (inadequate responses to pharmacologic stimuli as well as reduced endogenous GH secretion) has been observed in the post-transplant period (3, 13, 15, 16). It is important to note, however, that establishing a diagnosis of GH deficiency is complicated in children treated with TBI. The results of provocative testing may not be reproducible (12) and the plasma concentrations of the surrogate markers insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) are not reliable indices of GH status after radiation to the brain (13, 17). The poor correlation between the results of GH testing and the growth of many of these children suggests that additional factors such as radiation-induced skeletal dysplasia (18) play an important role in the disturbed growth that can be seen following transplant.

The response to GH treatment has been reported in a limited number of patients and the results have been variable. While some authors have observed only stabilization in height percentiles without evidence of catch-up growth on GH treatment (11, 19), we and others have noted catch-up growth in some subjects treated with GH (15, 16). Some of these differences might be due to the fact that younger patients and those exposed to fractionated, as opposed to single dose TBI, are likely to respond better to GH therapy.

Aside from the abnormalities of GH secretion noted above, the remainder of the hypothalamic-pituitary axis appears largely unaffected following stem cell transplantation. True precocious puberty has been recorded in children treated at a young age with CRT, followed later by a transplant with TBI-based cytoreduction (20).

### 2.1.1. Thyroid dysfunction

A spectrum of thyroid abnormalities has been described among long-term survivors of bone marrow/stem cell transplant. Therapy-induced primary hypothyroidism, autoimmune thyroid disease, and differentiated thyroid carcinoma have all been reported following transplant.

### 2.1.2. Therapy-induced primary hypothyroidism

The incidence of primary thyroid dysfunction has varied greatly from series to series, owing to differences in treatments delivered and the duration of follow-up. The overall incidence of hypothyroidism has been greater following single dose irradiation (23-73%) compared to that seen after fractionated radiotherapy (10-28%) (21-25). Moreover, the longer the follow-up time, the higher the incidence of impaired thyroid function. In a recently published analysis of thyroid function in 139 patients who had received hyperfractionated irradiation (ie, multiple fractions of radiation given daily for several days) for a

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**Table 2.** Clinical Characteristics of Subjects with Hyperthyroidism

Case	1	2	3
Sex	M	M	F
Diagnosis	CML	ALL	AML
Age BMT (years)	16	18	15.5
BMT	Conv	T-Depleted	Conv
	Bu/Cy	Thio/Cy/TBI	Bu/Cy
Interval (mos)	26	50	60

bone marrow transplant at our center (24), 21 patients (15.1%) became hypothyroid after a median follow-up period of 6.2 years. Hypothyroidism developed a median of 49 months (11-88) after bone marrow/stem cell transplant, considerably later than recorded following single dose irradiation. The majority of patients develop a mild, compensated primary hypothyroidism that is often transient and may resolve spontaneously. We and others have also observed a small number of patients who have developed mildly elevated TSH levels following cytoreduction with busulfan and cyclophosphamide (6, 24, 26).

### 2.1.3. Autoimmune thyroid disease

Several case reports have documented the occurrence of autoimmune thyroid disease in the recipients of a bone marrow/stem cell transplant (27). At our center, we recently diagnosed three cases of autoimmune hyperthyroidism that developed following bone marrow transplantation. The clinical characteristics and treatment variables for the three subjects are summarized in Table 2. Two of the individuals received conventional transplants following cytoreduction with busulfan/cyclophosphamide, whereas the third received a T-cell depleted transplant after treatment with a TBI-containing regimen.

Hyperthyroidism developed 26-60 months post-transplant. Two of the patients presented with unexplained weight loss, while the other was asymptomatic and was picked-up on routine screening of thyroid function performed during a follow-up visit to our clinic. All three had suppressed plasma concentrations of TSH, raised levels of T4 and/or T3, and evidence of thyroid autoimmunity; two of the three had markedly elevated levels of antibodies to the TSH receptor, the antibody which is responsible for the development of Graves' disease (Table 3). Studies performed on the blood of the three donors (two donors were siblings, one was unrelated) revealed that all three had elevated levels of antibodies to the TSH receptor but normal TSH levels (Table III). These data are consistent with the hypothesis that the patients' thyroid disorder was due to adoptive transfer of abnormal clones of T or B cells from donor to recipient (27, 28). Two of our patients required treatment with radioactive iodine to correct their hyperthyroidism, while the third patient's thyroid hyperfunction resolved spontaneously over a six month period of time.

### 2.1.4. Thyroid carcinoma

Radiation to the thyroid gland is a known risk factor for the subsequent development of thyroid neoplasms, both benign and malignant (29, 30). Among our cohort of bone marrow/stem cell transplant survivors, two

female subjects have been diagnosed with differentiated carcinoma of the thyroid, 8.6 and 10.9 years post-TBI. Similar cases have been described at other centers (31). Since the latency period between radiation and the appearance of thyroid neoplasms is often prolonged, the number of affected individuals will almost certainly increase over time.

### 2.1.5. Gonadal and reproductive function

#### 2.1.5.1. Males

Young boys and adolescent males who receive standard dose cyclophosphamide alone (200 mg/kg) as therapy for aplastic anemia appear to retain normal Leydig cell function; the vast majority are reported to have normal plasma concentrations of LH and testosterone and to enter and progress normally through puberty. Evidence of germ cell (ie, cells that produce sperm) damage, however, has been reported following this therapy and may be more common in those males treated during or after puberty compared to males treated prior to the onset of puberty. Sanders and colleagues report that the plasma concentrations of FSH remain normal in most boys who are now pubertal but were treated before puberty, whereas FSH levels are increased in nearly half the males who were treated during or after puberty (21). Nonetheless, semen analyses have been normal in approximately two-thirds of the males and a sizeable number of males, including two who were prepubertal at transplant, have fathered normal children after treatment with high-dose cyclophosphamide (21, 32).

Although the data are limited, Leydig cell function appears to be preserved in most males treated with the combination of busulfan and cyclophosphamide (6, 26). Most of these young men do appear to sustain damage to their germinal epithelium but the ultimate effect of this treatment on male fertility is currently not known

Males treated with TBI-based preparative regimens, both single dose and fractionated, generally retain their ability to produce testosterone regardless of their age at treatment (3, 21, 22). All fourteen evaluable males treated before puberty with 1375-1500 cGy hyperfractionated TBI plus a 400 cGy testicular boost at our institution have entered puberty spontaneously and have manifested normal secondary sexual characteristics (20). While the majority demonstrates age-appropriate plasma concentrations of testosterone, a third of the patients' baseline levels of LH are raised. We have found very similar data in our males treated after the onset of puberty, in keeping with the previous observation that Leydig cell function is preserved when the total dose of radiotherapy to the testis is <2000 cGy (33). In contrast, many males who have received testicular irradiation (eg, 2000-2400 cGy) before coming to transplant experience testicular failure and require androgen replacement therapy. Germ cell dysfunction is present in essentially all males treated with TBI (32). The vast majority of subjects will have increased plasma levels of FSH as well as reduced testicular volume, indices that correlate with impaired spermatogenesis. Azoospermia is the rule for patients studied in the first few years after treatment with TBI. Recovery of germ cell function

**Table 3.** Thyroid Data in Hyperthyroid Subjects and Their Donors

	Case			Donor		
	1	2	3	1	2	3
<b>TSH</b> (0.5 – 5.7)	<0.05	0.06	<0.05	2.7	0.9	2.1
<b>Free T4I</b> (3.6 – 14)	13.9	9.8	27.3	-	-	-
<b>T3</b> (70 – 140)	325	166	352	-	-	-
<b>TSHRab</b> (<10)	9	48	37	11	14	12
<b>ATA</b> (0 – 10)	7200	844	900	184	28	0
<b>APA</b> (0-5)	750	1500	760	50	0	0

TSHR ab = TSH receptor antibody; ATA = antithyroglobulin antibody; APA = Anti-peroxidase antibody

has occurred rarely and primarily following single dose irradiation (34). A few men have been reported to father a child following TBI (32). A sperm analysis is the only test that can establish whether or not a young adult survivor has the capacity to produce viable sperm.

#### 2.1.5.1. Females

Following transplant for aplastic anemia with high-dose cyclophosphamide, ovarian function has remained normal in females treated both prior to as well as after the onset of puberty (21, 35). Sanders *et al* (32) have observed a number of pregnancies and normal offspring in their cohort treated with cyclophosphamide alone. Data from patients treated with high-dose alkylating agents for other indications does suggest, however, that these subjects may be at increased risk of an early menopause as they reach the third decade of life (36).

Females treated with busulfan and cyclophosphamide are at very high risk of developing ovarian failure (6, 26, 2). This has been observed in patients treated before and after pubertal development, is characterized by menopausal levels of LH and FSH, delayed or arrested puberty, and amenorrhea. Recovery of function has been recorded only rarely but the follow-up time has been relatively brief for most of the patients. The majority of young girls treated with the combination of busulfan and cyclophosphamide will require long-term hormonal replacement therapy.

The outcome of ovarian function following TBI appears to be determined to a large extent by the age of the patient at the time of irradiation (37). Our data (20) as well as the data of others (21, 38) indicate that approximately 50% of prepubertal girls given fractionated TBI will enter puberty spontaneously and achieve menarche at a normal age. While plasma gonadotropins have been elevated in up to two-thirds of these patients early after transplant, normalization of the plasma concentrations of LH and FSH can occur over time (20). Ovarian failure is seen in essentially all patients who are greater than age 10 years at the time they are treated with TBI (20, 35, 37, 38). Patients require hormonal support in order to achieve normal sexual development and to maintain normal menstruation. Recovery of ovarian function has been documented in a small number of women who have received TBI (32).

In a recent series from Seattle, among the girls who were treated with TBI when they were prepubertal, all five pregnancies ended in spontaneous abortions (32). For women treated with TBI at an older age, the small number of pregnancies were associated with an increased risk of preterm deliveries and delivery of low birth weight infants (32). The infants, however, did not demonstrate an excess of congenital anomalies.

#### 2.1.6. Osteoporosis

Survivors of pediatric stem cell transplant appear to be at increased risk for the development of reduced bone density in later life (39-41). Both the therapies employed to treat these malignancies as well as a variety of treatment-related complications appear to interfere with normal bone accretion. Risk factors for reduced bone mineral density in survivors of stem cell transplant include treatment with glucocorticoids for chronic GvHD (42), prior cranial irradiation (a surrogate for GH deficiency) (43), and sex hormone insufficiency (39). Subjects deemed at high risk for the development of osteoporosis should undergo periodic bone density studies. Preventive measures (eg, supplementation with calcium and vitamin D, smoking cessation, weight bearing exercise) should be encouraged in all individuals with low or borderline bone mineral density. Therapeutic interventions (eg, sex hormone therapy, GH replacement, bisphosphonates) may prove beneficial for those with abnormally reduced bone density, but long-term follow-up data are currently not available.

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