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ORIGINAL ARTICLE

Endocrinological late complications after hematopoietic SCT in children

A Cohen[1], AN Békássy[2], A Gaiero[1], M Faraci[3], S Zecca[1], A Tichelli[4,5] and G Dini[3], on behalf of the EBMT Paediatric and Late Effects Working Parties

[1]*Department of Pediatrics, University of Genova, San Paolo Hospital, Savona, Italy;* [2]*Pediatric HSCT Program, University Hospital, Lund, Sweden;* [3]*Department of Hematology-Oncology, Gaslini Children's Hospital, Genova, Italy and* [4]*Division of Hematology, University Hospital, Basel, Switzerland*

The main challenge for a pediatric hemato-oncologist today is to obtain a cure for the sick child with the minimum of treatment-related complications. Children on their way to achieving adulthood face many risks after hematopoietic SCT (HSCT). Continuous follow-up includes assessment of organ function, focus on vaccinations and screening for secondary malignancies. Updated treatment protocols are already adjusted according to the knowledge obtained on late effects, and the potential risks for complications are well balanced with expected benefits hopefully resulting in decreased potential risk for organ damage but still maintaining an unchanged or improved survival rate. Recent developments on pre-HSCT regimens, such as the introduction of new anticancer regimens and immunosuppressive agents will hopefully contribute to minimize the frequency and the severity of late complications. Knowledge about increased risk for long-term complications due to cancer therapy and pre-HSCT preparative regimens should encourage each caring physician to stick to follow-up protocols and treatment guidelines not only to improve the survival rate of transplanted children but also to improve their quality of life. To achieve adulthood by maintaining cognitive ability and psychosocial skills is the highest goal for an individual to become a competent member of a society. This review of late endocrine complications after HSCT focuses on growth, pubertal development, thyroid disorders and glucose metabolism in long-term survivors.
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Introduction

An expanding population of long-term surviving children after hematopoietic SCT (HSCT) are patients treated for both malignant and non-malignant diseases. The historical majority of former patients with leukemia and hemoglobinopathies includes an increasing cohort of children who need to grow up. The survival rate for cancer patients has improved dramatically during recent decades. It is estimated that long-term survivors represent 1 in 900 people aged 15–44 years in the US.[1–3] New indications are accepted for transplantation (such as Wiskott–Aldrich syndrome, severe combined immunodeficiency, X-linked hyper-IgM), and the alternative donor pool, such as the employment of umbilical cord blood or unrelated HLA-matched stem cells, has been increased. In combination with improvements of supportive care, they all further increase the number of survivors. Careful follow-up is needed to improve the quality of life for this new cohort of 'former' patients in an attempt to identify late complications and treat in due course the problems related to previous therapy.[4–9]

The endocrine system, together with the central nervous and the immune systems, is responsible for the constant maintenance of homeostatic mechanisms that regulate and stabilize the internal environment, and also makes possible adaptations to extreme environmental changes. Hormones are specifically involved in reproduction, growth and development, and energy metabolism (production, storage and utilization). It is necessary to remember that the specific effect of HSCT on the endocrine system is considered separately in this review having in mind the treatment preceding and following transplantation for the primary disorder being the hematological malignant or non-malignant disease, solid tumor or inborn errors of metabolism. Cancer treatment in general and chemo- and radiotherapy in particular causes damage intentionally to a rapidly dividing cancer cell, but it does so unintentionally to those in the endocrine organs as well.

This review highlights the late endocrine complications in long-term survivors treated with HSCT during childhood, with particular emphasis on growth, gonad and thyroid activity, and carbohydrate metabolism. Unaware of signs and symptoms of organ failure during childhood,

Correspondence: Professor A Cohen, Department of Pediatrics, San Paolo Hospital, Savona 17100, Italy.
E-mail: a.cohen@asl2.liguria.it
[5]Chairman of the EBMT Late Effects Working Party.

the professionals not used to routinely seeing HSCT individuals must not misinterpret or fail to diagnose the late effects that contribute to the patients' impaired quality of life.

Growth

Growth is a complex process that involves all body systems (hormones, bones, muscles, adipose tissue and so on). The capacity for growth is genetically determined at conception, but continued interactions between hormonal secretion, nutrition and acute or chronic diseases influence the expression of such genes. The synergistic action of growth hormone (GH) and sex steroids during puberty induces growth spurt during adolescence contributing to pubertal growth.

Growth impairment in children who received HSCT is due to a complexity of factors. Radiation therapy has been recognized as one of the most important factors contributing to growth failure, both as a result of central damage to cranial neuroendocrine organs (hypothalamus and pituitary) and peripheral lesions of bones, cartilage and epiphyseal growth plate.[10–13] Furthermore, an associated gonad failure with delayed puberty, thyroid disorders and long periods of cortisone treatment can also have a considerable negative impact on growth.

A study conducted by the EBMT Late Effect Working Party on 181 patients, who received HSCT during childhood and who had reached their final height,[10] showed that 80% of patients achieved final adult height values within the normal range for the healthy population (above the third percentile). Irradiation (cranial and TBI) was the leading cause for decreased final height achievement. Fractionation of the irradiation dose delivered improved final height outcome. The loss of height was more severe in boys compared with girls and also in children who were transplanted at a younger age. Patients who were conditioned with chemotherapy only (CY or the combination of BU and CY) achieved final height values that were comparable with their predicted and genetic heights. Similar results were observed by Afify *et al*.[11] in a group of 23 children with AML who received pre-HSCT conditioning therapy with BUCY and showed no significant growth impairment.

Chemaitilly *et al*.[12] recently showed that the final height achieved in patients who received hyperfractionated TBI (total dose of 1375–1500 cGy) was similar to that in the group of patients who received standard fractionated TBI and that the main reduction in height in this group of patients was due to a reduction in sitting height, suggesting a more pronounced injury to the spinal column growth. A similar change in body proportions with decreased values of sitting height was also observed by Bakker *et al*.[13] in a group of 75 children who received TBI during pre-HSCT conditioning. In that study, a reduced pubertal growth and blunted pubertal growth spurt was also reported as a contributing factor for growth impairment in patients after HSCT.

Growth hormone deficiency has been incriminated by some authors as the leading cause of growth impairment in children who received HSCT. Nonetheless, data on impaired GH secretion in this group of children are contradictory and vary widely from 20 to 85%. Sanders *et al*.[14] showed that GH therapy in children who received HSCT before the age of 10 years and in those who have developed GH deficiency was associated with a significant improvement of final height. Nevertheless, GH therapy failed to improve growth in the group of older children with GH deficiency.

Data from the Childhood Cancer Survivor Study showed that the administration of GH to 361 children was not associated with increased risk for relapse of the original malignancy but was significantly associated with the development of secondary malignancies in 15 patients.[15] In view of the fact that this group of patients after HSCT is already at high risk for secondary tumors,[16,17] some concern is raised and caution is recommended in selecting patients as candidates for GH treatment as not all patients will respond to GH treatment, and data on the safety of GH therapy in survivors of childhood cancer are still limited and somewhat contradictory.

Growth and growth velocity measurements should be performed at 6-month intervals during childhood. Any decrease in the standard deviation score from age- and sex-expected means should alert the physician to start with a complete clinical and laboratory investigation to identify the cause of growth impairment.

Sexual maturation and puberty

Puberty is a physiological stage of transition from childhood to adulthood during which the maturational, hormonal and growth process lead to reproductive capability manifested by spermatogenesis in the male and ovulation in the female. The process of puberty results in the development of secondary sexual characteristics, changes in fat distribution, skeletal and somatic growth, and psychological changes. The timing of the onset of puberty in girls is normally from 8 to 13 years and is manifested by the appearance of breast buds, whereas boys start puberty at age 9–14 years with increased testicular volume (>4 ml). To accomplish pubertal development, a delicate balance among hypothalamic luteinizing hormone-releasing hormone, pituitary gonadotropins (luteinizing hormone and follicle-stimulating hormone) and sex steroid hormone secretion, together with increased target organ responsiveness is essential.

Gonad failure in patients who received HSCT has been mainly associated with irradiation therapy (TBI) and the use of BU during the conditioning regimen.[18–20] Gonadal damage caused by these agents induces hypergonadotropic hypogonadism in the majority of patients, and recovery is rare. The use of cranial irradiation (18–42 Gy), given to children with ALL to prevent meningeal leukemia, can potentially damage the hypothalamic pituitary region as well, resulting in gonadotropin-releasing hormone deficiency, especially in patients who received doses >30 Gy. In some rare cases, mostly girls who received cranial radiation in doses >24 Gy, precocious puberty was observed.

Males

Testicular damage is drug-specific and dose-related. High-dose chemotherapy and bilateral testicular direct irradiation used in pre-HSCT conditioning regimens may cause permanent damage to the germinal epithelium in the majority of men, with subsequent reduced spermatogenesis (azoospermia or oligospermia) and increased basal follicle-stimulating hormone concentrations.[21] Testicular Leydig cells are more resistant to irradiation and cytotoxic agents but some degree of damage is usually found,[22] resulting in slightly increased luteinizing hormone concentrations and normal to below normal testosterone levels (compensated hypergonadotropic hypogonadism). The majority of these children will spontaneously start and accomplish their sexual maturation with no need for hormonal replacement therapy. Nonetheless, testicular volume will remain below normal standards for the adult population.

The preparative regimen including BU 16 mg/kg and CY (200 mg/kg) before the transplant procedure was associated with damage in the testicular function as reported by Sanders *et al*.,[19] with 83% of patients (38 out of 46) defined by an altered luteinizing hormone, follicle-stimulating hormone and testosterone levels with no evidence of sperm production.

It seems, in contrast to the female gender, that the age and pubertal status of males at the time of chemo- or radiotherapy does not have any impact on the rate of testicular dysfunction. Hormone replacement therapy with testosterone is reserved only for those patients who have an extensive damage to the Leydig cell activity and who are not able to start and accomplish the pubertal process.

Apart from the problems related to cryostorage and thawing, sperm banking still remains the only method for preserving fertility in adults and sexually mature adolescent male patients undergoing HSCT. In the pediatric setting, however, this method is impossible to apply in a prepubertal child. Furthermore, the pretreatment semen quality in patients with cancer is poor. Newer technologies such as testis sperm extraction may be an option as demonstrated for male survivors of germ cell tumors who were unable to bank sperm and had post-chemotherapy non-obstructive azoospermia. Further advanced micromanipulative techniques, such as intracytoplasmic sperm injection, may be capable of using small and even poor quality cryopreserved previously extracted sperms for successful fertilization.

Females

The magnitude of ovarian damage in females who received HSCT is drug-specific and dose-related. Furthermore, the age at exposure has a fundamental role as older women need lower doses of irradiation and/or alkylating agents to produce irreversible ovarian failure, probably due to the physiologic decline in the number of follicles with increasing age.

Increased gonadotropin levels associated with low estradiol concentrations, and failure to start puberty (appearance of breast buds) or to accomplish puberty or to achieve sexual development spontaneously, are signs of ovarian failure in girls who received cancer treatment during the prepubertal phase. Girls who already had menstrual cycles before the commencement of cancer treatment will have amenorrhea in case of ovarian failure.

The irradiation dose needed to induce permanent damage in 50% of oocytes in humans (LD_{50}) is <2 Gy.[23] Permanent ovarian failure can be induced by radiation doses of 6 Gy in the adult female and more than 10 Gy in girls treated during childhood and adolescence. The usual doses of TBI used during pre-HSCT conditioning therapy induce ovarian damage in almost all girls older than 10 years and in only half of the girls below the age of 10 years.

Conditioning protocols that include BU are also associated with ovarian failure in almost all the cases,[19] and spontaneous recovery is extremely rare. CY also induces ovarian failure in HSCT female survivors though to a lesser extent. Female survivors of childhood cancer who have maintained normal ovarian activity after chemotherapy and radiotherapy have an increased risk for developing premature menopause. Women will suffer from its troublesome symptoms, such as the enhanced risk of osteoporosis and arterial vascular disease, and the loss of sexual interest. Sex hormone replacement therapy with estrogens and progestin is therefore indicated and is helpful in women with ovarian failure. The role of bisphosphonates, in association with sex hormone replacement therapy to prevent osteopenia and to reduce the risk of fractures, is promising in adults. In children undergoing HSCT, however, they have not been systematically studied.

Few patients may recover gonad function spontaneously even years after transplant. Spinelli *et al*.[24] and Sanders *et al*.[25] reported on the possibility of spontaneous return of menstrual cycles in women who were conditioned with CY or with TBI after varying intervals of time (1.8–7.2 and 0.25–3.5 years, respectively), with an actuarial probability of recovery of 0.35 at 10 years and 0.24 at 7 years, respectively. This suggests that, especially in women who received HSCT early in life, sex hormone replacement therapy should be stopped for a short period of 3–6 months every 3–4 years for re-evaluation of the hypothalamic–pituitary–gonad axis.

Girls with hypergonadotropic hypogonadism who fail to start with pubertal development spontaneously should receive replacement treatment with gradually increasing doses of estrogens to both induce the appearance of secondary and primary sex characteristics and to promote pubertal growth spurt.

Fertility

Pregnancy following HSCT is still considered to be a rare event.[19,26] Women who eventually become pregnant require high-risk obstetric care because of the high incidence of spontaneous abortions and premature births. In a multicenter European retrospective study on pregnancy outcomes after HSCT,[26] 312 conceptions were reported in 113 women and partners of 119 male patients.

A significantly higher than normal rate of preterm delivery producing low birth weight babies and increased frequency of cesarean section deliveries was observed in female recipients of allogeneic HSCT, especially those who received TBI during conditioning and who were conceived by artificial techniques. The rate of congenital abnormalities (0.82%) was similar to that of the general population. An association between pregnancy and high rate of relapse of chronic myeloid leukemia after HSCT was reported, probably due to a disturbance in GVL effect. Strategies to maintain fertility either by reducing the intensity of pretransplant conditioning regimens when possible or by cryopreservation of semen, oocytes, ovarian and testicular tissue are still sporadic and should be encouraged. Progress in reproductive endocrinology and fertility has resulted in the availability of several options for preserving or permitting successful conception in cancer patients. Although still experimental in laboratory animals, the cryopreservation of ovarian cortical tissue or enzymatically extracted follicles and their maturation *in vitro* are promising future approaches in prepubertal and postpubertal females. The majority of these options may not be readily available to the pediatric and adolescent patient, and the necessary delay in cancer therapy for ovarian stimulation or *in vitro* fertilization cycles is impractical. Furthermore, especially in patients with hematological or gonad tumors (infiltration), these methods harbor the risk that malignant cells will be present in the specimen and be reintroduced into the patient later in life.

Thyroid abnormalities

One of the common potential late endocrine complications will result in thyroid dysfunction in patients who received HSCT. Radiation therapy has been recognized to have a key role in inducing early and late thyroid damage. The irradiation dose and the number of fractions were found to correlate with the severity of thyroid dysfunction. Although Borgstrom *et al*.[27] found that 24 out of 27 patients (89%) who received 10 Gy single-dose TBI before HSCT showed some evidence of thyroid disease, Boulad *et al*.[28] reported on 22 out of 150 patients (15%) who received hyperfractionated TBI (11–12 fractions of 125 cGy each) with some evidence of thyroid dysfunction only.

The most frequent thyroid disorders in patients who received HSCT are:

- overt primary hypothyroidism: high serum TSH levels with low concentration of free T4;
- subclinical hypothyroidism (compensated hypothyroidism): slightly increased serum TSH level with normal concentration of free T4;
- autoimmune thyroid disorders;
- euthyroid sick syndrome;
- secondary thyroid carcinoma.

Hypothyroidism can be an early complication but is usually considered as a late complication identified several years after HSCT. Approximately 15% of patients develop overt primary hypothyroidism and 30% have compensated hypothyroidism. The incidence is lower in patients who received fractionated TBI and even lower in patients conditioned with chemotherapy alone. Treatment with L-thyroxine is indicated in all cases with overt primary hypothyroidism. The dosage should be tailored to each patient and adjusted according to serum basal thyroid hormone concentrations estimated every 6 months.

The majority of patients with subclinical hypothyroidism after HSCT will have a benign, mild, compensated and self-limited transitory alteration of laboratory thyroid function tests only. There is a debate on whether or not to treat these patients as L-thyroxine might induce iatrogenic hyperthyroidism, potentially accelerating early osteoporosis in patients who are already at risk of developing osteoporosis due to sex hormone deficiency. We therefore follow patients with slightly increased TSH and normal free T4 concentrations every 6 months and start hormone replacement treatment only if TSH remains high or increases.

Autoimmune thyroid disorders are considered as an 'adoptive transfer autoimmunity disorder' and have been described in some patients who received allogeneic HSCT from a donor affected with autoimmune thyroid disorder.[29,30] The majority of these patients developed autoimmune thyroiditis or Graves' autoimmune hyperthyroidism several months to 5 years after HSCT. The high levels of thyroid-specific antibodies (the most frequent being thyroid peroxidase antibodies, antithyroglobulin antibodies and anti-TSH receptor antibodies), laboratory thyroid function tests and ultrasound abnormalities can help identify this disorder and guide treatment selection. Euthyroid sick syndrome, is considered to be an early complication of the severely ill HSCT patient, caused by a change in thyroid physiology (pituitary changes in TSH regulation and abnormalities in peripheral hormone metabolism). Thyroid function abnormalities are gradually progressing with the patient's worsening clinical condition. As most of the controlled studies have not shown any beneficial effect of L-thyroxine or T3 treatment, it is still debatable whether therapeutic intervention should be initiated even in the more severely ill patients.

In a recent study conducted by the EBMT Late Effects Working Party,[31] secondary thyroid carcinoma was found to have a high standardized incidence ratio in the transplanted population (3.26). Multivariate analysis revealed that young age at transplant was the strongest risk factor for secondary thyroid carcinoma with a relative risk (RR) value of 24.61 for age 0–10 years and 4.8 for age 11–20 years). Other risk factors were irradiation (RR = 3.44), female gender (RR = 2.79) and chronic GvHD (RR = 2.94).

In conclusion, long-term survivors of HSCT are at increased risk for thyroid abnormalities. This knowledge should promote efforts for a regular screening policy to detect and treat thyroid illness early, especially in young adults transplanted during childhood and adolescence. The cost-effectiveness of any diagnostic procedure, such as laboratory investigation, ultrasound or fine needle aspiration, should be addressed in further specific studies, considering also the associated distress to the patient and invasiveness of some of the procedures.

Diabetes

The transitory impairment of pancreatic β-cell function is a well-known early complication occurring in HSCT patients. An extremely limited number of studies have reported data on abnormalities of glucose metabolism in long-term survivors after HSCT during childhood.[32–35] Many issues of diabetes mellitus in HSCT patients still remain unclear.

In a recent paper, Bonanomi *et al*.[35] reported 6 patients in a cohort of 201 patients transplanted before age 18 years who developed diabetes mellitus at a median age of 10.1 years (range 5.6–22.1). The unique clinical and laboratory features that characterized these patients with diabetes mellitus after HSCT suggested that this should be considered as a unique and specific entity within the commonly used classifications for diabetes mellitus. The authors recommend that in consideration of the relatively high prevalence of impaired glucose metabolism and the insidious onset of diabetes in this group of patients, clinicians should carefully evaluate even minor variations of fasting blood glucose, usually included in the routine biochemistry at follow-up. They also suggest that control of HbA1c be added to the follow-up program after HSCT.

Conclusions and practical guidelines for follow-up care

Identification, prevention and treatment of late complications in children who underwent HSCT may prolong their life expectancy and improve the quality of life. As these patients are at life-long increased risk for developing late complications, a regular follow-up should be scheduled, following protocols that include conventional minimal requirements. The Operational Manual of the EBMT published in 1999, includes some minimum practical information and guidelines for correct endocrine follow-up of children after HSCT.

Simple clinical parameters as weight and height measurements before HSCT and every 6 months thereafter until the final height is achieved should be checked in all children. Assessment of pubertal development by measuring testicular volume in boys and breast development in girls should also take place every 6 months until puberty is accomplished. Laboratory parameters should include measurements of serum glucose, thyroid-stimulating hormone, free T4, insulin-like growth factor-1, luteinizing hormone, follicle-stimulating hormone, testosterone in boys and estradiol in girls. Such a program can help the physician to screen for the most common endocrine late complications after HSCT. In cases with suspected endocrine-organ insult, the local endocrinologist should be consulted and pharmacological provocative tests as well as further radiological investigations should be carried out.

Conflict of interest

None of the authors declared any financial interests.

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