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NCI, NHLBI/PBMTC First International Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation: Endocrine Challenges--Thyroid Dysfunction, Growth Impairment, Bone Health, & Reproductive Risks

Christopher C. Dvorak[1], **Clarisa R. Gracia**[2], **Jean E. Sanders**[3], **Edward Y. Cheng**[4], **K. Scott Baker**[3], **Michael A. Pulsipher**[5], and **Anna Petryk**[6]

Christopher C. Dvorak: dvorakc@peds.ucsf.edu; Clarisa R. Gracia: cgracia@obgyn.upenn.edu; Jean E. Sanders: jsanders@fhcrc.org; Edward Y. Cheng: cheng002@umn.edu; K. Scott Baker: ksbaker@fhcrc.org; Michael A. Pulsipher: michael.pulsipher@hsc.utah.edu; Anna Petryk: petry005@umn.edu

[1]Division of Pediatric Blood & Marrow Transplant, University of California San Francisco, San Francisco, CA 94143

[2]Department of Obstetrics & Gynecology, University of Pennsylvania, Philadelphia, PA 19104

[3]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109

[4]Department of Orthopedic Surgery, University of Minnesota, Minneapolis, MN 55455

[5]Division of Hematology/BMT, University of Utah, Salt Lake City, UT 84113

[6]Division of Pediatric Endocrinology, University of Minnesota, Minneapolis, MN 55455

Abstract

The endocrine system is highly susceptible to damage by high-dose chemotherapy and/or irradiation prior to hematopoietic cell transplantation (HCT) during childhood. The specific endocrine organs most affected by HCT include the thyroid gland, the pituitary, and the gonads. In addition, hormones that support development and stability of the skeletal system are also affected. Insufficiency of thyroid hormone is one of the most common late sequelae of HCT, and occurs more often in young children. Deficiency in the pituitary's production of growth hormone is a problem of unique concern to the pediatric population. The reproductive risks of HCT depend on the patient's gender and pubertal status at the time of HCT. Pubertal or gonadal failure frequently occurs, especially in females. Infertility risks for both genders remain high, while methods of fertility preservation are limited in all but post-pubertal males. Bone health post-HCT can be compromised by low bone mineral density as well as avascular necrosis, but the data on both problems in the pediatric HCT population are limited. In this paper, the current state of knowledge, gaps in that knowledge, and recommendations for future research are addressed in detail for each of these systems.

Corresponding Author: Michael A. Pulsipher, MD, Division of Hematology/BMT, Primary Children's Medical Center, University of Utah School of Medicine/Huntsman Cancer Institute, 50 North Medical Drive, Salt Lake City, UT 84132, Phone: (801) 662-4830, Fax: (801) 662-4707, michael.pulsipher@hsc.utah.edu.

INTRODUCTION

The endocrine system is commonly affected by high-dose chemotherapy and/or irradiation prior to hematopoietic cell transplantation (HCT) during childhood (1). The risks for the development of endocrine dysfunction depend on a variety of factors, including age at HCT, the type of conditioning regimen utilized, and the gender of the patient. The specific endocrine organs most affected by HCT include the thyroid gland, the pituitary, gonads, and hormones that support development and stability of the skeletal system.

In April 2011 the NCI/NHLBI along with the Pediatric Blood and Marrow Transplant Consortium (PBMTC) sponsored a consensus conference of international experts in clinical and biological research into late effects after HCT convened to review the state of the science of pediatric studies and identify key areas for future research. This manuscript will describe the conclusions shared at that conference relating to key endocrine systems affected by HCT. Although there is a large body of research evaluating endocrinologic late effects after HCT in adults, the pediatric literature is relatively limited. Children, especially those who are pre-pubertal and still growing, are a unique population in which the data regarding sequelae in adults after HCT are not directly relevant. Therefore, endocrinologic late effects in children after HCT is an important field of research to both better understand the epidemiology and risk factors for the development of a particular endocrine dysfunction, but also to begin to develop strategies by which the incidence of these late effects can be minimized.

THYROID DYSFUNCTION

Thyroid dysfunction (TD) is a commonly encountered problem following HCT. TD can be screened for with serum free T4 (FT4) and thyroid-stimulating hormone (TSH) levels. There are several distinct patterns of TD, including overt hypothyroidism (low FT4), subclinical compensated hypothyroidism (high TSH with normal FT4), hyperthyroidism (high FT4), and rare classic autoantibody-mediated thyroiditis.

Current State of Knowledge

Centers have reported incidences of TD in pediatric patients undergoing HCT between 0 to 52%, depending upon the size of the cohort and the type of transplants performed (Table 1), with the larger series generally confirming a ~30% incidence (2–11). Of note, this is much higher than generally reported for adult patients, where rates are generally around 15% for patients receiving fractionated total body irradiation (TBI), and even lower for chemotherapy-based preparative regimens (12). Since a major risk factor for the development of TD post-HCT is undergoing HCT before the age of 10 years (2, 4, 8), this suggests that the developing thyroid gland may be more susceptible to damage. The group of children with the highest risk of TD were those patients undergoing HCT for treatment of Hodgkin lymphoma, with a very high cumulative incidence of 73% (2).

In general, radiation-based preparative regimens have been shown to be one of the most significant risk factors for the development of TD (12). Of note, fractionated TBI in combination with cyclophosphamide (CY) is not significantly more likely to cause thyroid dysfunction than busulfan (BU) in combination with CY or other alkylating agents. Since CY on its own as part of the preparative regimen for the transplant of patients with severe aplastic anemia (SAA) only induced a 7% incidence of thyroid dysfunction (2), it appears that the administration of BU may also be a significant risk factor, though other reports have challenged this (5–7).

Gaps in Current Knowledge

It remains to be determined if reduced-toxicity regimens incorporating BU in combination with the non-alkylating fludarabine produce a lower risk of TD than seen with classic BU plus CY regimens.

In children with SAA, single-agent GVHD prophylaxis was associated with extremely high rates of hypothyroidism 5 years post-HCT (82%) compared to those receiving 3-drug GVHD prophylaxis (16%) (13). Also children undergoing unrelated donor HCT are more likely to develop hypothyroidism than those receiving transplants from matched siblings (36% vs. 9%) (3). This suggests that a sub-clinical GVHD-like phenomena may play a role in the development of some cases of thyroid dysfunction following allogeneic HCT (7, 14).

Recommendations for Future Research

The majority of TD seen post-HCT is primary hypothyroidism, with central hypothyroidism being less common (2, 3). Therefore, local damage, especially from TBI, appears to be a common causal agent. To the best of our knowledge, an attempt to shield the thyroid during TBI has never been reported. However, this approach has been successfully applied to the gonads, thymus, eyes, and lungs (15–18). Obviously this approach would be easiest to implement in the rare patients receiving TBI for the treatment of a non-malignant condition. In patients with leukemia, care would need to be taken to ensure that the marrow cavities in the vicinity of the thyroid were properly treated, though actual recurrence of leukemia in the thyroid gland itself appears to be vanishingly rare (19). Another possibility would be to provide physiologic TSH-suppressive doses of exogenous thyroxine, in order to induce a metabolic quiescence in the thyroid gland. A small pilot trial in 14 patients undergoing irradiation for HL suggests that this method may be effective (20), and it would potentially be translatable to patients undergoing TBI. However, the delayed nature of TD post-HCT does present a significant barrier to adequately measuring the effect of an intervention, and TD is one of the easiest late effects to monitor for and manage, making prevention of TD a relatively lower priority topic to study.

GROWTH IMPAIRMENT

Problems obtaining final predicted adult height are a post-HCT complication unique to the pediatric population. Although pituitary production of growth hormone (GH) plays an important role in determining final height, many other factors play a role, including nutritional status, thyroid function, corticosteroid therapy, and the production of sex hormones during the pubertal growth spurt. One mechanism by which GH functions is via the stimulation of production of both insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGF-BP3), a carrier molecule which enhances the plasma half-life of IGF-1. In patients with decreased linear growth, measurement of serum levels of these two molecules is thus an easy method to screen for true decreased production of GH, as opposed to other etiologies for growth impairment.

Current State of Knowledge

There are major difficulties in interpreting the literature on growth impairment following pediatric HCT due to differences in how growth impairment is defined. As seen in Table 2, the exact incidence of GI post-HCT varies widely between reports, likely due to differences in the age of the patients at the time of HCT, the type of preparative regimen utilized, and the inclusion of patients who did or did not receive additional cranial irradiation (CI). Nevertheless, the reports demonstrate incidences ranging from 20–85% (9, 21–24).

Clearly, irradiation-based conditioning regimens play the largest role in the development of growth impairment post-HCT (5, 9). However, the exact role of BU or other alkylators in the development of growth impairment is less clear. Several groups have reported low rates of growth impairment with BU-based regimens (5, 6, 22, 25), unless they also received CI. In patients with genetic diseases undergoing HCT, growth is usually not affected by BU-based preparative regimens (26), unless the HCT is performed during the adolescent growth spurt (27), HCT may actually accelerate growth in patients where the underlying disease (such as thalassemia) was inhibiting it (28).

Similar to TD, age less than 10 years at the time of HCT is associated with the highest risk of growth impairment (24, 25). Fortunately, younger patients also show the best response to GH administration (24).

Gaps in Current Knowledge

It is still unknown what the impact of GH deficiency is on aspects of metabolism unrelated to linear growth, such as muscle and lean body mass. Similarly, we do not yet understand what happens to GH deficient patients that are treated with recombinant GH during adolescence, but then discontinue GH replacement once epiphyseal fusion occurs and final adult height is obtained. Another major gap in current knowledge regarding growth impairment is what the impact of non-TBI-based conditioning regimens, especially newer reduced intensity and non-myeloablative regimens. It is possible that as we move away from TBI-containing regimens growth impairment due to biochemical GH deficiency following HCT may become a thing of the past, or only occur rarely such as in patients who have significant pre-HCT radiation exposures.

Recommendations for Future Research

Since irradiation likely plays the largest role in the development of this late effect, given the practical difficulties of shielding the pituitary gland the easiest step will be the development of preparative regimens that avoid the use of full-dose TBI or preferably even no TBI, while still providing optimal engraftment and protection from malignant relapse.

BONE HEALTH: LOW BONE MINERAL DENSITY

Current State of Knowledge

Only seven studies have been published that address bone loss in pediatric HCT recipients (Table 3). Only one of these studies was prospective (29), the remainder were cross-sectional, and most of them were limited by small sample size (10–66 participants) (30–35). Bone mineral density (BMD) was determined by a dual-energy X-ray absorptiometry (DXA) scan in most studies (33). A mild reduction in mean BMD Z-score (either total body or lumbar) was observed (mean about −1.0, range −5.2 to +2.3). A significant proportion of pediatric HCT recipients transplanted between 0.6 and 18 years of age had a Z-score between −1 and −2 (18–33%), and even below −2 (6–21%).

The pathogenesis of bone loss after HCT is multifactorial. Some of the risk factors are general (gender, age, physical inactivity, poor nutritional status, inadequate intake of calcium and/or vitamin D, Caucasian or Asian race, family history), and some are specific to cancer treatment and/or HCT (chemotherapy, TBI/craniospinal irradiation, the malignancy itself, corticosteroids, cyclosporine, G-CSF, endocrine deficiencies, including growth hormone deficiency and hypogonadism, GVHD or its treatment, direct effects of conditioning regimens on bone marrow stromal cells, cytokine release after HCT, and reduced production of growth factors) (36–46). Notably, however, many of the purported

risk factors are only presumed as such based on their mode of action and effects on bone formation and/or resorption in various diseases, animal models, or *in vitro* experiments.

Only one prospective study in children has been published that longitudinally assessed changes in BMD before and after HCT (29). Most significant bone loss occurred within the first 6 months after transplantation. The number of patients with a Z-score below −1 increased from 34% at baseline to 52% one year after HCT. Several prospective studies in adult HCT recipients have demonstrated that a decrease in BMD is preceded by changes in the markers of bone turnover. A consistent finding in adult HCT is a decrease in bone formation and an increase in bone resorption.

There is insufficient data in pediatric HCT recipients to determine whether similar changes in bone turnover occur in children. Based on one prospective study, which examined the levels of serum bone specific alkaline phosphatase, osteocalcin (OCN), and urinary N-telopeptide before and up to 12 months after HCT (29), it appears that bone formation in children may be similarly reduced.

The mechanisms through which changes in bone turnover are evoked by the various risk factors have been previously reviewed (36, 40, 47). Of particular relevance to HCT recipients are direct effects of myeloablative regimens and the acute release of cytokines on osteoblastic and osteoclastic activity after HCT. Myeloablative therapy can directly damage the recipient's osteoprogenitor cells within the bone marrow stroma independently of secondary effects on gonadal function and growth hormone secretion, negatively affecting bone formation (41, 48, 49). Moreover, a marked "cytokine storm" (IL-6, IL-7, G-CSF, M-CSF, TNF-α) occurs within the first 3 weeks after HCT, which stimulates osteoclasts and increases bone resorption (43, 47, 48, 50, 51). The main mediator of these pro-resorptive effects on bone is thought to be the RANK/RANKL/OPG pathway (52, 53). Receptor activator of the nuclear factor-κB ligand (RANKL) and RANKL/OPG (osteoprotegerin) ratio increase after HCT, reaching a peak at 3 weeks, stimulating osteoclastogenesis (48, 54). It is currently unknown whether similar changes occur in children after HCT and whether OPG, a decoy receptor that competes with RANKL can counterbalance these effects.

Some of these biomarkers could be used as predictors of bone recovery. In children, the OCN level at 100 days after HCT predicted recovery from the initial bone loss by 1 year (29). In adult HCT recipients, lower IGF-I levels and higher cytokine levels after HCT correlated with lower BMD at 1 year (43, 48, 54).

Studies in adult HCT recipients have shown that BMD can improve years after HCT (39, 47, 55). Since peak bone mineral accretion occurs during adolescence and young adulthood, children who undergo HCT at a very young age would presumably still have time to regain BMD. Data to support this presumption is limited. Some studies have shown that, the potential for stromal reconstitution after HCT may be greater young children (34), especially those younger than 5 years compared to older than 8 years (49). However, Bhatia *et al.* found a positive correlation between age at HCT and BMD (30). Thus, it remains to be determined whether there is an age effect and how it affects BMD outcome.

Gaps in Current Knowledge

The limitations of the current studies in pediatric HCT recipients are several-fold. The first is that the majority of the studies have small sample sizes and are cross-sectional. Furthermore, it is unclear whether there are age-related differences in predisposition to bone loss and/or subsequent BMD recovery after HCT. In addition, markers of bone turnover have been insufficiently studied to determine if bone resorption is increased after HCT and

there is a potential for identifying biomarkers that would help identify patients at risk who would require closer follow up and an appropriate intervention to prevent or reverse bone loss.

Recommendations for Future Research

Prospective controlled studies are needed to define the time course of changes in bone turnover and BMD prior to and following HCT, incidence and severity of bone loss, and whether age at HCT is a factor in BMD recovery. By identifying risk factors, these studies should better define a population at risk. Future studies should also have multiple biologic aims: to identify the prevalence and the degree of vitamin D deficiency (which may be a significant contributor in certain geographic regions), to define biological predictors of BMD recovery, and to decide which markers of bone formation and resorption are most informative in children. Finally, we need to identify the time period and suitable mode of intervention to provide patients with weight-bearing exercise after HCT, as this intervention has been clearly shown to improve BMD.

BONE HEALTH: OSTEONECROSIS

Current State of Knowledge

Osteonecrosis (ON) was first recognized as a complication of HCT in 1987 (56). Only a few papers have addressed the occurrence of ON in pediatric HCT recipients where the prevalence ranges from 1.3% to 14% (9, 57–59), with even higher occurrence (44%) being found in pediatric allogeneic HCT recipients who underwent routine screening for ON by MRI (33). The true prevalence, however, is unknown as it can only be determined by prospective screening with MR, which is a much more sensitive method of detection of ON than plain radiographs (12, 58, 60–62).

In children, knees (31–40%) are the most frequent site of ON, followed by hips (19–24%), shoulders (9%), and other sites (33, 63–65). The majority of patients manifest ON in two or more joints (12, 59, 63, 65). Typically, ON occurs within 3 years after HCT, the earliest time point being 1–6 months after the onset of steroid therapy, particularly if MRI is used for detection (45, 59, 62, 63, 65–68). A median interval for the development of ON is 11 months after HCT in children (57).

Patients usually present with either vague, diffuse bone pain, presumably due to increased intraosseous pressure, or joint-related pain due to an effusion. Hip involvement is typically manifested by groin pain. Once subchondral collapse and articular deformity occur, arthritic-type joint pain predominates accompanied by functional limitation (limp, reduced range of motion) (66, 69) However, during early stages of ON, patients may have mild transient bone pain during treatment or they may be completely asymptomatic and not necessarily progress to symptomatic disease (33, 62). If left untreated, joint destruction usually occurs within 1–5 years after the onset of symptoms (66, 70). Once disease progresses beyond a certain point, collapse of necrotic bone is inevitable. The reparative processes are usually ineffective, and actually counterproductive, leading to further separation of acellular necrotic bone tissue from viable tissue by a fibrous layer, preventing revascularization (68, 69, 71). The risk of subchondral fracture of the necrotic bone leading to joint collapse is determined by the size (best assessed using the necrotic arc index) and location of the necrotic lesion (72). For example, involvement of less than 10–15% of the femoral head and less than a third of the weight-bearing portion carries a good prognosis, while involvement of more than 25% of the femoral head or more than two thirds of the weight-bearing portion carries a poor prognosis (68, 69, 73).

The pathogenesis of ON is multifactorial. Several mechanisms have been proposed, including increased intraosseous pressure or intraluminal obliteration that compromise intramedullary blood flow, leading to marrow ischemia, and ultimately necrosis (65) (Figure 1). The likely contributing mechanisms are defective bone repair due to damage to the bone marrow stroma, immunosuppression as well as radiation and drug induced injury to the vessel wall and vasculitis (59, 66, 68, 69, 71, 74–77).

There are multiple risk factors for the development of ON which occurs in pediatric HCT recipients at a median age of 14.4 years (57). Higher incidence of ON has been reported in patients exposed to TBI-based conditioning regimens (57, 59, 78), presumably due to radiation-induced microvascular damage (79), in adult patients with acute leukemia and aplastic anemia compared to AML, CML, and other diagnoses (59), and in recipients of allogeneic HCT (particularly unrelated) compared to autologous HCT (66, 74, 78). The latter likely explains an increase in risk in patients transplanted after 1985 when unrelated donor HCTs became more common and newer immunosuppressive agents were introduced (74). The data about the association between gender and the incidence of ON have been inconsistent. While GVHD, both acute and chronic, has been associated with ON, it is unclear whether it plays an independent pathogenic role since it is strongly correlated with the use of steroids (57–59, 66, 74, 80). An argument for an additional independent role of GVHD is that it increases the risk for microangiopathy (81–83). Corticosteroids are the strongest risk factor for ON, with both the cumulative dose and duration of treatment playing a role (57, 58, 65, 66, 77, 78, 84–86). Several mechanisms for this effect have been proposed, including altered lipid metabolism, adipocyte hypertrophy, stimulation of adipogenic differentiation of bone marrow stem cells at the expense of osteogenic differentiation, leading to the formation of fat emboli and fatty infiltration of the bone marrow, or a direct effect on osteocyte apoptosis (67, 68). The risk of ON increases with the number of drugs used for immunosuppression, including prednisone, cyclosporine (CSA), tacrolimus (FK506), and mycophenolate mofetil (MMF) (74, 78), due to their thrombogenic effects, as well as through vascular damage and dyslipidemia (87–90)

An association between low BMD and ON has not been characterized beyond the observation that both can coexist in pediatric HCT patients (65). While the causative link is absent, it is conceivable that higher BMD would likely improve the biomechanical properties of the bone, and perhaps delay the collapse of the necrotic bone. There is a significant overlap between the risk factors for low BMD and ON. In addition, the two conditions may share pathogenic pathways, and therefore have additive effects. For example, impaired osteoblast activity contributes to reduced BMD in both pediatric HCT and adult HCT patients (29, 43, 48, 91–93). Reduced number of osteoblast precursors may in turn adversely affect the regenerative potential of the osteogenic compartment and the course of ON (66, 77, 94, 95)

Gaps in Current Knowledge

The major limitation of current studies in pediatrics is the lack of an animal model, an insufficient number of patients to allow identification of patients at high risk for progression of ON, and inadequate assessment of asymptomatic disease. Furthermore, there is no consensus regarding optimal screening and treatment of early stage ON. Clearly MRI is the most sensitive screening modality, however, its cost effectiveness, especially in view of the lack of a reliably effective intervention in early stage disease, remains an obstacle.

Recommendations for Future Research

Prospective studies with screening MRIs are needed to identify the incidence of ON after pediatric HCT, the natural history of asymptomatic ON detected by MRI, and appropriate

preventive interventions. Given the significant prevalence of ON in non-HCT ALL patients, as part of a prospective study, a baseline MRI would need to be performed on all patients prior to HCT. Only then will progress be made in discerning the effectiveness and safety of pharmacologic interventions in preventing post-HCT ON.

REPRODUCTIVE RISKS

The reproductive risks of HCT include gonadal failure, infertility, and pubertal failure.

Current State of Knowledge

Post-Pubertal Individuals

Females: The ovary is particularly sensitive to the adverse effects of cancer treatments because of the finite number of germ cells present in the post-natal ovary (96, 97). Since reproductive lifespan is determined by the size of the follicular pool, cancer treatments that cause follicular depletion accelerate the onset of menopause (98). The irreversible gonadotoxic effects of some chemotherapeutic agents are well documented, particularly for alkylating agents such as CY (99, 100). In women 30–39 years of age, a dose of 9 gm/m^2 of CY results in ovarian failure, while in women who are a decade younger, 20 gm/m^2 causes a similar effect. In contrast, the prepubescent female has been shown to tolerate as much as 25–30 gm/m^2 of CY and still retain ovarian function (101).

Ovarian failure after HCT has been observed in 65–84% of pediatric transplant recipients (Table 4) (165–170). Exposure to CY, BU, and TBI are associated with gonadal failure while younger age at transplant is associated preservation of menstrual function (102, 103). It is important to recognize that studies assessing fertility after HCT are limited by the fact that they have not accounted for whether patients were actually trying to conceive. One of the most comprehensive studies of pregnancy in pediatric and adult HSC survivors reported that 32/708 (4.5%) of post-pubertal females became pregnant after HCT (104). Pregnancies were most likely to be reported in patients who had been exposed to CY only conditioning regimens (56/103, 54% reported pregnancy), compared to BU/CY (0/73, 0% reported pregnancy) or TBI (7/532, 1.3%). In general, studies indicate that fertility is most likely to be preserved in patients who undergo transplant as young adults (15–30 years) and receive non-TBI based conditioning regimens. Most pregnancies occur 5–10 years post-transplant. Nonetheless, pregnancy has been reported in patients who received high dose alkylator-based conditioning and TBI, and even in patients who underwent more than one transplant.

Males: Unlike the female, germ cells in the testes normally continue to produce sperm during adulthood. However, conditioning therapies such as CY and TBI destroy germ cells within the testes leading to low or absent sperm production which can subsequently lead to infertility (105). Impairment of spermatogenesis may be permanent or temporary following chemotherapy (105, 106). The chance of recovery of spermatogenesis following cytotoxic therapy and the extent and speed of recovery are related to the agent used and the dose received. Azoospermia develops in the majority of post-pubertal males exposed to over of 300 mg/kg of cyclophosphamide (105). Moreover, spermatogenesis is exquisitely sensitive to radiation and low doses (over 2–3 Gy) can cause significant impairment in function. Many (48–85%) males who undergo HCT will experience testicular failure with azoospermia (104, 105, 107). Similar to females, the risk of gonadal failure appears to be dependent on the type of therapy and the doses administered. Fertility data in the transplant population are limited and summarized in Table 4. A large study of HCT survivors found that 32/618 post-pubertal males fathered a child. Pregnancies were most likely to be reported in patients who had been exposed to CY only conditioning regimens (26/109, 24% reported

pregnancy), compared to BU/CY (3/46, 6.5% reported pregnancy) or TBI (6/463, 1.3%) (104).

Pre-Pubertal Individuals—Normal pubertal development requires a functioning hypothalamic-pituitary-gonadal axis. HCT can result in pubertal delay or failure in both sexes. Incomplete pubertal development or pubertal failure has been reported to occur in approximately 57% of prepubescent females following HCT (2). However the risk of delayed puberty is dependent on the conditioning regimen administered (16% after 200 mg/kg CY alone, 72% after 16 mg/kg BU plus 120–200 mg/kg CY, 71% after 10Gy single-exposure TBI, 57% after 12–15.75 Gy TBI) (11, 108). In males, incomplete pubertal development or pubertal failure has been reported to occur in approximately 53% of prepubescent males exposed to HCT (109). Similar to females, the risk of delayed puberty is dependent on the conditioning regimen administered (14% after 200 mg/kg CY alone, 48% after 16 mg/kg BU plus 120–200 mg/kg CY, 81% after 10Gy single-exposure TBI, 58% after 12–15.75 Gy TBI) (11, 108). Boys who receive high dose (>24 Gy) testicular irradiation for testicular relapse have a very high risk of pubertal failure requiring testosterone replacement to develop secondary sexual characteristics (109).

Fertility Preservation in Females—The ability to lead full reproductive lives is very important to both female and male HCT survivors. Indeed, there is evidence that HCT survivors have persistently elevated concerns about their fertility even 10 years after treatment (110). Therefore, there has been increasing interest in methods to expand the reproductive options for patients facing fertility-threatening treatments. While embryo cryopreservation remains the standard option for adult females with a committed sexual partner, oocyte cryopreservation and ovarian tissue cryopreservation (OTC) technologies have become clinically-available experimental options for females without a partner. These fertility preservation technologies have gained traction, particularly after the publication of the ASCO fertility preservation recommendations in 2006 (111). However, embryo and oocyte cryopreservation are limited by the need for ovarian stimulation and oocyte retrieval, which can delay treatment 2–4 weeks. This delay in treatment is usually not an option for patients with leukemia, who tend to be quite ill with impaired blood counts at initial presentation. OTC eliminates the need for ovarian stimulation and does not require a sperm source. While investigational, live births have been reported following OTC and transplantation in cancer patients (112). Currently, this is the only method available for fertility preservation in pre-pubertal girls (113–116). There is a significant concern regarding the potential for reseeding tumor cells following ovarian transplantation procedures in cancers that involve the ovary, such as leukemia. A recent study of 18 patients with leukemia (CML or ALL) showed that leukemic tumors occurred (4/18 cases) after thawed human ovarian cortical tissue was xenografted into mice (117). Therefore, transplantation of ovarian tissue is not recommended in patients with a history of leukemia. In order to achieve pregnancy without transplantation, it would be necessary to mature and fertilize oocytes from ovarian tissue *in vitro* for embryo transfer. This has only been possible in the mouse and ongoing studies are being conducted to move this technology forward (118).

Ovarian Suppression—The observation that cancer therapies were less gonadotoxic in pre-pubertal girls led to speculation that ovarian suppression in post-pubertal females might reduce the negative impact of cancer therapies on the ovary. Ovarian suppression with GNRH analogues administered during chemotherapy is the most common method of ovarian suppression employed. Several small short-term studies comparing GNRHa plus chemotherapy to chemotherapy alone have demonstrated that menstrual function is more likely to be preserved in women who receive GNRHa during treatment (119–121).

However, there are insufficient data to support the use of GNRH agonists in transplant recipients for the purpose of fertility preservation (121). Nonetheless, GNRH analogues have been shown to reduce menstrual bleeding during cancer therapy and may be useful for that purpose in the HCT population (122).

Fertility Preservation in Males—Sperm cryopreservation remains the best option for fertility preservation in adolescent and adult males diagnosed with cancer. All adolescents and young adults facing cancer therapy should be offered sperm cryopreservation as a way to preserve future fertility (123). Ideally, multiple samples should by cryopreserved before cancer treatment has begun. In situations where self-stimulation is unsuccessful, vibratory stimulation, electroejaculation, or surgical sperm extraction may be used to obtain sperm (124–127). Even though sperm banking is a relatively simple process, there is evidence that oncologists do not routinely discuss this option with their patients (128). Fertility preservation in pre-pubertal boys remains problematic and is an active area of investigation. Extracting and cryopreserving spermatogonial stem cells from boys in order to later autograft or to mature sperm *in vitro* are promising avenues of investigation. While transplantation of cryopreserved testicular tissue has been successful in mice and rats, data in humans are lacking (129, 130).

Pregnancy Outcomes—Overall, pregnancy outcomes appear to be reassuring in survivors of HCT (104, 131–133). Most pregnancies reported by HCT survivors and their partners result in a live birth. However, in female HCT survivors who were exposed to TBI, there appears to be an increased risk of preterm delivery and delivery of low birth weight infants. This is consistent with literature in childhood cancer survivors and is thought to be related to radiation-induced structural changes in the uterus (134, 135). In addition, female HCT survivors are at higher risk of cesarean section compared to the normal population (42% vs. 16%). This observation may be related to the perception that transplant survivors are higher risk and therefore pregnancies are managed differently than the general population. While pregnancy outcomes of male survivors of HCT have been reported to be reassuring overall, one study of childhood cancer survivors reported that the likelihood of having a live birth was lower among survivors compared to siblings (RR 0.77, $p = 0.007$) (136). Nonetheless, offspring of male and female HCT recipients do not appear to be at increased risk for birth defects, developmental delay, or cancer (132).

Gaps in Current Knowledge

While data from retrospective cohort studies exist estimating the risk of pubertal problems and gonadal failure after HSC, there are no accurate estimates of fertility in this population. It must be recognized that retrospective reports of pregnancy after HCT are limited by ascertainment bias and do not determine whether patients have actually tried to conceive and have experienced difficulty, or whether HCT survivors simply are less likely to attempt pregnancy. Moreover, there are limited data assessing the reproductive risk of newer conditioning regimens prior to HCT. While lower-intensity conditioning regimens without exposure to CY and TBI appear to be less deleterious to reproductive function, more research is needed to determine which regimens are least gonadotoxic but equally effective for treatment. Such information would be useful in order to adequately counsel patients regarding their reproductive horizon and target fertility preservation technologies to those at highest risk.

After HCT, some females will resume menstrual function. While measures of ovarian reserve are likely to be impaired post treatment, it is not clear whether these measures predict fertility and age at menopause in cancer survivors. Understanding the significance of

measures of ovarian reserve would greatly improve counseling about fertility, contraception, and long-term ovarian function post-HCT.

There are also significant gaps in knowledge in the areas of contraception and hormone replacement therapy after HCT. While the risk profile of hormonal contraceptives may be less favorable in HCT survivors with concomitant medical problems compared to the general population, the safety and efficacy of contraception has not been studied in this population. Moreover, in female HCT survivors with premature ovarian failure, the optimal regimen for hormone replacement therapy is not known. Data on the long-term benefits and risks to the reproductive system of various regimens used for HCT are lacking.

Recommendations for Future Research

As outlined above, major gaps in knowledge regarding the reproductive risks, fertility preservation options, and long term contraceptive and endocrine needs of the HSC population exist. Therefore, there is an urgent need to conduct research in various aspects of reproductive health in the transplant population. Large prospective cohort studies assessing clinically meaningful reproductive outcomes in HCT recipients receiving newer preparative regimens are needed to better define the reproductive risks associated with these therapies. Furthermore, more data are needed to determine whether ovarian suppression during HCT decreases risk of reproductive and/or gonadal failure.

Additional research is necessary to determine whether measures of ovarian reserve predict fertility and time to menopause in menstruating transplant survivors. This would greatly improve post treatment counseling regarding fertility, contraception and anticipated timing of menopause. Studies assessing the safety and efficacy of contraceptives and hormone replacement regimens may transform care and could have a major impact on the long health and quality of life of HCT recipients.

CONCLUSIONS

The developing child is significantly more likely to be affected by endocrinopathies or poor bone health than a fully mature adult, therefore, the need for research and interventions in this unique patient population is significant. A large prospective trial which evaluates pre-HCT endocrine function and then follows the same tests on a routine basis post-HCT would significantly add to our current knowledge and assist in defining interventions.

Although thyroid dysfunction and growth impairment can be managed with replacement hormones, this damage can be permanent and result in life-long need for medications. Similarly, low bone mineral density or avascular necrosis following HCT can lead to significant long-term problems with ambulation and quality of life. Finally, for many parents of young children being considered for HCT, the thought that their child may be sterile can be emotionally devastating and may prohibit them from proceeding with HCT. Advances that could minimize this risk would likely increase the acceptance of HCT as a therapeutic alternative, particularly for some non-malignant conditions. Thus, in order to maximize both access to HCT and the quality of life post-HCT for our pediatric patients, further research is urgently needed in the field of endocrinopathies, bone health, and fertility.

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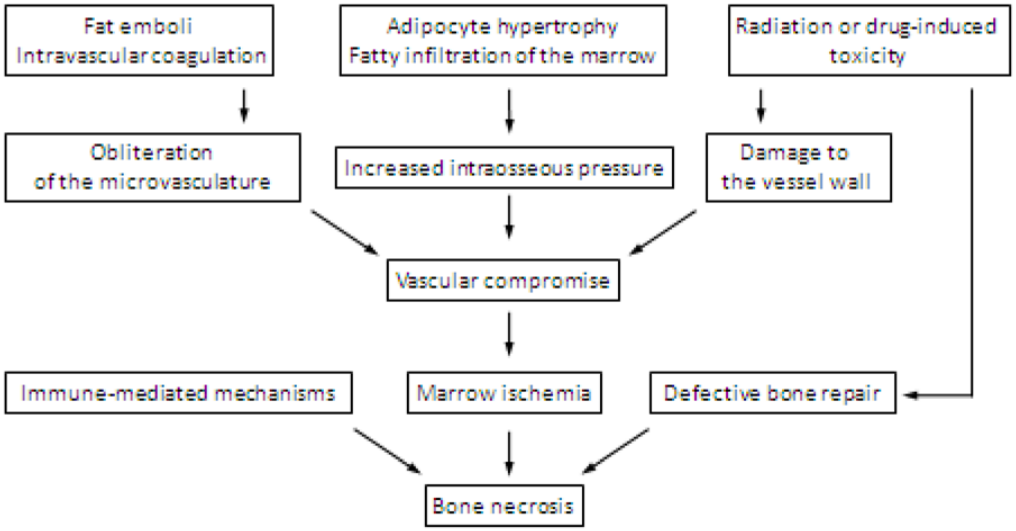

Figure 1.
Pathophysiology of AVN after HCT

Table 1

Studies of Thyroid Dysfunction (TD) Following Pediatric HCT*

	Reference	Incidence of TD	Number	Disease	Conditioning	F/U Median (range)	Risk Factors
Michel et al. 1997	5	9%	26	AML	BU + CY	5.9 yrs (1–9)	None
Afify et al. 2000	6	0%	23	AML only	BU + CY	4.9 yrs (2–10)	None
Slatter et al. 2004	7	11%	83	PID only	BU + CY	NR (2–4.5)	Autoimmunity?
Ishiguro et al. 2004	4	30%	147	Varied	Varied	11.1 yrs (5.8–21.5)	Age <10 yrs
Berger et al. 2005	8	27% 29%	101 14	ALL only ALL only	FTBI + Chemo BU + Chemo	8.5 yrs (5–16.5)	Age <10 yrs; Transplant in >CR1
Leung et al. 2007	9	34%	155	Varied	Varied	9 yrs (3.1–15.9)	Young age; higher dose TBI
Sanders et al. 2008	2	32% 23%	538 108	Varied Varied	FTBI + CY BU + Chemo	NR (1–30)	Age <10 yrs; Malignancy
Dvorak et al. 2008	10	8%	25	Varied	Varied	6.5 yrs (1–15)	Only seen in FTBI recipients
Bailey et al. 2008	3	52%	33	Mainly malignancy	FTBI + Chemo	4 yrs (0.5–8.5)	Unrelated Donors
Sanders et al. 2011	11	12%	137	SAA only	CY/CY + TBI	21.8 yrs (1–38.1)	TBI

*Studies including only unfractionated TBI were excluded

AML Acute Myeloblastic Leukemia

ALL Acute Lymphoblastic Leukemia

SAA Severe Aplastic Anemia

PID Primary Immunodeficiency

BU Busulfan

CY Cyclophosphamide

FTBI Fractionated Total Body Irradiation

NR Not Reported

Table 2

Studies of Growth Impairment Following Pediatric HCT*

	Reference	Incidence of Growth Impairment	Number	Disease	Conditioning	F/U Median (range)	Risk Factors
Huma, et al. 1995	21	20%	72	Leukemia	FTBI + Chemo	7.1 yrs (1.2–12.9)	CI, HCT for ALL
Giorgiani, et al. 1995	22	54% 9%	37 22	Varied Varied	FTBI + Chemo BU + Chemo	> 2 yrs (NR)	Prior CI
Cohen, et al. 1996	23	82%	28	Varied	Varied	7.9 yrs (3.2–11.4)	TBI, CI
Sanders, et al. 2005	24	84%	107	Varied	FTBI + CY + CI	11 yrs (2.7–23)	CI, HCT for ALL
Leung, et al. 2007	9	39%	155	Varied	Varied	9 yrs (3.1–15.9)	Young age; higher dose TBI
Dvorak, et al. 2008	10	24%	24	Varied	Varied	6.5 yrs (1–15)	Only seen in FTBI recipients

*Studies including unfractionated TBI were excluded

BU Busulfan

CY Cyclophosphamide

FTBI Fractionated Total Body Irradiation

CI Cranial Irradiation

NR Not Reported

Table 3

Studies of Low Bone Mineral Density (BMD) Following Pediatric HCT*

	Reference	Number	Disease	Age at HCT (years)	Age at Study (years)	F/U Median (range)	Z-score		Z-score −1 to −2	Z-score <−2
							Total body	Lumbar		
Bhatia et al. 1998	30	10	AML, CML	5.0^{Mdn} (3.0–18.0)	12.0^{Mdn} (4.0–22.0)	2.0 yrs^{Mdn} (1.0–10.0)	-0.5^{Mdn} (−2.0 to 1.0)	NR	NR	NR
Nysom et al. 2000	31	25	ALL, AML, CML, NHL	11.3^{Mdn} (5.7–17.6)	17.2^{Mdn} (11.3–26.5)	7.5 yrs^{Mdn} (3.6–12.6)	-0.5^{M}	-0.5^{M}	NR	NR
Daniels et al. 2003	32	15	Varied	NR	15.2^{M} (9.4–17.7)	6.3 yrs^{M} (1.0–12.2)	−0.7 to -0.9^{M}	−0.7 to -0.9^{M}	NR	NR
Kaste et al. 2004	33	43	Varied	10.3^{Mdn} (1.6–20.4)	15.8^{Mdn} (4.4–27.2)	5.1 yrs^{Mdn} (1.0–10.2)	NR	$-0.9^{Mdn,\wedge}$ (−3.3 to 2.3)	26%	21%
Petryk et al. 2006	29	21	Varied	10.2^{M} (5.1–17.9)	10.2^{M} (5.1–17.9)	≤1.0 yrs	NR	-0.9^{M} (−2.9 to 1.1)	33%	19%
Perkins et al. 2007	34	17	ALL, AML	1.7^{M} (0.6–3.0)	13.2^{M} (3.8–23.8)	11.6 yrs^{M} (3.3–22.3)	NR	-0.3^{M} (−2.4 to 2.0)	18%	6%
Carpenter et al. 2007	35	66	ALL, others	(1.1–17.9)	(2.0–18.2)	NR	NR	-3.6 to -2.5^{Mdn} (−5.2 to −0.9)	NR	NR

*Studies without data on lumbar and/or total body BMD were excluded

ALL Acute Lymphoblastic Leukemia

AML Acute Myeloblastic Leukemia

CML Chronic Myelogenous Leukemia

MDS Myelodysplastic Syndrome

NHL Non-Hodgkins Lymphoma

$^{\wedge}$ by QCT

M_{mean}

Mdn_{median}

NR Not Reported

Table 4

Studies of Fertility Following HCT

	Reference	Type of Study	Number of Patients	Summary of Findings
Sanders et al. 1996	104	Retrospective Cohort	1326 (708 females, 618 males)	15.5% of females had ovarian function & 4.5% conceived 24.4% of males had testicular function & 5.7% of partners conceived 79% of pregnancies resulted in a live birth Females had an increased risk of PTD and LBW infants
Salooja et al. 2001	132	Retrospective Cohort	37,362 (all females)	0.6% HCT recipients or female partners conceived 87% of pregnancies resulted in a live birth Female HCT recipients had an increased risk of PTD, LBW, and Cesarian Deliveries
Carter et al. 2006	131	Retrospective Cohort	619 (292 females, 327 males) >2 years post-HCT Compared to sibling controls	5.5% HCT recipients or female partners conceived 85% of pregnancies resulted in a live birth Risk of miscarriage and stillbirth was no different that sibling controls Older age, female sex, exposure to TBI = less conception
Loren et al. 2011	133	Case Series	178 HCT (83 females, 95 males)	Fertility is most likely to be preserved in patients: undergo HCT as young adults (15–30 years) receive non-TBI conditioning regimens males

PTD Preterm Deliveries

LBW Low Birth Weight