Growth, endocrine function and quality of life after haematopoietic stem cell transplantation

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General discussion

In this general discussion, the most important long-term endocrine effects of haematopoietic stem cell transplantation (HCT) will be discussed, combining the results presented in this thesis with other data from the literature. The first 3 paragraphs discuss growth, growth hormone (GH) secretion and effects of GH therapy, followed by 3 paragraphs on ovarian, testicular and thyroid function respectively. In the last paragraph, conclusions and recommendations are presented.

Longitudinal growth and final height in recipients of HCT

Longitudinal growth is a complex process that is influenced by genetic, metabolic, hormonal, nutritional and emotional factors. Disturbances of any of these factors can lead to impaired growth. Impaired growth has long been recognised as an important side effect of HCT [1], and many factors may contribute to this delay, e.g. anorexia, graft-versus-host disease (GVHD) of the intestine, use of glucocorticosteroids, hypogonadism, hypothyroidism, growth hormone deficiency (GHD), growth hormone resistance caused by growth plate damage. When growth ceases and the epiphyseal growth plates close, final height, the end result of longitudinal growth, is reached. The influence of impaired growth on final height depends on the capacity for catch-up growth, which is determined by both the cause and the duration of impaired growth [2].
Only recently data on final height after HCT were published (*chapters 5 and 7 included*) [3-8]. These data confirm that radiation is the major etiological factor in impaired growth after HCT, as patients who were not irradiated showed virtually no decrease in final height. In an attempt to reduce radiation-induced growth impairment, radiation-free conditioning regimens with high doses of busulphan and cyclophosphamide (Bu/Cy) have been used, especially in young children, but data on final height are limited. Most centres report no negative effect of Bu/Cy conditioning on growth several years after HCT [9-11]. However, in a small number of children without a history of cranial irradiation growth is delayed after radiation free, Bu/Cy-Based conditioning [12-14] (*see also chapter 9*). Therefore, larger populations and a longer follow-up period are needed to assess the effect of radiation-free Bu/Cy-Based conditioning regimens on growth after HCT.
Of the patients who do receive radiotherapy prior to HCT, the type of radiation most often used in conditioning for HCT is total body-irradiation (TBI). In

patients receiving TBI, final height standard deviation scores (SDS) are approximately 1 to 2 SD lower than the height SDS at the time of HCT [3;5-8] (*see also chapters 5, 6 and 10*) . In contrast to most of the earlier reports on growth after TBI [15], final height (FH) data do not support a major beneficial effect of fractionation on the reduction of adult height. Decrease in height SDS between HCT and FH reported by centres using single fraction TBI (7-8 Gy) [6;8] (*see also chapter 7*) are comparable to that reported by a large centre using fractionated TBI [7]. In addition, a large multi-centre study found no significant difference in either FH or decrease in height SDS between HCT and FH, between 39 patients receiving single fraction TBI and 39 patients receiving fractionated TBI (*chapter 5*) [5].

Radiation-induced decrease in height SDS is more prominent in patients receiving HCT at a younger age. The influence of age can be explained by the higher growth potential at younger ages. By the time final height is reached, permanent impairment of growth will therefore lead to a greater decrease in height SDS in younger children. In addition, younger children appear to be more sensitive to radiation damage, resulting in a faster decrease in height SDS in younger children (*chapter 7*) [8].

In most studies on final height, decrease in height SDS after TBI is more prominent in boys compared to girls [5;7;8;16] (*see also chapter 7*). The difference in loss of height SDS between boys and girls is attributed to blunting of the growth spurt. As the absolute height gain during the pubertal growth spurt is greater in boys than in girls, significant blunting of this growth spurt will lead to a more prominent decrease in final height SDS in boys. Another factor that could contribute to the difference in loss of height SDS between boys and girls is the timing of puberty after TBI. As hypergonadotrophic hypogonadism is much more frequent in girls than in boys [16;17], a great proportion of the girls will not enter puberty spontaneously (*chapter 6*). In these girls, puberty is frequently induced with relatively low doses of oestrogens and at a higher age compared to the mean age of spontaneous puberty in healthy girls. The late introduction of low doses of oestrogens may have a positive effect on final height.

Aetiology of impaired growth after HCT

As stated earlier, the most important contributor to growth impairment after HCT is radiation. There are several ways in which radiation may lead to

impaired growth, some of which are easily detectable and reversible (e.g. radiation induced hypothyroidism and hypogonadism). Other ways in which radiation leads to impaired growth are by damaging the hypothalamic-pituitary axis, resulting in impaired growth hormone (GH) secretion, and, probably more importantly, by damaging the growth plate, resulting in GH resistant impaired growth. Other factors contributing to impaired growth after HCT are chemotherapy induced hypogonadism, chronic GVHD and, even more important, its treatment with glucocorticosteroids.

Radiation-induced damage to the epiphyseal growth plate

Besides radiation-induced GHD, radiation-induced damage to the growth plate probably plays an important role in impaired growth after HCT as well, as impaired growth also occurs after conditioning for HCT with total lymphoid irradiation (TLI) or thoraco-abdominal irradiation (TAI), even though the hypothalamic-pituitary axis lies outside the irradiated field in these patients [5]. For obvious reasons, most data on radiation damage to the growth plates comes from animal experiments. Local irradiation of long bones with doses comparable to those used in TBI, results in massive structural damage of epiphyseal growth plates and permanent impairment of longitudinal growth [18;19]. The cause of this impairment of growth is unknown, but recent evidence suggests a role for the parathyroid hormone-related peptide (PTHrP), a paracrine/autocrine factor that co-ordinates proliferation, differentiation and structural integrity in the growth plate. Irradiation decreases the expression of PTHrP in growth plate chondrocytes both in vitro (at mRNA level) [20] and in vivo (at protein level) [21;22] (*see also chapter 3*). In addition to PTHrP, other factors will probably also contribute to the damage of the growth plate; therefore, more (animal) studies are needed to clarify the mechanisms of radiation-induced growth impairment by damage to the growth plate.

Radiation-induced damage to the hypothalamic-pituitary region

Irradiation of the hypothalamic-pituitary region can disturb the regulation of GH secretion by a yet unknown mechanism [23], with a decrease in spontaneous GH pulse amplitude but with preserved pulsatility and diurnal variation [24;25], resulting in GHD or GH neurosecretory dysfunction (GHND). In GHND the regulation of GH secretion is disturbed and spontaneous GH secretion is impaired. GH secretion in response to pharmacological stimuli, used as

diagnostic tool for GHD, however, is intact [26]. The incidence of radiation induced alterations in GH secretion increases with radiation dose and with time interval after irradiation [27;28;28-31], with disturbances at the hypothalamic level probably preceding those at the pituitary level [32].
The underlying mechanism of radiation-induced GHD is unknown. Recently a possible role for leptin in radiation induced GHD was suggested [33;34]. Apart from being a satiety signal that plays an important role in energy balance regulation, leptin is thought to influence endocrine axes, including suppression of GH secretion [35]. Brennan et al. found increased leptin levels in adults treated with cranial irradiation for childhood acute lymphoblastic leukaemia (ALL), the majority of whom had developed GHD [33]. They stated that the increase in leptin was either caused by GH deficiency or by radiation-induced damage to the hypothalamic region, resulting in leptin insensitivity. Couto-Silva et al. found a negative correlation between leptin and stimulated GH secretion after HCT and TBI, and suggested that leptin could be used as a marker for radiation induced hypothalamic-pituitary lesions [34]. Adan et al. also found increased leptin levels in patients with GHD after cranial irradiation during childhood (n=90), but in contrast to Brennan and Couto-Silva, they found no relation with GH peak response to pharmacological stimuli [36]. Whatever the cause of radiation-induced GHD, however, GH replacement therapy should result in significant catch-up growth in the absence of other causes of impaired growth (e.g. radiation damage to the growth plate).

GH secretion after HCT

There is a large variation in the reported incidence of GHD after HCT [37], which can be explained by differences in study populations such as different conditioning regimens (TBI doses, fractionation, dose rate), different proportions of patients with GVHD or a history of cranial irradiation, and differences in duration and structure of follow-up. In addition, various studies have used different criteria for the diagnosis of GHD, and many fail to use assay specific references [38]. Therefore, comparing the results of different studies should be done with caution.
Although GHD and GHND are often related to cranial irradiation prior to HCT, they also occur after TBI without a history of cranial irradiation [6;7;10;13;39-47] (*see also chapter 8*). Sanders [15] gathered information from 8 publications on the

results of GH secretion tests in 243 TBI patients (prior cranial irradiation excluded) and found that GHD was present in 64% of the patients tested, whereas we found GHD only in 9% of our TBI treated patients (*chapter 8*) [47]. Possible explanations for the low incidence of GHD in our population are the use of strict criteria for GHD [38] and the lower total TBI doses used in our transplant centre.

Radiation-free conditioning and GH secretion

As already stated, impaired growth is not a well-established complication of Bu/Cy-Based conditioning regimens, and decreased GH secretion is rare (GHD and GHND is reported in six children without a history of cranial irradiation) [13;14] (*see also chapter 9*). The high dose of busulphan (which easily crosses the blood-brain barrier) was suggested as probable cause of GHD in these patients in one report, as the plasma levels in the two patients with GHD were higher compared to other children receiving Bu/Cy [13]. Afify et al. [11], however, did not encounter impaired growth in any of their 23 Bu/Cy patients, even though their unique dosage of busulphan (150 mg/m^2 *once* daily compared to the commonly used 4 mg/kg divided in 4 gifts) will have resulted in very high peak plasma levels of busulphan. Therefore, more data are needed to establish the role, if any, of decreased GH secretion in patients conditioned with Bu/Cy.

Complications in the evaluation of GH secretion after HCT

The diagnosis of decreased GH secretion is often based on indirect markers of spontaneous GH secretion. The most important marker is the GH response to pharmacological stimuli, supported by serum levels of IGF-1 and IGFBP-3 and by auxological data such as decreased growth rate and an increased body mass index (BMI). The correlation between two consecutive GH provocation tests is poor in children treated with HCT [34], and the possibility of GHND makes GH provocation tests less sensitive in the diagnosis of decreased GH secretion. In addition, failure to use assay-specific references may result in false positive diagnosis of GHD [48]. Serum IGF-1 and IGFBP-3 levels can be used to support the diagnosis, but several studies have shown that plasma levels of IGF-1 and IGFBP-3 have only limited value in diagnosing GHD after low-dose cranial irradiation and TBI [34;36;43;49]. In idiopathic GHD, BMI is an indirect marker for the decreased GH secretion. Growth hormone, however, is only one of many factors influencing BMI; other important factors are nutritional

status and leptin. Poor nutritional status can obscure a possible effect of GHD on BMI, but in a combined European study nutritional status after TBI appeared to be good [50]. Although all indirect markers for decreased spontaneous GH secretion have a limited value in diagnosing radiation induced decreases in GH secretion, in combination (e.g. stimulated GH secretion and serum levels of IGF-1 and IGFBP-3) they could be used as an indicator. The best way to diagnose disturbances of GH secretion after cranial irradiation, however, is by constructing spontaneous GH secretion profiles, which is a costly and time-consuming method [30;51].

Value of evaluating GH secretion after HCT

The influence of GH on longitudinal growth does not only depend on GH secretion, but also on the capacity of epiphyseal chondrocytes to respond to stimuli from the somatotrophic axis. As radiation may alter this capacity to respond to the growth-promoting stimuli (sometimes referred to as GH resistance), the relation between GH secretion and longitudinal growth becomes less clear. Indeed, in our experience, GH secretion, IGF-1 and IGBP-3 do not correspond well with either the magnitude of impaired growth or with growth response to GH therapy. Therefore, evaluation of GH secretion after TBI and HCT is not only complicated, it also has limited value in predicting the response to GH therapy, as the contribution of partial resistance of epiphyseal chondrocytes to GH is not known (chapter 8) [47]. However, GH is not only involved in longitudinal growth, but also in many other processes (e.g. bone mass, body composition, regulation of lipid- and glucose metabolism), and the effect of severely decreased GH secretion on these processes provides additional arguments for the evaluation of GH secretion. We therefore believe that GH secretion should be evaluated (using pharmacological tests) in children with impaired growth after HCT, in spite of the limited value in predicting growth response to GH therapy.

GH therapy after HCT

Effects of GH therapy

In a multi-centre evaluation of growth and final height after HCT [5], changes in HSDS between HCT and final height in patients treated with GH were similar to

the changes in patients not treated with GH. The authors' conclusion that GH therapy did not influence final height, however, is open for debate. One must assume that patients only received GH therapy on indication (e.g. more profound growth retardation or decreased GH secretion). Therefore, GH therapy was given to a selected sub-population, in which growth is more likely to be impaired, and decrease in HSDS is expected to be greater. One could argue, therefore, that similarity in height SDS changes may be interpreted as a positive result of GH treatment. Furthermore, many patients were treated at a time that GH therapy was not readily available, and GH dosages are likely to be lower than those used in the last decade, when recombinant human GH has become readily available. Most single-centre reports of GH treatment after HCT show some positive effect of GH therapy on growth. Some studies show restoration of growth without catch-up growth [45;46], whereas others show catch-up growth as well. [13;40;42]. Recently, several centres have reported final heights after GH therapy in children with a history of TBI (*chapter 8*) [47]. Using multiple regression analysis, Frisk et al. reported an estimated effect of GH therapy on height SDS of approximately 0.2 SD for each treatment year [6], whereas Sanders et al. report an estimated effect on final height of +0.86 SD [7]. In both reports children treated with GH were considered GH deficient. We recently analysed the effect of GH therapy on growth after pre-pubertal TBI in 20 patients using a random effects model, which resulted in an estimated effect of +1.2 SDS five years after initiation of GH therapy, even though 16 of them (80%) were not GH deficient.

Safety of GH therapy after HCT

Recombinant human GH is considered as a safe therapeutic agent and the general consensus is that it does not increase the risk of malignancies in patients with idiopathic GHD. We reported a relapse leukaemia in one of the 23 patients receiving GH therapy after HCT, compared to six relapses in the 43 patients not treated with GH (*chapter 8*) [47]. So far, none of the other single-centre studies on the effect of GH therapy in BMT-patients have reported a relapse of the initial disease after onset of GH therapy [6;7;13;40;42;43;45;46;52-54]. We also reported two secondary malignancies in patients treated with GH (one thyroid carcinoma and one osteosarcoma), compared to one in 43 untreated patients (malignant schwannoma) (*chapter 8*) [47]. Sanders et al. reported 6 secondary malignancies in 42 GH treated patients, compared to 8 in 48

untreated patients [7]. A large study by Sklar et al. [55] on 5-year survivors of childhood cancer revealed no evidence that treating survivors of childhood leukaemia or non-Hodgkin lymphoma with GH increased the risk of either disease recurrence or death. They did, however, observe a slight increase in the risk of secondary solid tumours (not secondary leukaemia) in patients receiving GH (n=122) compared to those who did not (n=4545), but the number of patients was small (6 solid tumours in 122 patients treated with GH; relative risk 4.98, 95% CI 1.95-12.74). In patients with other types of malignancy, no significant increase in secondary tumours was found. In addition, all six secondary solid tumours occured in patients who had received irradiation, an important risk factor for both secondary tumours and GH deficiency. Therefore, no definite conclusions can be drawn from these data, and further studies will be necessary to assess the clinical importance of these findings. It is important that the patient and/or his parents are informed about all possible risks and benefits of GH treatment before GH therapy is given to survivors of HCT.

Ovarian function

After a fixed maximum at 5 months gestational age, the number of primordial follicles in the human ovary progressively decreases with increasing age in a bi-exponential fashion, resulting in the menopause at about the age of 50 years [56]. Both chemotherapy and radiotherapy will accelerate oocyte depletion, resulting in premature ovarian failure.

Effects of chemotherapy

Radiation-free busulphan-based conditioning regimens are very gonadotoxic. In pubertal and post-pubertal females, recovery of gonadal function after Bu/Cy-based conditioning is reported in 3 of 125 women (2.4%) [57-59]. In younger women, incidences of recovery are not much higher. Combining our data (chapter 9) with several other reports [10;11;60-62], recovery of gonadal failure after Bu-based conditioning is seen in 5.3 % of 75 girls. In contrast to these data, Shah et al. conclude that long term endocrine side effects of Bu/Cy (16/200 mg/kg) conditioning for leukaemia are minimal [63]. In this study, however, only 13 of 26 relapse-free survivors (both boys and girls) were tested for ‘endocrinopathies’ and gonadal failure was reported in 2 girls using age

specific references for LH and FSH. As this report does not mention sex, age or pubertal status of the 13 patients tested, we believe the conclusions drawn by the authors are premature.

Effects of TBI

Depletion of the number of primordial oocytes after a given dose of radiotherapy is proportional to the size of the oocyte pool. As younger patients have more oocytes, the number of remaining oocytes after radiotherapy is higher in younger patients. Therefore, premature ovarian failure will occur after longer post-irradiation intervals in younger patients, giving the impression that the cytotoxic effect of radiation on the ovary is less severe in younger women [64].

Besides the age at HCT and the radiation dose, cumulative dose of gonadotoxic chemotherapeutic agents also influence the incidence of ovarian failure. The sparing effect of fractionation of TBI is unclear. As the ovary is a radiosensitive organ (radiation dose required to kill 50% of oocytes (LD_{50}) is less than 2.0 Gy) [65], the theoretical benefit of fractionation is limited, and fractionated TBI may be more damaging due to the higher total radiation dose required. In girls receiving TBI before onset of puberty, the number of patients without a spontaneous onset of puberty can be used as an indicator of gonadal failure (provided that age at TBI does not differ largely between patients). Combining the results of single centre studies that report incidences of spontaneous pubertal development after pre-pubertal TBI-based conditioning, using the most recent publication with useful information for each centre, yields the following results: the incidence of spontaneous puberty after 10 Gy sf-TBI (29 patients) is 41 % [61;66;67], whereas after 12-15.75 Gy f-TBI (63 patients) it is 43% [17;61;67;68]. In our centre, relatively low doses of sf-TBI are used (7-8Gy), which resulted in spontaneous onset of puberty in 6 of 10 (60%) patients (*chapter 6*). Frisk et al. also used 7.5 Gy sf-TBI. They reported induction of puberty in 3 of 6 girls (50%) receiving TBI before puberty [6].

In females receiving TBI-based conditioning during or after puberty, recovery of ovarian function after TBI can be used as an indicator of gonadal damage. The only study correcting for age at TBI in multiple regression analyses, reported a 4.8 times higher likelihood of recovery from initial ovarian failure after 6 x 2.0 Gy f-TBI compared to either 10 Gy sf-TBI or 7 x 2.25 Gy f-TBI [69]. The number of patients in this study, however, is limited, with recovery of gonadal function

in patients who received TBI at ages ≤ 25 years only (9 recovered: 7 of 29 after 12 Gy f-TBI; 2 of 36 after 10 Gy sf-TBI; 0 of 11 after 15.75 Gy f-TBI). In addition, the same authors reported recovery in 18 of 61 women (30%) after 8-10 Gy sf-TBI, 28 of 272 (10%) after 10-12 Gy f-TBI and 11 of 203 (5%) after 14-15.75 Gy f-TBI [15]. Unfortunately, in this report age at TBI was not reported, but unless the sf-TBI patients were significantly younger at the time of TBI, these data do not support a beneficial role of fractionation of TBI dose for gonadal function.
Based on the available data, there is insufficient evidence for a sparing effect of fractionation on the ovaries. A large (multi-centre) study, correcting for age at TBI, is needed to clarify this issue.

Testicular function

Of the three major cell types in the human testis (germ cells, Leydig cells and Sertoli cells), the germ cells are the most sensitive to cytotoxic effects of radiation and certain types of chemotherapy, especially alkylating agents, with a higher sensitivity in more primitive cell types (i.e. spermatogonia > spermatocytes > spermatids) [70;71].
Recovery of spermatogenesis occurs from surviving stem cells, and duration of azoospermia is dose-dependent and may last several years, with only partial recovery after higher doses [70;72]. There is evidence that recovery of spermatogenesis is more likely if males are treated before onset of puberty [72;73].

Effects of Chemotherapy

In men receiving radiation-free conditioning for HCT, Sanders et al. reported evidence of sperm production in 61% of patients receiving cyclophosphamide only (Cy, 200 mg/kg, n=109), and in 17% of patients receiving Cy (200 mg/kg) and busulphan (Bu, 16 mg/kg, n=46) [57]. Although the addition of Bu probably accounts for much of this difference in incidence of recovery of spermatogenesis, other chemotherapeutic agents could also contribute to the difference, as indication for HCT may have influenced the type of conditioning, e.g. Cy in patients with severe aplastic anaemia and Bu/Cy in patients with

haematological malignancies (the latter group probably had received gonadotoxic agents prior to conditioning).
Grigg et al. reported a higher incidence of recovery of spermatogenesis after radiation-free, Bu/Cy-Based conditioning with lower doses of Cy (Bu 16 mg/kg, Cy 120 mg/kg) in adults who had not received prolonged therapy with alkylating agents [58]. In this study, sperm was detectable in semen of 21 of 26 patients with semen analyses (11 had sperm count >20x10^6/ml). There was a negative correlation between serum levels of FSH and sperm count. In addition, in 6 of 21 patients without semen analyses recovery was based on successful procreation, with normal FSH levels in 4 of the 15 remaining patients. Differences in doses of cytotoxic agents, duration in follow-up (median 2 versus > 5 years), or gonadotoxic treatment prior to conditioning may account for differences in recovery between the two studies. All other studies on testicular function after radiation-free, Bu/Cy-Based conditioning have limited numbers of patients and do not report semen analysis. In our own Bu/Cy population, all 4 boys who had received low dose Bu/Cy (8 mg/kg Bu) and 2 of the 5 boys receiving high dose Bu/Cy (16-20 mg/kg Bu) with at least 2 years of follow-up during puberty, had recovery of gonadal function after Bu/Cy-Based conditioning without prior gonadotoxic treatment (*chapter 9*).
Leydig cell function is normal in most patients after Bu/Cy (*chapter 9*), although in some patients, LH is slightly elevated and serum testosterone is in the lower range of the reference interval, suggesting some Leydig cell dysfunction [10;11].

Effects of TBI

The germinal epithelium is one of the most radiosensitive human tissues, and azoospermia occurs after a single radiation dose of 0.8 Gy [74]. Complete recovery of spermatogenesis will take more than 9 months after 1 Gy, with time to recovery increasing with increasing radiation dose (e.g. > 5 years after doses of 4 Gy and higher). Both animal and human data suggest that fractionation increases gonadal toxicity of radiation [71;75]. Recently, two reviews have addressed the issue of recovery of spermatogenesis after TBI-based conditioning, and both report that the chance of recovery is small [37;76]. One review suggested a higher incidence of recovery after sf-TBI compared to f-TBI [37]. However, Sanders et al. reported comparable incidences of recovery of spermatogenesis after sf-TBI and f-TBI: 20% of 71 males receiving 10 Gy sf-TBI % and 17% of 392 males receiving 12-15.75 Gy f-TBI [57]. In theory, patients

receiving relatively low dose (7-8 Gy) sf-TBI before onset of puberty should have the highest incidence of recovery of spermatogenesis. In our study population, however, only 1 of 13 boys receiving TBI before onset of puberty showed evidence of recovery of spermatogenesis (*chapter 6*), even though 10 of 13 received 7-8 Gy sf-TBI. Three possible explanations for this low incidence are 1) the small size of the population, 2) the use of a high instantaneous dose rate (0.23 Gy/min) and 3) differences in additional gonadotoxic effects of chemotherapy prior to conditioning in our patients compared to those in the studies of Sanders et al.

Leydig cell damage occurs after a single dose of 0.75 Gy or fractionated total dose of 2 Gy in adults, resulting in transient elevation of LH but unchanged testosterone levels [74;77]. After radiation doses of 14-20 Gy to testes of patients with carcinoma in situ, Leydig cell dysfunction is often permanent [78;79], with elevated LH levels and testosterone at the lower limits of the reference interval. After doses of 18 to 20 Gy, 29% of adult patients required permanent testosterone substitution [80]. Recovery of Leydig cell function, however, can be seen after total doses as high as 24 Gy [66]. In contrast to germ cells, Leydig cells appear to be more radiosensitive in pre-pubertal males compared to adult males [73], resulting in severe hypogonadism in most boys receiving 20 Gy testicular irradiation before puberty. In our clinic, all patients who had received 10 Gy testicular irradiation in addition to sf-TBI had severe Leydig cell failure, resulting in hypergonadotrophic hypogonadism and absent pubertal development or pubertal arrest (*chapter 6* and unpublished data).

Thyroid function

Both chemotherapy and radiation can result in thyroid dysfunction, with compensated primary hypothyroidism in the majority of the patients. The incidence of thyroid dysfunction found in the different studies, however, is influenced by many other factors besides conditioning regimen, e.g. duration of follow-up, definition of compensated hypothyroidism, follow-up protocol (standard performance of TRH test at regular times versus symptoms-based screening) etcetera.

Effects of chemotherapy

After radiation-free conditioning, (compensated) hypothyroidism occurs in 10-15 % of both children [10;11;81] and adolescents [59;82-85]. In addition, Somali et al. describe exaggerated TSH responses to TRH in 61% of patients after radiation-free conditioning [85]. As they defined exaggerated response as more than 5-fold increase in TSH from baseline without any consideration for the absolute levels of TSH, this figure is likely to be an over-estimation of thyroid dysfunction in these patients.

Effects of TBI

There is some evidence that fractionation of TBI has a sparing effect on thyroid function, but reported incidences of thyroid dysfunction show a large variation between different centres. After fractionated TBI, some centres report incidences of 10-20 % [84;86] whereas others report 30-35% [87;88]. After sf-TBI thyroid dysfunction is more common, with incidences up to 87% reported by Borgström et al. [89]. In that study, the diagnosis of (compensated) hypothyroidism was based on basal values of TSH and free T4 in 48% of 27 patients after 10 Gy sf-TBI. An additional 41% had exaggerated TSH responses to TRH stimulation. Other studies using 9-10 Gy sf-TBI report incidences of hypothyroidism of 46-73 % [88;90;91].
In our single centre evaluation (*chapter 4*), the incidence of thyroid dysfunction after sf-TBI was just 11% in 18 patients. Reviewing the data of all patients in the various studies presented in this thesis, thyroid dysfunction after 7-12 Gy sf-TBI was diagnosed in 40% of 96 patients (unpublished data). These data support a role for fractionation of TBI in the preservation of thyroid function.

Conclusions and recommendations

Growth and GH secretion

In the majority of the patients receiving radiation-free conditioning for HCT, growth will not be impaired. Some patients, however, do suffer from impaired growth, and GHD could be diagnosed in few of these patients. Therefore, growth should be monitored closely after radiation-free conditioning for HCT, and further testing for GHD should be performed if growth is impaired. The use of radiation-based conditioning regimens in the preparation for HCT often leads

to impaired growth, which is a combined result of decrease in GH secretion due to radiation-induced damage to the hypothalamic-pituitary region and GH resistance due to radiation-induced damage to the epiphyseal growth plate. The value of standard tools for the diagnosis of decreased GH secretion is limited and the evaluation of GH secretion is not helpful in predicting growth responses to GH therapy. As decreased GH secretion has consequences for other metabolic processes as well (e.g. peak bone mass), Shalet et al. suggested that GH replacement therapy should be considered in all patients with GH deficiency, irrespective of auxology [92]. In children treated with HCT, GH secretion should be analysed by pharmacological tests if impaired growth is present. Due to radiation-induced growth plate damage, the results of these analyses are not related to the growth response to GH therapy, and patients with normal stimulated GH secretion may benefit from GH therapy (*chapter 8*) [47]. Therefore we would suggest that a one-year trial-period of GH therapy should be considered in all patients with impaired growth after TBI, irrespective of GH secretion status.

Gonadal function

The majority of children receiving TBI and/or high-dose chemotherapy during conditioning for HCT will suffer germ cell damage, resulting in premature ovarian failure in girls and impaired spermatogenesis in boys. Overt Leydig cell failure occurs after higher doses of irradiation and/or chemotherapy. Therefore, hypogonadism in boys is generally associated with additional gonadotoxic treatment (e.g. prophylactic testicular irradiation). We recommend routine screening for hypogonadism after HCT in all patients, with prompt initiation of sex hormone replacement therapy in cases with either hypergonadotrophic hypogonadism or delayed puberty. In view of the high incidence of infertility, we recommend attempts to preserve fertility using semen cryopreservation in all adolescent boys before initiation of gonadotoxic treatment. In girls, cryopreservation of ovarian cortical strips is an option, but expertise in both preservation and re-implantation techniques are very limited, and restoring fertility from cryopreserved ovarian tissue is still experimental [64]. In addition, in patients treated for a haematological malignancy, the risk of re-introducing malignant cells by re-implantation of ovarian tissue is of great concern.

Thyroid function

In view of the high risk of (compensated) hypothyroidism, which appears to increase with time since HCT, we recommend evaluation of thyroid function at regular intervals in all patients after HCT. Although interesting from a scientific point of view, standard dynamic testing of the hypothalamus-pituitary-thyroid axis is not recommended, as it has no therapeutic consequences. Substitution with levothyroxine is indicated in patients with overt hypothyroidism and recommended in patients with compensated hypothyroidism (the latter in an attempt to reduce the risk of thyroid malignancy and/or developmental delay) [37].

Fractionation of TBI

Endocrine late effects of HCT occur in the majority of patients receiving HCT, especially if TBI or busulphan based conditioning regimens are used. Fractionation of TBI may decrease the incidence of (compensated) hypothyroidism, but a sparing effect of fractionation is not evident for gonadal function or final height. As radiation induced thyroid dysfunction is limited to compensated hypothyroidism in most patients, and hypothyroidism is easily correctable with substitution therapy, we believe that late effects of the endocrine system do not offer solid grounds for the introduction of fractionated TBI in our clinic.

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