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

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Summary

This thesis contains the results of several studies on the long-term consequences of the myeloablative conditioning for haematopoietic stem cell transplantation (HCT) during infancy and childhood, with the emphasis on late effects on endocrine functions.

Chapter 1 gives a general introduction to late effects after HCT. First, the etiological roles of chronic graft-versus-host-disease and conditioning regimens are discussed, and some background information on the basic aspects of the radiobiology of total-body irradiation (TBI) is given. In addition, the most important endocrine late effects are briefly introduced.
Chapter 2 describes the effects of TBI as single toxic agents on growth, pituitary and thyroid gland in non-human primates. TBI had a negative effect on body fat. There was no evidence of (compensated) hypothyroidism, but dose dependent decrease in thyroid weight and changes in follicular structure suggest some effect of TBI on the thyroid gland. The decreased IGFI/IGFBP-3 ratio in the high-dose group may indicate that the somatotrophic axis was mildly affected by TBI.
In **chapter 3** the direct effects of radiation on the tibial growth plate of rats are studied. Radiation resulted in persistent growth delay of the irradiated tibiae, with a difference in length of more than 10% between the irradiated and the non-irradiated tibiae 15 weeks or more after irradiation. The growth plate architecture was disturbed, and the expression of both PTHrP and IHh was decreased in the irradiated tibiae. As PTHrP and IHh are key regulators of both the pace and the synchronisation of the differentiation of growth plate chondrocytes, the reduced expression of PTHrP and IHh may contribute to the changes found after irradiation.
In **chapter 4** results of a cross-sectional study on both endocrine and non-endocrine late effects of HCT during childhood are presented in a population of adult survivors of childhood HCT. Final height was reduced, with a median reduction of 1.6 SDS compared to height SDS at time of HCT as well as compared to the target height. The majority of the girls developed gonadal failure, with recovery in 2 of them. Reproductive gonadal function was decreased in the majority of the men. Hypothyroidism was diagnosed in 10% of patients. Osteopenia was found in 68% of patients, osteoporosis in 10%. Restrictive lung function was present in 67%; renal function was normal in all patients. Cataract was diagnosed in 79 % of patients who had received TBI,

the majority of these did not receive eye shielding during TBI. These data give some insight in the late effects in our centre.

Chapter 5 describes results of a large multi-centre study on final height after HCT before onset of puberty. Data on 181 patients with aplastic anaemia, leukaemia, and lymphoma were analysed. An overall decrease in final height standard deviation score (SDS) was found compared to height SDS at HCT and to genetic height SDS. Irradiation, male gender and young age at HCT were major factors contributing to decreased final height. The combination of previous cranial irradiation and single-dose TBI caused the greatest negative effect on final height. Fractionation of TBI reduces this effect significantly and conditioning with busulphan and cyclophosphamide seems to eliminate it. Nevertheless, the majority of patients (140/181) have reached adult height within the normal range of the general population.

In **chapter 6** results of a study on the pubertal development and growth of 40 children receiving TBI and HCT for haematological malignancies are presented. In the 19 boys who had not received additional testicular irradiation, penile growth and pubic hair development was normal and all had serum testosterone levels within the adult range. The majority of them, however, had incidental elevations of LH, suggesting minor Leydig cell damage. Testicular volume at the last measurement was small (mean: 10.5 ml) and serum FSH levels were elevated in all boys, suggesting severe impairment of reproductive gonadal function. Normalisation of FSH occurred in one boy. Puberty developed spontaneously in 6/10 girls who received HCT before puberty. In the remaining four girls, puberty was induced after they had developed hypergonadotrophic hypogonadism. Recovery of gonadal function after cessation of substitution was seen in one girl, who became pregnant twice (both pregnancies ended in spontaneous abortions). Decrease in height SDS was seen in the majority of patients and was positively correlated with male gender and lower age at the time of HCT. We concluded that careful monitoring of both gonadal function and growth after bone marrow transplantation and total body irradiation is warranted in order to detect disturbances early and ensure normal pubertal development in children treated for haematological malignancies.

Chapter 7 describes patterns of growth and body proportions of 75 children receiving TBI and HCT before onset of puberty. Thirty-two patients had reached final height (FH). Median change in height SDS between HCT and FH

was -1.7 in boys and -1.1 in girls. Peak height velocity (PHV) was decreased in the majority of the patients. Decrease in sitting height SDS did not differ between boys and girls (0.15 SD/yr). In boys, decrease in leg length SDS was of comparable magnitude (0.12 SD/yr), whereas in girls decrease in leg length was less pronounced (0.02 SD/yr), leading to a significant decreased sitting height/height ratio SDS in girls only. The sex-specific effects of several variables on height SDS (e.g. age at HCT, time since HCT, onset of puberty) were analysed by linear mixed-effects modelling, showing a slightly faster decrease in younger children, and a more pronounced decrease during puberty in boys compared to girls. We conclude that 1) younger children are more susceptible to growth retardation after TBI and HCT, 2) pubertal growth is more compromised in boys, and 3) leg growth is relatively less affected in girls, possibly due to a high incidence of gonadal failure in girls.

In **chapter 8** results of evaluation of growth hormone (GH) secretion in 29 children with impaired growth after TBI and HCT are presented. Impaired GH secretion was diagnosed in 8 patients, and GH therapy (1.33 mg/m^2) was started in 23 of the 29 patients tested. Height SDS increased in the first year of treatment in the vast majority of patients receiving GH (mean increase 0.35 SDS). The effect of GH therapy was estimated by comparing growth of individual patients after onset of GH therapy to the predicted growth based on individual growth before onset of GH therapy and the model derived from the study described in chapter 7. The calculated net effect of GH therapy on height SDS was +1.1 SDS. Response to GH therapy did not correlate to the parameters of GH secretion, which suggest that variable degrees of GH resistance (due to damage to the epiphyseal growth plates inflicted by the irradiation) are probably more important than GH secretion status. As GH therapy was effective in patients, irrespective of GH secretion status, we propose a trial of GH therapy in all children with impaired growth and expected low adult height after TBI.

Chapter 9 describes growth and endocrine function after busulphan (Bu) based conditioning in 64 children without a history of irradiation. Mean height standard deviation scores remained stable, but unexplained disturbances of growth after HCT were found in 17/48 (35%) of the children without growth-limiting disorders (10/23 in patients treated for haematological malignancies). In 10 patients, growth hormone (GH) secretion status was evaluated, and insufficient GH secretion was diagnosed in four patients. Thyroid function was

evaluable in 52 patients. Two developed antibody-mediated thyroid disorders and 10 (19%) compensated primary hypothyroidism. Gonadal function was evaluable in 21 patients and was normal in all seven patients treated with low-dose Bu (8 mg/kg), whereas seven of the 14 children receiving high-dose Bu (16–20 mg/kg) developed gonadal failure; the majority of these patients had not been exposed to gonadotoxic therapy prior to conditioning. Of the 49 evaluable patients, 16 developed subclinical hyperparathyroidism. We conclude that, besides gonadal and thyroid dysfunction, impaired growth and hyperparathyroidism often occur after busulphan based conditioning for HCT and that growth impairment may be the result of insufficient GH secretion.

In **chapter 10** Quality of life (QOL) is investigated in 22 adult survivors of childhood HCT, using both generic and disease-specific questionnaires. HCT-related variables were obtained from medical files. Of the generic QOL measures, most results fell within the normal range of functioning, although some illness-related impairment was reported on subscales for general and work-related functioning. Compared to a reference sample of patients who had received HCT as adults, patients involved in this study scored significantly higher on the 'emotional well-being' subscale of the disease specific QOL instrument, indicating significantly better emotional functioning. The age at HCT and TBI were not related to patients' QOL. We conclude that on the long term, having received HCT during childhood does not negatively affect the QOL of patients.

In **chapter 11** the most important long-term endocrine effects of HCT are discussed, combining the results presented in this thesis with other data from the literature. At the end of this chapter, conclusions and recommendations are given.