Final Height and Growth Hormone Secretion after Bone Marrow Transplantation in Children

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Abstract. Growth hormone (GH) deficiency has been regarded as a principal determinant for growth failure following bone marrow transplantation (BMT). We herein analyzed final height and GH secretion in the patients who received BMT during childhood. The study on final height in 30 patients (23 males; 19 with malignant disease) who underwent BMT before or at the onset of puberty showed the following findings: (1) Final height SD score (SDS) significantly decreased compared to pretreatment height SDS. (2) Patients who underwent BMT before the age of 10 years showed significantly greater reduction in height SDS compared to those who received after the age of 10 years. (3) The type of disease or a difference in preconditioning regimen did not influence the outcome of growth. (4) No patient showed GH deficiency. The study on GH secretion included 71 patients who had been followed for more than 5 years and who underwent insulin tolerance test more than twice following BMT. Thirteen patients experienced poor GH response at least once. Two of these patients had poor GH response repeatedly. In conclusion, children who undergo BMT at younger age have a higher risk of growth failure, and GH deficiency is not a major contributing factor for growth impairment following BMT.

Key words: Growth: Growth hormone, Growth hormone deficiency, Bone marrow transplantation

Bone marrow transplantation (BMT) has become a standard treatment for various hematological or non-hematological disorders. Since the number of long-term survivors is increasing, insult on growth and endocrine function has become an essential issue. Suppression of linear growth is one of the important sequelae among children who underwent BMT. It has been repeatedly stated that impaired growth hormone (GH) secretion is responsible for decline in linear growth [1-3]. Recent studies including ours, however, show that GH deficiency may not be a major factor [4-8].

In our institution, over 200 patients received BMT during the past 18 years, and the number of recipients who reached final height has been increasing. We herein describe our data on the growth of the patients who attained final height and on the status of GH secretion in young marrow recipients.

PATIENTS AND METHODS

Study 1: Growth and GH Secretion among Patients Who Reached Final Height

The study on final height consisted of 30 patients (23 males and 7 females), who underwent allogeneic BMT before or at the onset of puberty. Nineteen patients had malignant disease including leukemia or non-Hodgkin lymphoma, and 11 patients had non-malignant disease including severe aplastic anemia, Wiskott-Aldrich syndrome, or Fanconi anemia. The
age at BMT ranged from 2 to 14 years (median, 10.1 years), and the follow-up duration ranged from 8 to 16 years (median 12 years). No patients received GH treatment.

**Study 2: Changes in GH Secretion after BMT**

The study on GH secretion consisted of 71 patients (40 males and 31 females) who had been followed for more than 5 years after allogeneic BMT and underwent insulin-tolerance test more than twice following BMT. The patients in Study 1 are included. Forty-eight patients had malignant disease including various types of leukemia or lymphoma, and 23 patients had non-malignant disease consisting of aplastic anemia, Fanconi anemia, Wiskott-Aldrich syndrome or metabolic disease including Gaucher disease. The age at BMT ranged from 0.1 to 21.1 years (median, 9.1 years), and the follow-up duration was from 5 to 18 years (median, 10 years).

**Preconditioning for BMT and Prevention of Graft-Versus-Host Disease**

The preconditioning regimes were irradiation and chemotherapy. Patients with malignant disease received 8 to 12 Gy of total body irradiation (TBI) as six fractions, and those with non-malignant disease were given 3 to 8 Gy of either fractionated TBI or thoracoabdominal irradiation (TAI). Three and seven patients in Study 1 and 2, respectively, underwent BMT without irradiation. Chemotherapy consisted of cyclophosphamide (50 to 60 mg/kg/dose, iv, for 2 to 4 days), cytosine arabinoside (3 g/m² /dose × 2/day, iv, for 5 days), etoposide (50 to 60 mg/kg × 1, iv), and antilymphocyte globulin, either alone or in combination.

For graft-versus-host disease (GVHD) prevention, patients were given cyclosporine A (3 mg/kg/day, iv) and/or methotrexate (15 mg/kg/day, iv, initially and 10 mg/kg/day, iv, for three times thereafter).

**Evaluation of Growth and GH Secretion**

Growth data of each patient were evaluated by analyzing changes in height SD score (SDS). The patient was defined to have achieved final height when the growth rate became less than 1 cm/yr for two consecutive years. Final height SDS was compared with pre-transplantation height SDS. The cross-sectional data of height based on the National Survey in Japan in 1990 were used as the reference standard.

GH secretion was repeatedly assessed by insulin tolerance test after BMT. Regular insulin (0.1 U/kg) was injected intravenously in the morning after an overnight fast, and blood was obtained every 30 min until 120 min from an indwelling venous catheter. Patients were regarded as GH-deficient if peak GH response was constantly below 10 ng/ml. GH was assayed by either radioimmunoassay or immunoradiometric assay. Plasma IGF-I concentration was determined in unextracted plasma by radioimmunoassay before 1993, and in extracted plasma by immunoradiometric assay after 1994.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using paired t-test, Mann-Whitney test, or one-way ANOVA depending on the situation.

**RESULTS**

**Changes in Growth among Patients Who Achieved Final Height (Study 1)**

Fig. 1 shows the changes in height SDS of the patients who reached final height. Final height SDS significantly decreased from the pretreatment values.
both in boys (pre-BMT −0.08 vs. final −1.12, p < 0.001) and in girls (pre 0.04 vs. final −1.64, p < 0.01). Except for one boy with aplastic anemia whose final height SDS increased by 0.13, all patients experienced decline in linear growth following marrow grafting.

Fig. 2 shows the difference in the outcome of growth according to the age at BMT. Patients who received marrow grafting before 10 years of age showed a significantly greater reduction in height SDS from pretransplant value compared to those who received after 10 years of age (−1.51 ±/− 0.93 vs. −0.83 ±/− 0.57, p < 0.05). Thus, the decrease in height SDS was significantly greater in patients who underwent BMT at younger age.

Next we examined whether there was a difference in linear growth depending on the type of underlying disease (Fig. 3). Although a decrease in height SDS was greater in patients with malignant disease (−1.32 ±/− 0.80) than those with non-malignant disease (−0.97 ±/− 0.91), no significant difference was observed statistically (p = 0.14). Concerning the mode of irradiation, patients who received TBI tended to experience a greater decrease in final height SDS, although statistical analysis was not possible due to the small number of patients who did not receive irradiation (Fig. 4). There was no statistical difference in the changes in height SDS between males and females (p = 0.0627).

Since there was a remarkable variation in the peak GH response to insulin loading test in each individual, it was necessary to repeat stimulation test and to add other indices including plasma IGF-I concentration in order to make a diagnosis of GH deficiency. Only one male patient with acute lymphoblastic leukemia constantly showed poor GH response and decreased plasma IGF-I levels. He had a mild reduction in height SDS (−0.85) from the pretreatment value, ending up with the final height SDS of −1.50. Another female patient with non-Hodgkin lymphoma experienced insufficient GH secretion at provocative test. However, her plasma IGF-I concentration, which was below normal at 0.2 U/ml initially, became normal thereafter, excluding the possibility of the presence of GH deficiency.
Changes in GH Secretion after BMT (Study 2)

The status of GH secretion was prospectively studied in a larger number of patients who received repeated GH provocative test (Fig. 5). Of the 71 patients studied, 13 experienced poor GH response at least once. Of these 13 patients, two exhibited poor GH response repeatedly. One male patient with acute myelocytic leukemia, whose height SD score decreased by 0.85, showed decreased plasma IGF-I levels constantly (0.73 to 0.93 U/ml). The other female patient with non-Hodgkin lymphoma, whose height SD score decreased by 1.04, had normal plasma IGF-I concentrations (250 to 300 ng/ml). Of the remaining 11 patients who had poor GH response at least once, two showed constantly low plasma IGF levels. Their height SD score decreased by 1.07 and 1.76.

**DISCUSSION**

Growth impairment is one of the significant late sequelae among long-term survivors following BMT. In this study, growth suppression was observed in 29 out of 30 marrow recipients who achieved final height. However, the occurrence of GH deficiency was rare.

Previous studies emphasized the significance of GH deficiency as the major factor for growth suppression after BMT, and the induction of GH treatment was advocated for those who were GH deficient [1-3]. Other studies, however, cast doubt on the role of GH as the principal determinant of impaired growth [4-8]. Thomas et al. found that the response to GH treatment was inadequate in children with impaired growth after BMT [4]. Brauner et al. described that there was no correlation between GH secretion and the height loss, and suggested that skeletal lesion induced by irradiation may be responsible for growth impairment [5]. We also have previously shown that the secretory status of GH did not predict the future growth pattern of marrow recipients [6].

Several investigators have reported analysis of growth and growth hormone secretion among patients who achieved final adult height. As the number of cases who reached adult height increased, it has become clear that growth suppression, which occurs in most of the children who received TBI, is not necessarily severe. Cohen et al. found that among 28 patients who reached final adult height, only one ended up with an adult height below −2.0 SDS, indicating that most of the patients stay in the normal height range despite the tendency to experience growth suppression after BMT [7].

Clement de Boers et al. found that insufficient pubertal height gain was mainly responsible for growth suppression after BMT, and that no patient showed GH deficiency in the 30 patients who reached final height [8]. Holm et al. reported the increased tendency of loss of final height among children who received BMT at younger age [9]. They described improvement of GH secretion may occur who ex-
experienced GH insufficiency after BMT. Therefore, recent studies oppose the liberal use of GH for those who experienced growth suppression after BMT.

Our results agree with these recent data that GH deficiency is not a major contributor for reduced growth velocity and final height. We are aware that more than two provocative tests are necessary to confirm the diagnosis of GH deficiency. However, since it was practically impossible to repeat two provocative tests on a regular basis, we analyzed GH secretion by interpreting the results of ITT and basal plasma IGF-I levels. Interpretation of plasma IGF-I levels requires special caution including age, sex, and general condition of the patient. It has been known that subnormal IGF-I is not an indicator of insufficient GH secretion, since various disease status or undernutrition can cause low plasma IGF-I levels [9, 10]. On the contrary, the possibility that patients with normal IGF-I levels have GH deficiency is considered to be low. In our survey, only one patient showed blunted GH response and low plasma IGF-I levels continuously. As Shalet and Brennan described, the cause of the growth disturbance is multifactorial [11]. Other factors including an insult on the epiphyseal plate of the long bone by irradiation or relatively inadequate nutrition around the time of BMT would be responsible for impaired growth [12]. Continuous growth failure despite the presence of normal levels of plasma IGF-I may suggest the presence of resistance to IGF-I due to irradiation, resulting in the defective longitudinal bone growth as described by Brauner et al. [10].

Most recently, growth of the bone marrow recipients who reached final adult height was reported by Cohen et al. [13]. They found that male gender, irradiation, and young age at BMT were major factors affecting subsequent growth impairment. They also found that GH did not influence final height.

In conclusion, the analysis of long-term survivors who received BMT in childhood showed a significant reduction in final height SDS, especially if the patient who underwent transplant at younger age. The incidence of GH deficiency was low, and GH deficiency is not a major determinant of growth failure following BMT.

References

