To the editor:

Final height after transplantation in childhood

With interest we read the paper by Sanders et al\(^1\) in which it is concluded that growth hormone (GH) therapy can increase final height in young children after hematopoietic cell transplantation (HCT). We do not disagree with the general conclusion that GH is efficacious in these children, but we would like to make several comments.

The paper does not offer information on the GH assay used. GH immunoassays show poor interassay agreement, with interassay variability up to 330\%, depending on assays and international standard reference preparations (66/217 1 mg = 2 IU; 80/505 1 mg = 2.6 IU; 88/624 1 mg = 3.0 IU) used.\(^2\) With most modern assays and new reference standards, the historical cutoff levels for peak GH after pharmacologic stimulation (7-10 ng/mL) should be reduced by 30\% to 50\%.\(^3,4\) Without information on assay and pulse-detection method used, interpretation of the 3 criteria for normal spontaneous (assumed nocturnal) GH secretion is impossible. Both the high incidence (84\%) of GH deficiency (GHD) in patients routinely tested and references for spontaneous GH secretion from the literature justify concerns about the diagnostic criteria. With regard to the criterion of more than 3 spontaneous peaks, we would like to point out that in non–GHD-deficient children the mean number of peaks is 4 to 5, with 3 peaks in a substantial number of children.\(^5,6\) In addition, in GHD (radiation induced or idiopathic) the peak amplitude is decreased, but peak frequency is preserved.\(^7,8\) With respect to the criterion that the highest peak should be more than 18 ng/mL (we assume that ng/dL is an administrative error), we comment that many studies report even lower mean or median values for maximum peak GH in non–GHD-deficient children.\(^8-11\) As there is no evidence that the spontaneous nocturnal peak GH is higher than the peak GH after pharmacologic stimulation, we believe that the cutoff for maximum GH should be the same for spontaneous and stimulated GH secretion (8.6 ng/mL). With respect to the criterion that the mean GH should be more than 3 ng/mL, we acknowledge that this cutoff was used in several older studies, but in more recent studies\(^4,6,8-11\) it is comparable with the mean (or median) value for average nocturnal GH levels in non–GHD-deficient children (median < mean due to skewed distribution of results).

Apart from the definition of GHD, we question the definition of final height (height measured closest to age 16 years). In healthy boys, there is a more than 3-cm difference between height at age 16 years and final height, and height velocity at age 16 years is approximately 3 cm/y. Therefore the article of Sanders et al\(^1\) reports about height at age 16 years rather than about final height. As this definition is used in both treated and untreated groups of patients, the results of the group comparison are still valid, but then only for the height at age 16 years. Actual final height could differ by 0.5 SD in boys.

GH treatment had a significant effect in children undergoing HCT before the age of 10 years, but not at more advanced ages. One could argue that age at start of GH therapy is more likely to influence the effect of GH therapy on final height than age at HCT: starting GH therapy at age 15.9 years (as one patient did) will probably have less effect than starting GH at age 12 years, irrespective of age at HCT. We are very interested in the effect of age at diagnosis of GHD/start of GH on final height, which could be helpful in deciding which patients should be considered for GH therapy.

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References


Response:

Growth hormone analyses among survivors of hematopoietic-cell transplant survivors

We appreciate the comments by Bakker et al regarding the challenges of doing growth studies and interpreting results in children after total body irradiation (TBI) as detailed in the paper “Final adult height of patients who received hematopoietic cell transplantation in childhood.”1 The children evaluated in this article underwent transplantation between July 1978 and July 2000. We acknowledge that the results of growth hormone (GH) testing performed over a 22-year period in patients undergoing transplantation may be difficult to compare with contemporary assays and definitions of growth hormone deficiency. However, during that time nearly all of our patients had GH analyses performed using one of 2 different assay methods. From 1978 to 1994, GH measurements were obtained using the immunoradiometric assay from kits purchased from Hybritech (San Diego, CA), and from 1994 to 2000 GH analyses were performed using the Nichols Institute (San Juan Capistrano, CA) HGH 100T kit. Thus interassay variations as referred to by Bakker et al were not a significant variable for the determination of GH deficiency. Pulse detection involved GH sampling every 20 minutes for a total of 12 hours from 8:00PM through 8:00 AM of GH deficiency. Pulse detection involved GH sampling every 20 minutes for a total of 12 hours from 8:00PM through 8:00 AM and measurement of the GH produced at each time point. We elected to use the same criteria for definition of GH deficiency throughout the study period based on what the laboratory performing the test considered “normal” for the methodology used. Changing the definition to those suggested by Bakker et al, however, would not have made a difference in the number of patients with GH deficiency, as the number of small amplitude “peaks” varied from 1 to 2 for patients determined to be GH deficient. Similarly, clonidine stimulation was essentially “flat” for those determined to have GH deficiency. In no instance were patients determined to have GH deficiency who had near-normal GH production as defined in the paper or as defined by Bakker et al.

We chose the age of 16 years as the age nearest final height since few boys had growth beyond that age. Based on follow-up data, we evaluated growth among the GH-treated and the untreated GH patients and found that their height Z score at a median of 20.0 (range, 15.7-31.6) years of age was −1.4 SD below the mean compared with what was reported in the article of −1.5 SD below the mean for the same patients at a median age of 16.5 (range, 15.6-22.3) years. Thus, the patients who received TBI did not increase their growth 0.5 SD as suggested by Bakker et al.

We elected to evaluate the impact of patient age on subsequent height from the time that the patients received their TBI since the impact on growth initiated from the time TBI was administered to all of the growth plates in these patients. By using the multiple linear regression models to evaluate the impact of GH therapy on growth, we found that GH treatment had a significant effect on final height among children who received TBI before 10 years of age. Among the 35 children who underwent transplantation before 10 years of age, GH therapy was initiated at a median age of 11.3 (range, 7.1-14.8) years compared with a median age of 14.0 (range, 12.6-15.4) years among the 7 patients who received TBI when older than 10 years. As stated in the paper, we selected the age of 10 years primarily because all of these children were prepubertal and had not yet begun their height growth spurts prior to receiving TBI. There are many possible explanations for the observed effect of transplant age, including the age at which GH therapy was initiated, the duration of GH therapy, and the dose of GH used. Age at HCT is only one factor to be considered in predicting an individual patient’s response to therapy.

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References

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