

Outcomes of Growth Hormone Replacement Therapy in Survivors of Childhood Acute Lymphoblastic Leukemia

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Purpose: Little is known about the long-term efficacy or adverse effects of growth hormone (GH) replacement therapy in survivors of childhood acute lymphoblastic leukemia (ALL) who have GH deficiency. We investigated the adult height of patients who had received GH and estimated their risk of leukemia relapse or development of a second malignancy.

Patients and Methods: Of 910 patients treated for ALL at a single institution, 47 had received GH replacement therapy. The linear growth of these 47 patients was retrospectively evaluated. Their risk of leukemia relapse or second malignancy was compared with that of survivors who did not undergo GH therapy.

Results: The median height SD score at the start of GH therapy had decreased by 1.0 since the time of diagnosis of ALL. After a median duration of 4.5 years

of GH therapy, adult height SD scores improved and approached height SD scores at the time of diagnosis of ALL. The median adult height for male patients was 173.2 cm (range, 157 to 191.9 cm), and for female patients, it was 158.1 cm (range, 141 to 168 cm). None of the patients developed adverse effects requiring discontinuation of GH treatment. At the 7-year and 11-year landmarks in continuous hematologic remission, there was no statistical evidence that GH therapy was associated with leukemia relapse or development of a second malignancy.

Conclusion: This study suggests that GH replacement therapy is safe and efficacious for the correction of GH deficiency in survivors of childhood ALL.

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APPROXIMATELY 75% TO 80% of pediatric patients with acute lymphoblastic leukemia (ALL) are cured by current treatments.¹ Long-term follow-up studies found that the heights of more than one fourth of the survivors of childhood ALL were below the fifth percentile of population normative values.²⁻⁵ The general pattern is one of retarded growth velocity during therapy for ALL, subsequent normalization of height velocity but without catch-up growth, and a second period of retarded linear growth during the pubertal years.^{5,6} The etiology of short stature may be multifactorial,^{6,7} and growth hormone (GH) deficiency is a contributing factor for many severely affected patients.^{3,8,9} Some children have been treated with recombinant human GH replacement therapy, but little is known about its long-term efficacy or adverse effects.¹⁰ Whether GH therapy increases the risk of ALL relapse or second malignancy is unknown. Therefore, we evaluated the adult height of 47 patients who had received GH replacement therapy. Their risk of leukemia relapse or second malignancy was compared with that of long-term survivors of ALL who did not undergo GH therapy.

PATIENTS AND METHODS

Identification of Patients

A review of the database of all patients treated for ALL (n = 910) at St Jude Children's Research Hospital from September 1978 to October 1989 identified 47 patients who had received GH replacement therapy for GH deficiency. All 47 patients achieved adult height, as defined by a height velocity less than 1 cm/yr or by epiphyseal closure observed on a radiographic image of the hand. The institutional

protocols Total IX through XII that were used during this review period have been previously described in detail.¹¹⁻¹⁴ CNS-directed therapy included intrathecal chemotherapy with or without cranial irradiation (18 to 24 Gy). Four patients also had testicular irradiation before receiving GH therapy. This retrospective study was approved by the institutional review board of the hospital.

Evaluation of Growth

Male patients younger than 16 years and female patients younger than 14 years were offered a comprehensive evaluation by a pediatric endocrinologist if they had completed therapy for ALL at least 18 months earlier, if their leukemia was in remission, and if they met the following criteria: (1) loss of more than 1 SD in height since the time of diagnosis of leukemia and a height velocity below the 50th

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percentile for bone age during the previous year, (2) height velocity below the 25th percentile for bone age regardless of absolute height, or (3) predicted adult height less than 1.64 SD below the mean of the normal population of the same sex. Bone age was determined by radiographic analysis of the left hand and wrist. Endocrinologic evaluation included assays of serum cortisol, thyrotropin, free thyroxine, testosterone (boys) or estradiol (girls), luteinizing hormone, follicle-stimulating hormone, prolactin, and insulin-like growth factor-1. Arginine and L-dopa stimulation tests were used to evaluate the GH response.¹⁵ GH deficiency was diagnosed and replacement therapy was initiated if the peak serum concentration of endogenous GH produced in these growth-retarded patients in response to these two pharmacologic stimuli was less than 10 ng/mL. Adult height was predicted by using the TW Mark II equations, which are derived from chronologic age, height, and bone age at the time of growth evaluation.¹⁶

GH Therapy

Synthetic GH was given at a dose of 0.3 mg/kg/wk subcutaneously in three to seven divided doses. Treatment with GH was continued until a height acceptable to the patient was attained or the patient had reached final adult height, unless a contraindication to continuation of treatment developed (eg, leukemia relapse). Four patients had early puberty (onset at 8 to 10 years) and were also treated with gonadotropin-releasing hormone analog.

Follow-Up Procedures

Routine follow-up procedures at the institution and reports of late relapse or second malignancy among long-term survivors who were treated at St Jude have been described previously.^{17,18} Briefly, after completion of leukemia therapy, remission status and late effects of treatment are comprehensively assessed at least annually by a primary attending oncologist. After 1984, follow-up assessments have been performed by the staff of the After Completion of Therapy Clinic. Patients who are at least 18 years old or whose leukemia has remained in remission for at least 10 years after diagnosis are discharged from the institution and followed thereafter by their community physicians. The staff of the St Jude Tumor Registry annually monitors the status of discharged patients by mailing a two-page questionnaire that elicits information, including current medical status and history of physician visits. Reports of serious sequelae, such as late relapse or development of second malignancy, are confirmed by contacting the local physicians, the survivors, or their family members and by reviewing the survivors' medical records and the pathology reports from local hospitals. At the time of this report, 70.6% of the long-term survivors of ALL treated at St Jude had been followed-up within the past year, 92.5% within the past 2 years.

Statistical Analyses

Height SD scores were calculated by using the following equation: (patient's height minus mean height of persons of the same sex and age)/(SD of height for persons of the same sex and age). Pediatric growth data available on the Centers for Disease Control and Prevention Web site (<http://www.cdc.gov/growthcharts>) were used to determine normal values. The SD scores for adult height were calculated by using the data of 20-year-olds of the same sex in the general population.

For the analysis of the subsequent risk of relapse of ALL or of a second malignancy in survivors whose leukemia was in continuous hematologic remission before receiving GH, the GH-treated patients were compared with a control group of long-term survivors who never

received GH after the diagnosis of ALL between September 1978 and October 1989. Cumulative incidence functions of hematologic relapse and second cancer were estimated as described by Kalbfleisch and Prentice,¹⁹ and these estimates were compared by using Gray's test.²⁰ Patients with isolated CNS relapse, testicular relapse, or both were considered to be in continuous hematologic remission until hematologic relapse. Second malignancy, relapse of ALL, and death resulting from other causes were considered mutually competing events. Data for patients who were alive and free of ALL or second cancer were censored at the time of last follow-up.

There is an inherent bias in this type of comparative analysis, because patients must survive for several years before they can become a candidate to receive GH therapy. Therefore, the initiation of GH therapy was considered a time-dependent variable, and a landmark method²¹ was used to display the effect of GH therapy on the cumulative incidence of relapse of ALL or of a second malignancy, according to whether or not GH therapy had been started before the landmark. Patients who began GH replacement after the landmark were censored at the time of initiation of GH therapy. The approximate median time (7 years) and maximum time (11 years) of the start of the GH therapy after achieving complete remission of ALL were chosen as landmarks. Among the 47 patients who were treated with GH and the 863 who were not, four study subjects and 319 control subjects were not included in these comparative analyses because they did not survive in continuous hematologic remission before the first (7-year) landmark. The median length of follow-up for the remaining 43 study subjects and 544 control subjects was 15.6 years (range, 7.3 to 22.1 years) since the diagnosis of ALL. The χ^2 test was used to compare the distributions of presenting features of subjects with those of controls.

RESULTS

GH Therapy

Forty-seven GH-deficient pediatric patients (34 male patients and 13 female patients) were treated with recombinant GH. The median age at the beginning of GH therapy was 10.9 years (range, 6.9 to 14.7 years), the median bone age was 10 years (range, 5 to 14 years), and the median SD for height was -1.2 SD (range, -3.4 to 0.2 SD). The median time at which GH therapy was initiated was 7.1 years (range, 4.3 to 11.4 years) after ALL entered complete remission. The median duration of GH therapy was 4.5 years (range, 1 to 8 years). No patients developed hyperglycemia or other adverse effects requiring discontinuation of GH.

Adult Height

The median height SD score at the time at which GH therapy was initiated decreased by 1.0 since the time of diagnosis of ALL (Fig 1). After a median of 4.5 years of GH therapy, the SD scores for adult height improved and approached the height SD scores at the time of diagnosis of ALL. The anthropometric characteristics of these patients are listed in Table 1. The median adult height for male patients was 173.2 cm (range, 157 to 191.9 cm), and for female patients, it was 158.1 cm (range, 141 to 168 cm).

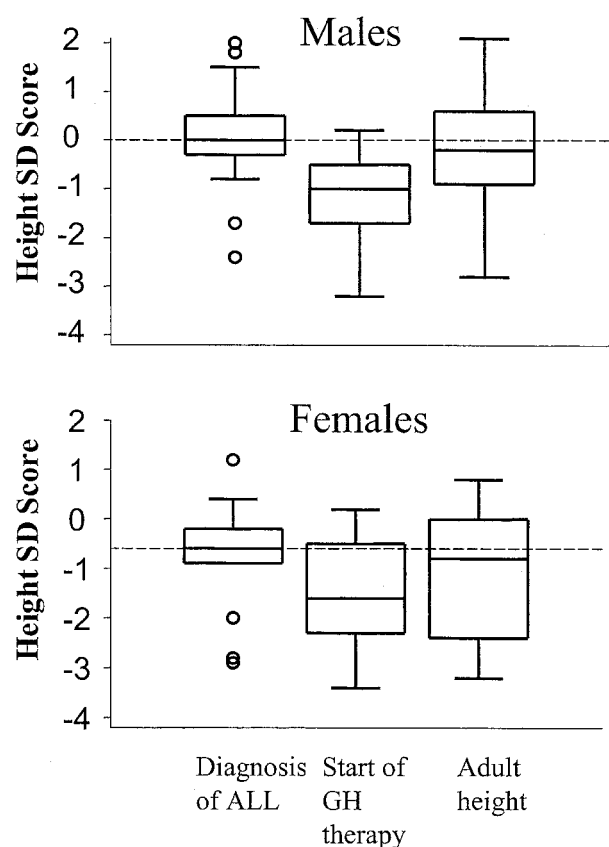


Fig 1. Box plot of height SD scores of survivors who received GH. The solid line in the middle of box represents 50th percentile, the box extends from 25th to 75th percentile, and whiskers extend to the upper and lower adjacent values that are ≤ 1.5 times the interquartile range. More extreme values, if any, are individually plotted (open circles).

The adult height was greater than that predicted at baseline in 76% of the male survivors and in 46% of the female survivors using the TW Mark II equations.

Risk of Relapse and Second Malignancy

We compared the risk of relapse of ALL and that of a second malignancy of survivors who received GH with

Table 1. Anthropometric Characteristics of GH-Treated Survivors of Childhood ALL*

Characteristic	Males (n = 34)	Females (n = 13)
Age at baseline,† years	11.3 \pm 2.0	9.4 \pm 1.4
Height at baseline, cm	138.0 \pm 13.8	124.9 \pm 11.5
Bone age at baseline, years	10.5 \pm 2.3	8.8 \pm 1.6
Predicted adult height at baseline, cm	170.7 \pm 7.0	157.4 \pm 8.2
Duration of GH therapy, years	4.4 \pm 1.6	4.5 \pm 1.4
Height gain since baseline, cm	36.4 \pm 11.9	31.6 \pm 9.0
Final adult height, cm	174.4 \pm 8.4	156.5 \pm 9.1

*All data are mean \pm SD.

†The time of evaluation for GH deficiency.

those of survivors who had not. Patients who received GH therapy were younger, more likely to be male, and more frequently had undergone cranial irradiation (Table 2). None of the 43 patients in the GH-treated group experienced leukemia relapse. One patient had a sclerosing sweat duct carcinoma of the scalp develop 8 years after the diagnosis of ALL, 6 years after cranial irradiation, and 4 months after cessation of GH therapy that lasted 3 years. A second patient experienced myelodysplastic syndrome 12 years after the diagnosis of ALL, 10 years after cranial irradiation, and 2 months after cessation of GH therapy that lasted 4 years. There were eight leukemia relapses and 16 second malignancies among the 544 control subjects. By landmark analysis using the 7-year (the approximate median time at which GH therapy was initiated) and 11-year landmarks (the approximate maximum time at which GH therapy was initiated), there was no statistical evidence that GH replacement therapy was associated with relapse of ALL or second malignancy (Fig 2).

DISCUSSION

This retrospective study of patients who received GH therapy and reached adult heights provides evidence that GH replacement therapy is safe and effective in promoting linear growth in survivors with GH deficiency secondary to ALL treatment. With GH therapy, there was significant catch-up growth resulting in adult heights within the normal range in the majority of the patients. Their adult heights were comparable with those estimated by using the height SD score at diagnosis of ALL or by using the TW Mark II formula before the start of GH therapy. Without GH, these patients would not have achieved the height predicted at baseline. In a study by the Genentech Growth Study Group involving 121 United States children with idiopathic GH deficiency who had received biosynthetic GH administered at the same weekly dose used in this study for an average of 8 years, the adult height of the boys (171.6 \pm 8.2 cm) and that of the girls (158.5 \pm 7.1 cm) are similar to those attained by the GH-treated survivors of ALL described herein.²²

Our GH-treated cohort was predominately male, which is a common feature among other reports of the use of GH in patients with idiopathic GH deficiency,²² in short normal children,²³ and in children with chronic renal failure.²⁴ Perhaps the perception that it is socially more acceptable for girls than for boys to be short has led to girls being less likely to be referred and treated with GH. An additional reason for patients or families to decline GH therapy is the need for frequent injections.²³

Whether GH therapy increases the risk of leukemia in patients who do not have cancer or increases the risk of

Table 2. Patient Characteristics

Characteristics	Received GH (n = 43)*		No GH (n = 544)*		P
	No. of Patients	%	No. of Patients	%	
Age at diagnosis					
< 1 year	1	2.3	5	0.9	
1 to 9 years	42	97.7	413	75.9	
≥ 10 years	0	0	126	23.2	.001
Sex					
Male	30	69.8	279	51.3	
Female	13	30.2	265	48.7	.020
WBC count at diagnosis					
< 50 × 10 ⁶ /mL	29	67.4	435	80.0	
≥ 50 × 10 ⁶ /mL	14	32.6	109	20.0	.052
Cranial irradiation					
No	11	25.6	236	43.4	
Yes	32	74.4	308	56.6	.023
Lineage of ALL					
T-cell	2	4.7	47	8.6	
Non-T-cell	41	95.3	497	91.4	.363
National Cancer Institute risk†					
Standard	29	67.4	345	63.4	
High	13	30.2	194	35.7	.547

*Survivors who were not in continuous hematologic remission before the 7-year landmark were excluded from this comparative analysis.

†The National Cancer Institute criteria exclude patients younger than 1 year; therefore, one GH-treated patient and five control subjects were excluded.

relapse or second malignancy in survivors of childhood leukemia, is not known. Since 1977, investigators have hypothesized that GH may be involved in the development of ALL.²⁵ During the late 1980s, there were several reports of leukemia in otherwise normal children whose primary GH deficiency had been treated with GH.²⁶⁻²⁹ Because of this possible link between leukemia and GH therapy, there has been reluctance to use GH in long-term survivors of childhood ALL, despite the availability of synthetic GH in the United States since 1985. However, data from several large national registries of patients who did not have cancer have not confirmed the relationship between GH therapy and leukemia, including studies by the Lawson Wilkins Pediatric Endocrine Society, National Hormone and Pituitary Program, National Cooperative Growth Study, and the Foundation for Growth Science.³⁰⁻³² The National Hormone and Pituitary Program study reported an increased risk of leukemia in only those GH-treated patients who had antecedent craniopharyngioma treated with irradiation.³⁰ The study performed by the Foundation for Growth Science also found that an increased risk of leukemia with GH treatment was limited to patients with risk factors such as prior radiation or chemotherapy.³² However, it is unclear whether this increased risk is caused by GH therapy or by cancer therapy because these studies did not include a control group of cancer patients who did not undergo GH therapy. Our study compared the risk of ALL relapse and the risk of a second malignancy in survivors of ALL who had received

GH with those risks in survivors who had not. The initiation of GH therapy was considered a time-dependent variable, and a landmark method was used to avoid survival bias. With a median follow-up of more than 15 years, we found no statistical evidence of an association between GH therapy and ALL relapse or second malignancy, despite the fact that a larger proportion of patients in the GH treatment group than in the control group had undergone cranial irradiation (Table 2).

This study is not without limitations. First, the retrospective nature of this study creates specific limitations: underreporting and incomplete surveillance of survivors, particularly those who did not receive GH, may contribute to an underestimation of the rate of late relapse or second malignancy. Propitiously, more than 90% of our survivors were last evaluated within 2 years of this analysis. Second, although the ascertainment of cases was vigorous and resulted in high internal validity, the external generalizability of our findings to survivors of childhood ALL who received different antileukemia treatment is uncertain. Third, although we reviewed the data of more than 900 children with ALL, the number of survivors with second malignancies was small; therefore, we could not adjust the effects of other risk factors such as age at the time of diagnosis of ALL, sex, and history of cranial irradiation. However, the potential biases mentioned above seem more likely to bias against the GH-treated group than the controls.³³ Because the interval between the remission of the

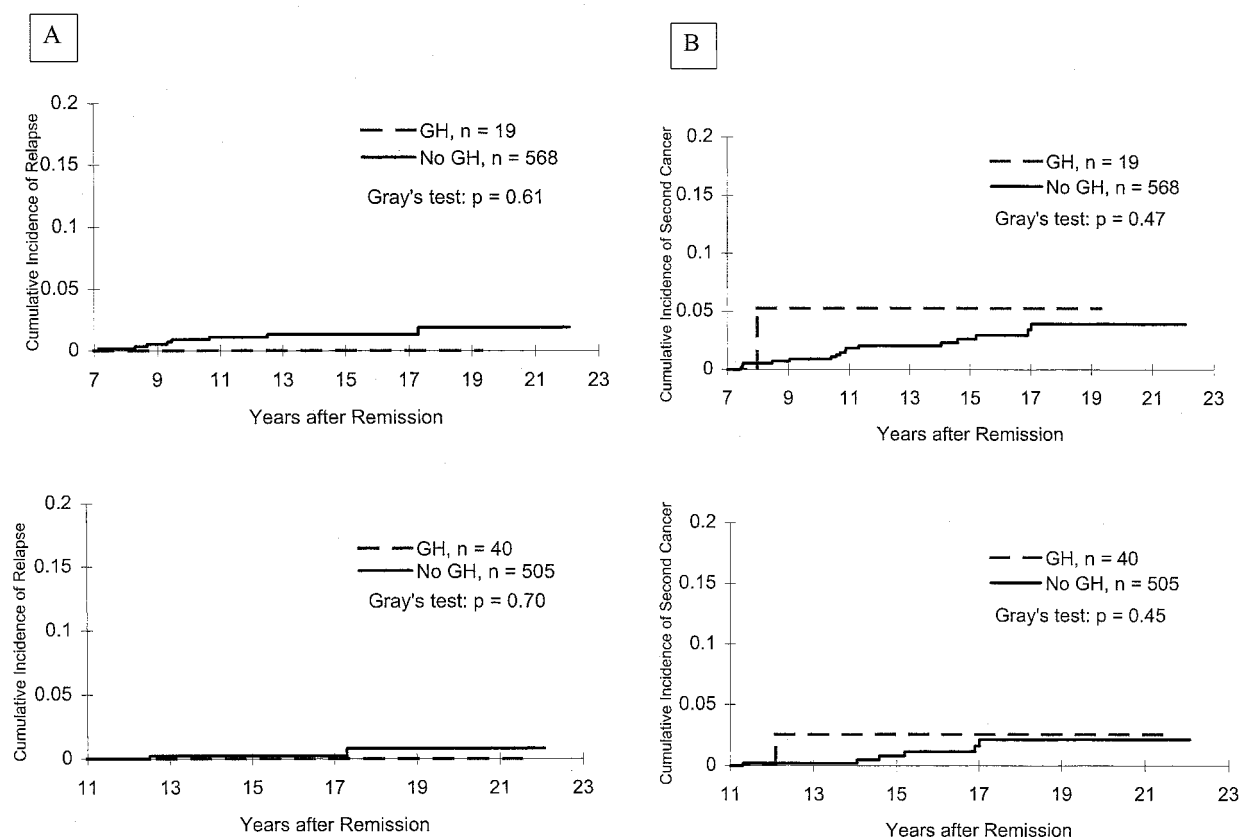


Fig 2. Cumulative incidence of (A) leukemia relapse or (B) second malignancy after remission of ALL, analyzed and displayed according to whether or not GH therapy had been started before the landmark. (Above) Beginning at the 7-year landmark in continuous hematologic remission. (Below) Beginning at the 11-year landmark in continuous hematologic remission.

primary ALL and the development of a second malignancy is long and a small number of additional cases could significantly alter the estimation of the risk, meticulous reporting and continued surveillance of this and other larger cohorts are necessary.

In summary, our results suggest that GH replacement therapy for survivors of ALL with GH deficiency is safe and effectively promotes linear growth. Because of the lack of evidence of an increased risk of relapse or second malignancy, and because of other potentially beneficial effects of

GH replacement therapy (restoration of normal body composition, improved muscle and cardiac function, increase in bone mineral density, normalization of serum lipid concentrations, and improved quality of life),³⁴ studies of continuation of GH replacement therapy in postpubertal survivors of ALL are warranted.

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