Growth Hormone Treatment in Children is not Associated with an Increase in the Incidence of Cancer: Experience from KIGS (Pfizer International Growth Database)

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Objective To assess the incidence of cancer in patients treated with growth hormone (GH) in KIGS—the Pfizer International Growth Database—without cancer or any other condition in medical history known to increase the risk of cancer.

Study design Data were analyzed from patients with growth disorders enrolled in an observational survey KIGS who had no known increased risk of developing cancer before starting recombinant human GH treatment. The incidence of cancer in this patient cohort (overall, site-specific, and according to etiology of growth disorder) was compared with the incidence in the general population by using the standardized incidence ratio (ie, relating the observed to expected number of cases with stratification for age, sex, and country).

Results A total of 32 new malignant neoplasms were reported in 58 603 patients, versus the 25.3 expected (incidence, 16.4 per 100 000 patient-years; standardized incidence ratio, 1.26; 95% confidence interval, 0.86-1.78). No category of growth disorder showed a statistically significant difference in observed compared with the expected number of cases.

Conclusion There is no evidence in this series that GH treatment in young patients with growth disorders results in an increased risk of developing cancer relative to that expected in the normal population. However, surveillance for an extended time should continue to allow further assessment. *(J Pediatr 2010;157:265-70)*.

Treatment of short children with recombinant human growth hormone (GH) is associated with significant improvements in linear growth, leading to attainment of normal or near-normal final height.[1,2] Treatment also has a beneficial impact on body composition.[3] In addition, GH is considered to be well tolerated, with few reported adverse reactions.[4] The possibility of an increased risk of cancer in patients receiving GH treatment, however, has been discussed since the first report of leukemia in GH-deficient children undergoing GH replacement therapy in 1988.[5] The role of the GH–insulin-like growth factor I (IGF-I) axis in tumori-genesis has been studied extensively. Although it is known that IGF-I is a mitogen, animal models suggest permissive rather than causative roles for both IGF-I and GH in tumor-genesis.[6] The identification of 2 cases of colorectal cancer in a long-term cohort study of children and adolescents treated with pituitary-derived GH prompted the authors to suggest that the risk of developing cancer increases after GH treatment.[7] There are also data suggesting an increased risk of malignancy in GH-treated survivors of childhood cancer[8] and in GH-treated patients with other conditions associated with an increased risk of cancer.[9] The aim of this study was to assess the incidence of cancer in patients treated with GH in the Pfizer International Growth Database (KIGS) without cancer or any other condition in medical history known to increase the risk of cancer.

Methods

KIGS is a large international pharmacoepidemiological database that was established in 1987 to monitor long-term clinical and safety outcomes in children with growth disorders who are receiving recombinant human GH (Genotropin; Pfizer, New York, New York). Any patient who is taking or will be treated with GH is eligible to be included in KIGS. The study is conducted in compliance with and is consistent with the Declaration of Helsinki. All applicable local regulatory requirements in the countries involved are adhered to. Relevant independent ethics committees

GH	Growth hormone
GHD	Growth hormone deficiency
IARC	International Agency for Research on Cancer
IGF-I	Insulin-like growth factor I
KIGS	Pfizer International Growth Database
NCGS	National Cooperative Growth Study
SGA	Small for gestational age
SIR	Standardized incidence ratio

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in each participating country approved the study. Patients were enrolled after informed consent. The database protocol requires that physicians report all adverse events in patients followed in KIGS, regardless of whether they are associated with GH treatment. As of August 2008, KIGS contained data from 58 603 patients with no history of neoplasm or any other medical condition presumed to increase the risk of cancer (eg, neurofibromatosis, Langerhans cell histiocytosis, renal transplantation with subsequent immunosuppressive therapy, Fanconi anemia, and Down syndrome). Patients with Turner syndrome were included despite evidence that there is an increased risk of certain types of cancers associated with this chromosomal disorder.[10-14]

A total of 197 173 patient-years of follow-up were available for analysis. A total of 98.5% of patient-years were accumulated during the first 10 years of follow-up. The mean duration of follow-up was 3.6 years. The mean patient age (plus or minus SD) at enrollment in KIGS was 10.3 (± 4.0) years. Fifty-eight percent of patients were male. The mean dose of recombinant human GH at start was 0.24 mg/kg/week, and for the entire duration of treatment, it was 0.25 (± 0.10) mg/kg/week. In >95% of patients, GH treatment was administered.

For each patient, follow-up time in patient-years was calculated from the date of enrollment in KIGS or GH treatment start, when this was later than entry into KIGS, until either the date of the last documented visit, the date of exit from the register (for patients with an exit date), the date of a reported malignant neoplasm, or the date of death, whichever was earliest. Patient-years were stratified by country, sex, and attained age at follow-up. Thirty-one percent of the patients had received GH before enrollment in KIGS, representing 43 080 patient-years (mean, 2.4 years) not included in the risk analysis.

Growth disturbance was the result of idiopathic growth hormone deficiency (GHD) in 54% of patients, Turner syndrome in 11% of patients, congenital GHD in 5% of patients, being born small for gestational age (SGA) in 7% of patients, and acquired GHD in 3% of patients. A number of other conditions, including chronic renal insufficiency and Prader–Willi syndrome, were responsible for short stature in the remaining patients.

The development of a neoplasm in a patient in KIGS is recorded as a serious adverse event. In our analysis, we included all malignant neoplasms reported during the time at risk, defined as aforementioned. The incidence of cancer in KIGS (overall, site-specific and according to etiology of growth disorder) was calculated in relative terms by using the standardized incidence ratio (SIR), a statistical measure that quantifies the relationship between the observed and expected number of new cancers. The latter number was calculated overall or for each cancer site by using the age-, sex-, and country-specific cancer incidence rate from the general population published by the International Agency for Research on Cancer (IARC) in *Cancer Incidence in 5 Continents*, volume IX,[15] multiplied with the correspondingly stratified number of patient-years in KIGS. These stratum-specific expected values were summed over strata to get the total expected value. "Attained age" was stratified in 5-year bands, "sex" in male and female patients, and "country" in 50 countries. Forthy-three of these countries, contributing with 98.5% of all patient-years in this study, had reference incidence rates published in IARC. For the 7 countries (contributing with 1.5% or 2956 patient-years) without reference rates in IARC, IARC incidence rates from a neighboring country was used as a proxy. Results were similar when excluding these 7 countries without direct representation in IARC.

In a separate analysis, the temporal pattern of SIR was assessed. Time was classified into 0 to <2 years, 2 to <5 years, and 5 to <10 years since GH start within KIGS. The interval >10 years included a limited number of patient-years (3019 patient-years) and no cases and was therefore excluded from this time-trend analysis.

In a third analysis in patients not treated with GH before entry into KIGS ("GH-naïve"), data from the first year after the start of GH treatment were omitted to avoid the potential inclusion of cancer cases that were present but undiagnosed before KIGS entry.

The observed number of cancers was assumed to follow a Poisson distribution. 95% confidence intervals (CIs) were calculated by using Byar's approximation formula.[16]

Results

Between January 1987 and August 2008, new malignant neoplasms were reported in 32 patients in KIGS who had no known factors conveying an a priori increased risk. Twelve neoplasms were reported in male patients, and 20 neoplasms were reported in female patients (7 in girls with Turner syndrome). **Table I** shows information on GH treatment, the etiology of the growth disorders, and the specific malignancy for each patient in whom a malignant neoplasm developed. Cancer was diagnosed at a mean age of 11.9 years (range, 5.0-17.6 years). The mean duration of GH therapy in KIGS before the diagnosis of cancer was 3.6 years (range, 0.08-9.70 years). Eight of 32 patients with a new cancer were treated with GH before enrollment in KIGS for a median of 0.7 years (range, 0.06-4.5 years). A total of 7626 patients were observed in KIGS after GH was discontinued. In 6 of these patients, a malignant neoplasm was reported for as long as 3.1 years after stopping GH. The mean dose of GH in patients in whom a neoplasm developed was 0.26 (± 0.08) mg/kg/week (range, 0.12-0.48). Serum IGF-I levels measured 1 to 12 months before the onset of a neoplasm were only available for 7 patients. Three patients had IGF-I SD scores >0 (range, 0.6-1.7), whereas 4 patients had IGF SD scores between –0.6 and –1.9.

The overall incidence of cancer in this patient cohort was similar to that in the general population, with 32 cases reported in KIGS versus the 25.3 expected (**Table II**). This corresponds to an SIR of 1.26 (95% CI, 0.86-1.78). Seventeen cases were reported within the first 2 years in