CLINICAL STUDY

Incidence of second neoplasm in childhood cancer survivors treated with GH: an analysis of GeNeSIS and HypoCCS

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Abstract

Objective: Childhood cancer survivors are commonly treated with GH for GH deficiency that develops either as a result of primary malignancy or its treatment. One study – the Childhood Cancer Survivor Study (CCSS) – demonstrated increased risk of second neoplasm (SN) in GH-treated childhood cancer survivors compared with non-GH treated, after adjusting for key risk factors. We assessed the incidence of SN in GH-treated childhood cancer survivors in outpatient observational studies of GH replacement. **Design:** Retrospective analysis of two prospective cohort studies that collected data on safety of GH replacement as prescribed in clinical practice.

Methods: Childhood cancer survivors enrolled in Eli Lilly and Company's pediatric (Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)) and adult (Hypopituitary Control and Complications Study (HypoCCS)) observational studies of GH treatment were assessed for incidence of SN.

Results: The percentage of childhood cancer survivors treated with GH who developed a SN was 3.8% in pediatric GeNeSIS participants and 6.0% in adult HypoCCS participants. The estimated cumulative incidence of SN at 5 years of follow-up in these studies was 6.2 and 4.8% respectively.

Conclusions: The incidence of SN in GeNeSIS and HypoCCS GH-treated participants is similar to the published literature and is thus consistent with increased risk of SN in childhood cancer survivors treated with GH. As follow-up times were relatively short (<3 years), longer observation is recommended. Nevertheless, clinicians should be alerted to the possibility of increased risk of SN in childhood cancer survivors treated with GH and continue chronic surveillance.

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Introduction

GH deficiency (GHD) is an endocrinopathy found in childhood cancer survivors, resulting from tumors affecting the hypothalamic–pituitary axis or from cancer therapy, especially cranial irradiation (1, 2, 3). For example, GHD has been found in 58% of long-term survivors of childhood acute lymphoblastic leukemia treated with ≥ 24 Gy whole brain radiation (4). Although GH replacement therapy is often used to stimulate growth in these patients, there have been concerns regarding long-term safety. Preclinical studies have demonstrated that both GH and insulin-like growth factor 1 (IGF1) have mitogenic properties, stimulating cellular proliferation and inhibiting apoptosis in a variety of *in vitro* assays and possibly being tumorigenic in animals under certain conditions (5, 6). In humans,

epidemiological studies have shown a positive correlation between IGF1 blood levels and the risk of certain tumors (colorectal, prostate, and breast (7, 8, 9)). Despite these associations, increased risk of *de novo* or recurrent malignancy in GH-deficient patients treated with GH has not been confirmed (10, 11, 12, 13, 14, 15, 16, 17).

Two analyses from a single database, the Childhood Cancer Survivor Study (CCSS) (18, 19), have reported that GH treatment is associated with an increase in the relative risk of second neoplasm (SN) in childhood cancer survivors. Exposure to radiation and alkylating agents were identified as additional risk factors for the development of SNs. As a result of these findings, the Food and Drug Administration in the USA requested in 2006 that all GH product labels should be strengthened to reflect increased risk of SN in childhood cancer survivors.

The aim of the current analysis was to assess the risk of SN in childhood cancer survivors enrolled in Eli Lilly and Company's pediatric (Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)) and adult (Hypopituitary Control and Complications Study (HypoCCS)) observational studies of GH treatment. To our knowledge, this is the first analysis to examine the risk of SN in childhood cancer survivors enrolled in large postmarketing observational studies of GH-treated individuals.

Materials and methods

Study databases

GeNeSIS (ClinicalTrials.gov, NCT01088412) is an international, open-label postmarketing surveillance program (prospective cohort study) established in 1999. The aim of GeNeSIS is to collect information on the clinical management and treatment outcomes of pediatric patients with short stature, growth disorders, or disorders of hypothalamic–pituitary function who are treated, at the discretion of the participating physician, with GH (Humatrope; somatropin, Eli Lilly and Company), according to standard pediatric endocrinology practice. The current analysis is based on data included in the February 2008 database lock (data to September 2007). At that time, the database included 11 258 participants who had at least one follow-up visit recorded and were eligible for analysis; of these, 11 136 had received at least one GH dose during GeNeSIS participation (GH-treated group) and 122 had no reported GH therapy.

HypoCCS (ClinicalTrials.gov, NCT01088399) is a postmarketing surveillance program (prospective cohort study) with a primary objective to determine whether long-term GH replacement therapy in GH-deficient adults is associated with a changed incidence of clinically significant adverse events. All participants in HypoCCS had an established diagnosis of adult GHD, either alone or combined with other pituitary hormone deficiencies, as determined by clinical history and/or biochemical testing (20). The diagnostic approach used and the decision to administer GH was at the discretion of the investigating physician. Patients were considered ineligible for HypoCCS enrollment if they had unresolved or unstable conditions listed as contraindications or precautions for GH therapy. Such conditions include evidence or suspicion of active malignancy or evidence of ongoing pituitary or other intracranial tumor activity. Patients from North America and Europe were originally enrolled in separate studies. In 2002, a global protocol was initiated, and by 2005, all data were merged into a single database. The current analysis was based on the merged HypoCCS database of October 2008 (data to July 2008). At that time, the HypoCCS database included 7785 hypopituitary participants who

had at least one follow-up visit recorded; of these, 6840 had received at least one GH dose during HypoCCS participation (GH-treated group), 940 had no reported GH therapy during HypoCCS participation, and five were of unknown treatment status (excluded from analysis). Of the 6840 GH-treated participants, 5522 (80.7%) were reported as having adult-onset GHD and 1299 (19.0%) as having childhood-onset GHD (onset type not reported for 19 participants).

Both HypoCCS and GeNeSIS are conducted in accordance with the Declaration of Helsinki and adhere to applicable regulatory requirements in the participating countries. Institutional review board approval and written informed consent from participants, parents, or legal guardians for data collection, electronic processing, and publication were obtained in accordance with national laws. Study data were collected as provided by the study investigator and were cross-referenced with the Lilly Safety System (LSS) pharmacovigilance database to confirm accuracy or obtain additional details. LSS is a separate database that collects detailed information on serious adverse events for all company products (for studies such as HypoCCS and GeNeSIS, this information is provided by the study investigator). The participants for the current HypoCCS analysis were recruited from 16 countries: Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Iceland, Italy, Norway, Spain, Sweden, The Netherlands, UK, and the USA. The participants for the GeNeSIS analysis were recruited from these 16 countries plus 14 additional countries: Australia, Finland, Greece, India, Japan, Kazakhstan, Lithuania, Pakistan, Russia, Singapore, Slovakia, South Africa, Taiwan, and Thailand.

Definition of childhood cancer survivor

Only childhood cancer survivors, defined as participants whose initial cancer diagnosis occurred at age <21 years, were eligible for inclusion in these analyses. For GeNeSIS, identification of this cohort was based on data collected at study entry, which included information regarding diagnosis of GHD and previous neoplastic conditions. Additional information on previous neoplastic conditions was ascertained from reports of SNs as serious adverse events in the LSS pharmacovigilance database. A total of 491 childhood cancer survivors were identified in GeNeSIS, of whom 70 were excluded because no follow-up data were available (Fig. 1A). Thus, 421 GeNeSIS childhood cancer survivors were included in our analysis. For HypoCCS, identification of the childhood cancer survivors was more challenging because the current global database is a merger of three similar, but not identical, protocols. Consequently, we used broad search criteria to capture all potential childhood cancer survivors in the database and included all data collection modules that might provide pertinent information. Further in-depth review by two study physicians confirmed that 310 participants met eligibility criteria;

Figure 1 Flow diagram of patients enrolled in the GeNeSIS (A) and HypoCCS (B) programs who were included in this analysis. SN, second neoplasm.

30 of these were excluded from the analysis because of missing follow-up data (Fig. 1B).

Identification of SN cases among childhood cancer survivors

Study adverse event records were reviewed to ascertain SN cases. A SN was defined as a benign or malignant neoplasm following a previous childhood cancer, but excluding metastases or recurrence of the primary cancer. A SN may have a different histological type and may occur in the same or different organs as the previous neoplasm, in all cases arising from an independent oncogenic event.

The criteria for determination of benign and malignant primary neoplasms and SNs, from the diagnoses provided by study investigators, were identical for both GeNeSIS and HypoCCS. In cases where tumor categorization was uncertain, the following rules were applied: i) pituitary tumors and craniopharyngiomas were considered benign, unless specifically denoted as malignant; ii) meningiomas of low or unspecified

grade were classified as benign because transition to malignancy is rare; iii) cases of histiocytosis, neurofibromatosis, and teratoma were considered benign, unless specifically denoted as malignant; iv) gliomas and astrocytomas were considered malignant, unless specifically described as low grade or pilocytic, or as pleomorphic xanthoastrocytomas (per World Health Organization criteria (21), these specific tumor types were considered benign, although transition into malignancy is possible); v) pineal region neoplasms for which malignancy was not specified were considered malignant; vi) cases where available information indicated total body irradiation were considered to have had a previous malignancy; and vii) ambiguous cases where the tumor type was not specified were not considered as malignancies.

IGF1 concentrations

Where possible, serum IGF1 concentrations were measured centrally using a RIA (University of Giessen, Germany in Europe and Esoterix Endocrinology, Calabasas Hills, CA, USA), and IGF1 SDS were calculated as described previously (22, 23). Additionally, in GeNeSIS, a number of IGF1 concentrations were determined by local laboratories and converted to central laboratory values by cross-calibration of the assays used (24).

Statistical analysis

As GeNeSIS and HypoCCS are separate studies with distinct protocols and data collection methods, data from each study were analyzed separately. Demographic data were summarized as median and first (Q1) and third (Q3) quartiles, and the proportion of patients with a SN was calculated with 95% CIs for both study populations. Cumulative incidence (with S.E.M.) of SN was estimated using death as a competing risk, adjusting for varying follow-up times per patient and censored data for those patients without a SN or death (25). If there were no competing risk events (deaths), the methodology is equivalent to using a Kaplan–Meier curve to estimate the percentage of patients without a SN at a given time point and subtracting the Kaplan–Meier estimate from 1. For GeNeSIS, the cumulative incidence of SN was calculated from the start date of GH therapy. For HypoCCS, as the GH start date was not always known for participants who started GH therapy before study entry, the cumulative incidence of SN was calculated from the date of enrollment into HypoCCS. Finally, because of baseline demographic differences between GH-treated and non-GH-treated participants, and lack of other key information that should be adjusted for in a formal comparison (e.g. radiotherapy and chemotherapeutic agent dose information), a formal statistical comparison between treatment groups was not considered appropriate.

Results

GeNeSIS analysis

Demographics In GeNeSIS, 491 childhood cancer survivors were identified, of which 421 had at least one follow-up visit and were included in the analysis (Fig. 1A). The most common primary cancers were medulloblastoma ($n=140$, 33.3%) and leukemia ($n=63$, 15.0%). Among the 394 (232 male and 162 female) GH-treated childhood cancer survivors, the age of primary cancer diagnosis was documented in 352, with a median (Q1, Q3) age of 5.4 (3.0, 8.5) years. Median age at the start of GH therapy was 10.8 (8.9, 12.9) years and median duration of treatment was 2.9 (1.4, 4.8) years. Among the 27 (19 males and eight females) non-GH-treated childhood cancer survivors, 26 had the age of primary cancer diagnosis documented, with a median of 7.5 (3.6, 10.3) years. Overall, the median time enrolled in GeNeSIS was 2.1 (1.1, 3.5) years.

Incidence of SN There were 15 cases of SN identified among the 394 GH-treated participants (Fig. 1A, Table 1), corresponding to a calculated SN proportion of 3.8% (95% CI, 2.2–6.2%), and no cases of SN among the 27 non-GH-treated participants. SN followed medulloblastoma in 10 of 15 cases (Table 1). The most common SN reported was meningioma (three cases) and all followed therapy for medulloblastoma. All but one case of SN occurred in participants who had received both chemotherapy and radiation exposure as

part of their primary cancer treatment. The median time (Q1, Q3) from primary cancer diagnosis to development of SN was 8.4 (6.3, 10.6) years and the median time from start of GH therapy to SN was 2.4 (1.6, 4.4) years. The cumulative incidence of SN from the start of GH treatment was estimated for the 394 GH-treated childhood cancer survivors (Fig. 2) and was 6.2% (S.E.M., 1.9%) at 5 years of follow-up. Seven deaths were reported in this population of 394 GH-treated participants during the follow-up period. Three deaths were associated with SN (Table 1) – neuroblastoma following acute lymphocytic leukemia, acute myeloid leukemia following medulloblastoma, and myelodysplastic syndrome following medulloblastoma (with death due to complications associated with graft vs host disease after bone marrow transplant). Three deaths were due to recurrences of primary cancers (astrocytoma, medulloblastoma, and neuroblastoma), and the remaining case due to a road traffic accident. Additionally, there was one death among the 27 non-GH-treated patients (medulloblastoma recurrence).

GH dose and IGF1 SDS The mean GH dose after 1 year of treatment was 0.22 (S.E.M., 0.03) mg/kg per week in the GH-treated participants who developed a SN and 0.24 (S.E.M., 0.01) mg/kg per week in those who did not. Mean baseline IGF1 SDS was -1.7 (S.E.M., 0.66) in those who developed a SN and -3.2 (S.E.M., 0.23) in those who did not. Both groups of GH-treated participants had improved mean IGF1 SDS after initiation of GH therapy (Fig. 3A).

Table 1 Childhood cancer survivors in GeNeSIS who developed a second neoplasm.

Patient numbers	Sex	Primary cancer	Second neoplasm ^a	Time from GH start to SN onset (years)	Age at SN onset (years)	Time between PC and SN onset (years)
1	M	Ependymoma	Bone sarcoma	9.8	15.7	13.4
2	M	Leukemia	Bone cyst	1.6	11.6	9.1
3	M	Medulloblastoma	Acute lymphocytic leukemia	1.8	13.9	8.4
4 ^b	M	Medulloblastoma	Acute myeloid leukemia	2.2	18.1	5.2
5	F	Medulloblastoma	Lingual granular cell tumor	3.0	15.1	6.3
6	M	Medulloblastoma	Low-grade astrocytoma	8.8	14.1	11.1
7	M	Medulloblastoma	Low-grade glioma	1.4	14.0	4.7
8	M	Medulloblastoma	Meningioma	1.9	15.7	13.3
9 ^c	M	Medulloblastoma	Meningioma	3.0	13.2	7.4
10 ^d	M	Medulloblastoma	Meningioma	5.0	14.9	7.3
11 ^b	F	Medulloblastoma	Myelodysplastic syndrome	2.4	14.6	6.1
12 ^e	M	Medulloblastoma	Spinal cord neoplasm	1.6	11.9	10.6
13	M	Neuroblastoma	Pheochromocytoma	4.4	9.5	8.6
14	F	Neuroblastoma	Osteochondroma	1.6	14.6	10.4
15 ^b	M	Acute lymphocytic leukemia	Neuroblastoma	4.4	13.0	7.2

F, female; M, male; PC, primary cancer; SN, second neoplasm.

^aAll childhood cancer survivors in the GeNeSIS who developed a second neoplasm were treated with GH. All participants had a history of radiation therapy as part of treatment for their primary cancer.

^bPatient died with cause of death associated with second neoplasm.

^cThis patient had a history of Gorlin syndrome and had additional second neoplasms (basal cell carcinoma and benign soft tissue lesion).

^dAll patients had been treated with chemotherapy for their primary cancer except this patient.

^eThe second neoplasm in this patient was not confirmed by repeated magnetic resonance imaging.

Figure 2 Cumulative incidence curve for incidence of second neoplasm (SN) or death (not associated with SN) in GH-treated childhood cancer survivors enrolled in GeNeSIS. The cumulative incidence of SN is shown by the upper solid line with the cumulative incidence ± 1 S.E.M. indicated by the dashed lines. The cumulative incidence of death is shown by the lower solid line but does not include three cases where death was associated with SN. The number of patients at risk at year 0 was 394.

HypoCCS analysis

Demographics A total of 310 participants were confirmed as childhood cancer survivors, of whom 280 (252 GH-treated and 28 non-GH-treated) had a follow-up visit recorded and were included in the analyses (Fig. 1B). In the 280 participants overall, the most common primary cancer diagnoses were germinoma ($n=60$, 21.4%), leukemia ($n=51$, 18.2%), medulloblastoma ($n=44$, 15.7%), and astrocytoma ($n=44$, 15.7%). Of the 252 (117 males and 135 females) GH-treated childhood cancer survivors, the age of primary cancer diagnosis was documented in 107 participants, with a median age (Q1, Q3) of 8.4 years (4.1, 12.2). Among all 252 GH-treated participants, the median duration of GHD at study entry was 6.8 years (0.8, 14.6) and the duration of follow-up in HypoCCS was 2.9 years (1.5, 5.1). Of the 28 non-GH-treated participants, only seven had the age at primary cancer diagnosis recorded, with a median age of 8.7 years (4.1, 13.6). Among all 28 non-GH-treated participants, the median duration of GHD at study entry was 13.8 years (5.1, 20.1) and median duration of study follow-up was 2.6 years (1.8, 3.7).

Incidence of SN After case review, a total of 27 (23 GH-treated and four non-GH-treated) SNs were identified in 280 childhood cancer survivors, ten of which occurred before enrollment in HypoCCS (Fig. 1B, Table 2). Of these ten cases, four were naïve to GH therapy at the time of enrollment and six had been treated previously with GH; the timing of SN development relative to previous GH therapy in these cases was unknown. The SN proportion during HypoCCS was 6.0% (95% CI, 3.4–9.6%) based on 15 cases in 252

GH-treated childhood cancer survivors and 7.1% (95% CI, 0.9–23.5%) based on two cases in 28 patients with no GH treatment. As with GeNeSIS, the most common SN was meningioma (10 of 27; 37.0%). Among all childhood cancer survivors who developed a SN and had a known exact event date, the median time (Q1, Q3) between primary cancer diagnosis and SN was 20.3 years (18.1, 28.9; $n=14$) in GH-treated participants and 29.5 years (10.8, 31.2; $n=3$) in non-GH-treated participants. The estimated cumulative incidence of SN at 5 years of follow-up was 4.8% (S.E.M., 1.6%) in GH-treated participants (Fig. 4). For the purposes of this analysis, the ten cases of SN that occurred before study enrollment were included in the group without a SN. Although none of these ten cases reported a new third neoplasm during HypoCCS participation, two cases did report recurrence of the SN (both meningiomas; Table 2). A total of four deaths were reported in the overall population of 280 childhood cancer survivors during the follow-up period. Three deaths were in GH-treated participants, one of which was due to a SN (glioblastoma following medulloblastoma; Table 2). The cause of death was not reported in one GH-treated patient with history of medulloblastoma and in a patient with history of germinoma was due to acute

Figure 3 Insulin-like growth factor 1 (IGF1) SDS in GH-treated childhood cancer survivors enrolled in GeNeSIS (A) and HypoCCS (B). Shown are mean ($\pm$ S.E.M.) IGF1 SDS at baseline (BL; time of enrollment) and at years 1, 2, and 3 (Y1, Y2, and Y3) for survivors with and without a second neoplasm.

Table 2 Childhood cancer survivors in HypoCCS who developed a second neoplasm.

Patient numbers	Sex	Primary cancer	Second neoplasm	Primary cancer treatment RT/CT	Naïve to GH at study entry	Duration of GHD (years)	Age at SN onset (years)	Time from enrollment to SN or last contact ^a (years)	Time between PC and SN onset (years)
Developed second neoplasm after HypoCCS enrollment									
<i>Treated with GH while enrolled in HypoCCS</i>									
1	M	Acute lymphocytic leukemia	Ewing's sarcoma	RT/CT	Yes	0.4	16.8	2.04	14.7 ^b
2	F	Acute lymphocytic leukemia	Malignant melanoma	RT/CT	No	17.7	31.4	0.02	27.2
3	F	Acute myelogenous leukemia	Basal cell carcinoma	NR/NR	No	5.0	30.6	1.62	17.3
4	F	Acute lymphoblastic lymphoma	Meningioma	RT/NR	Yes	0.1	33.4	10.06	28.9
5	M	Non-Hodgkin's lymphoma	Meningioma	RT/NR	Yes	0.6	32.9	5.88	18.1
6	F	Germinoma	Meningioma	RT/NR	No	1.6	30.1	1.17	26.9 ^b
7	F	Germinoma	Hepatic adenoma	RT/NR	No	9.9	28.4	7.86	17.8 ^b
8	M	Pineal dysgerminoma	Glioblastoma multiforme	RT/CT	No	16.7	31.4	2.42	19.1
9	F	Astrocytoma	Benign nervous system neoplasm	NR/NR	Yes	9.0	48.3	0.73	34.3 ^b
10	M	Astrocytoma	Basal cell carcinoma	RT/CT	No	0.003	27.5	0.02	20.7 ^b
11	M	Optic glioma	Gastrointestinal stromal tumor	RT/NR	Yes	0.3	39.9	8.07	31.6
12 ^c	M	Medulloblastoma	Glioblastoma	RT/NR	No	14.1	20.2	0.29	17.1
13	F	Medulloblastoma	Meningioma	RT/NR	Yes	0.1	35.5	7.59	26.3
14	M	Medulloblastoma	Thyroid carcinoma	RT/NR	Yes	22.8	34.9	7.59	30.4
15	F	Pharynx cancer	Meningioma	RT/NR	Yes	1.5	33.1	3.41	21.2
<i>Not treated with GH while enrolled in HypoCCS</i>									
16	M	Astrocytoma	Glioblastoma multiforme	RT/NR	Yes	5.0	24.4	5.04	10.8
17	F	Astrocytoma	Breast cancer	NR/NR	Yes	24.8	39.2	0.65	25.5 ^b
Developed second neoplasm before HypoCCS enrollment									
<i>Treated with GH while enrolled in HypoCCS</i>									
1	M	Acute myelogenous leukemia	Papillary thyroid carcinoma	NR/NR	No	19.9	21.7	1.21	19.3
2	F	Medulloblastoma	Follicular thyroid carcinoma	NR/NR	Yes	0.07	28.1	4.64	18.1
3	M	Medulloblastoma	Meningioma	NR/NR	No	Unknown	38.9	2.28	28.9
4	M	Medulloblastoma	Meningioma ^d	RT/CT	No	18.5	20.1	2.99	16.6
5	F	Germinoma	Meningioma ^d	RT/NR	No	0.04	33.2	7.79	24.3 ^b
6	F	Germinoma	Hemangioma	RT/NR	No	19.6	22.9	1.76	14.3 ^b
7	M	Pinealoma	Hemangioma	RT/NR	No	18.3	11.9	1.54	2.5 ^b
8	F	Choriocarcinoma	Basal cell carcinoma	RT/NR	Yes	16.1	32.7	0.73	17.3 ^b
<i>Not treated with GH while enrolled in HypoCCS</i>									
9	F	Glioma	Meningioma	NR/NR	Yes	0.06	38.0	2.23	29.5
10	M	Ewing's sarcoma	Meningioma	NR/NR	Yes	0.9	39.8	0.40	31.2

CT, chemotherapy; F, female; GHD, GH deficiency; M, male; NR, not reported; PC, primary cancer; RT, radiation therapy; SN, second neoplasm.

^aTime from enrollment in HypoCCS to second neoplasm (for patients enrolled before second neoplasm) or to last contact (for patients enrolled after second neoplasm).^bThe time between primary cancer and second neoplasm in these patients was estimated based on the age at hypothalamic-pituitary disease or GHD diagnosis.^cPatient died with second neoplasm as cause of death.^dThese two patients reported recurrence of the second neoplasm.

Figure 4 Cumulative incidence curve for incidence of second neoplasm (SN) or death (not associated with SN) in GH-treated childhood cancer survivors enrolled in HypoCCS. The cumulative incidence of SN is shown by the upper solid line with cumulative incidence ± 1 S.E.M. indicated by the dashed lines. The cumulative incidence of death is shown by the lower solid line but does not include one case where death was associated with SN. The number of patients at risk at year 0 was 252.

fulminant pancreatitis. One non-GH-treated patient with a history of germinoma died of 'hepatic coma'.

GH dose and IGF1 SDS Mean GH dose was calculated annually for the first 3 years of treatment for GH-treated participants stratified by whether or not they developed a SN. In participants with a SN, mean GH dose was 0.472 (S.E.M., 0.071) mg/day in year 1, 0.554 (S.E.M., 0.098) mg/day in year 2, and 0.517 (S.E.M., 0.109) mg/day in year 3. In participants without a SN, mean GH dose was 0.500 (S.E.M., 0.022) mg/day in year 1, 0.525 (S.E.M., 0.032) mg/day in year 2, and 0.515 (S.E.M., 0.029) mg/day in year 3. The mean baseline IGF1 SDS was -3.0 (S.E.M., 0.56) in those who developed a SN and -3.8 (S.E.M., 0.22) in those who did not. Both groups of GH-treated participants had improved IGF1 SDS after initiation of GH therapy (Fig. 3B).

Discussion

To our knowledge, this is the first report to assess the incidence of SN in childhood cancer survivors enrolled in large, observational studies of GH treatment of both pediatric and adult patients. The percentage of GH-treated childhood cancer survivors who developed a SN was 3.8% in pediatric GeNeSIS participants and 6.0% in adult HypoCCS participants. The estimated cumulative incidence of SN at 5 years of follow-up in these studies was 6.2 and 4.8% respectively.

Childhood cancer survivors are at increased risk of second malignancies – the Surveillance Epidemiology and End Results (SEER) program showed a sixfold increased risk of subsequent malignancy compared with the general population (26). Our patient population is not directly comparable because subjects had childhood malignancies that resulted in GHD. Our study

population is enriched with patients with the known second malignancy risk factors of CNS malignancy and radiation exposure (26).

The results of our analysis are consistent with previously published data from the CCSS (18, 19). In the initial CCSS report (19), the percentage of GH-treated childhood cancer survivors who developed a SN during a median of 6.2 years of follow-up was 4.2% (15 SNs in 361 GH-treated childhood cancer survivors). The relative risk (adjusted) of SN in GH-treated vs non-GH-treated participants was 3.21 (95% CI, 1.9–5.5; $P < 0.0001$). After an additional 32 months of follow-up, the relative risk of SN in the same cohort of GH-treated vs non-GH-treated participants was 2.15 (95% CI, 1.3–3.5; $P < 0.002$) (18). Our results are consistent in terms of the proportion of patients with SN observed in GH-treated childhood cancer survivors and support the reproducibility of the CCSS data in two separate large patient cohorts (GeNeSIS and HypoCCS). However, there are some notable differences between our studies and the CCSS. Unlike the retrospective cohort CCSS, our studies only prospectively followed GH-treated patients. Additionally, the duration of follow-up was much longer in the CCSS and the incidence of SN is known to increase with longer periods of observation (27).

Our findings are also similar to those of a recent retrospective study by Mackenzie *et al.* (28), in which 4.5% (5 of 110) of GH-treated cancer survivors who had received cranial radiotherapy subsequently developed a SN. In contrast to the CCSS, the incidence of SN in the Mackenzie *et al.* study was not significantly greater in GH-treated patients than in matched, non-GH-treated control patients (2.7%, 3 of 110; $P = 0.72$). Notably, the median follow-up period in that study was 14.5 years, similar to that of the CCSS. More than 60% of the patients were adults when diagnosed with their primary cancer; however, among the childhood-onset subgroup, SNs occurred in five of 41 GH-treated patients and two of 42 non-GH-treated patients. Although the incidence of SN was 2.6-fold greater in the GH-treated patients, the difference was not statistically significant (28).

In both GeNeSIS and HypoCCS, as well as the CCSS (18, 19), meningiomas were the most common SN. The occurrence of three cases of osteosarcoma in GH-treated survivors of hematopoietic malignancies was considered a striking finding in the CCSS (19); no osteosarcomas were reported as SNs in GeNeSIS and HypoCCS. In all three studies, nearly all participants with a SN had a reported history of exposure to radiation as a consequence of treatment for their primary cancers. The primary cancers were frequently CNS malignancies or leukemia, which are known to be associated with an increased risk of SN (29, 30). Additionally, the time between primary cancer diagnosis and SN development was quite prolonged in GH-treated childhood cancer survivors, ranging from a median of 8.4 years in GeNeSIS to 20.3 years in HypoCCS

participants. This timing is not inconsistent with that observed in the CCSS where the median time between primary cancer diagnosis and SN was 12.6 years (18). However, we note that childhood cancer survivors do not enroll into HypoCCS until after diagnosis of adult GHD, which may have prolonged the latency we observed.

There are limitations in the data described in this report. Neither GeNeSIS nor HypoCCS was specifically designed to evaluate the effect of GH treatment on the development of SN in childhood cancer survivors, as this information had not been published at the time of study design. As case report forms did not always contain details of the initial diagnosis and treatment of primary cancers, it is impossible to fully assess all the potential contributing factors to the development of the SN. Although broad search criteria were used to identify potential primary cancers and SNs, some cases may have been inadvertently omitted because of missing information. Potentially, some SN cases may have been omitted at the point of data inclusion for these analyses because of the open enrollment period and potential for loss to follow-up in observational research. In addition, as SNs may present many years after the primary childhood cancer and its treatment, the relatively short average duration of follow-up in these analyses limits their ability to capture all potential SN cases and limits the ability to interpret any relation of the observed SN to GH therapy. Another potential bias may be unknown differences between those patients who drop out of the study early vs those who are followed for longer; for example, there may be patients for whom concern of the risk for development of a SN or primary cancer recurrence increases. Data collection on SNs is as provided by the study investigators, the majority of which are endocrinologists and not oncologists, potentially leading to under-reporting of events. However, such potential may be mitigated by the vigilance for such outcomes, as stipulated in study protocols and product labeling, especially in childhood cancer survivors known to be at risk of SN. Furthermore, despite the large size of both GeNeSIS and HypoCCS databases, there were relatively few cases of childhood cancer survivors and even fewer SNs, further limiting our analyses. There were too few non-GH-treated childhood cancer survivors included from either database to draw meaningful conclusions about a potential increased risk of SN due to GH treatment. It is also difficult to assess the true risk of developing a SN from these databases, as a clinical bias is likely against starting GH in these patients, particularly adults, who have had a prior malignancy or disease with a worse prognosis.

In summary, the incidence of SN in both GeNeSIS and HypoCCS GH-treated childhood cancer survivors is consistent with the published literature, suggesting increased risk of SN in childhood cancer survivors who may be treated with GH. Longer observation is recommended to further clarify the extent of any risk.

Declaration of interest

W W Woodmansee is a former employee and stockholder of Eli Lilly and Company. C J Child, A G Zimmermann, Q Rong, and W F Blum are employees and shareholders of Eli Lilly and Company. E M Erfurth, L L Robison, P Beck-Peccoz, and W W Woodmansee are members of medical research advisory boards for, and have received consulting fees from Eli Lilly and Company. E M Erfurth has also received consulting fees from Pfizer.

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