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Assessment of Primary Cancers in Growth Hormone (GH)–Treated Paediatric Patients Compared with Population Databases: An Epidemiological Analysis of a Large, Multinational, Prospective Observational Study

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1) BACKGROUND AND AIMS

Background

- Because of the general growth-inducing effect of GH, concern remains regarding the potential influence of GH treatment on neoplastic cell growth.
- No increased primary cancer rate in patients without history of malignancy who received childhood GH treatment was observed in previous studies (1-3).
- A higher risk for colorectal cancer, based on 2 cases, was observed in a single-country cohort of patients treated with pituitary GH (4).
- Associations between high serum IGF-I concentrations and certain cancer types in adulthood have been identified in epidemiological studies (5).

Aims

- We assessed the reported primary cancer occurrence in the prospective, multinational GeNeSIS observational study of paediatric GH use and compared observed cases with expected cases from general population cancer registries.
- Comparison was by calculation of standardised incidence ratios (SIRs) and associated 95% confidence intervals (CI) for all cancer types and sites combined.

2) PATIENTS AND METHODS

Ascertainment of historical malignancies and incident primary cancer malignancies

- GH-treated patients with ≥1 follow-up visit from 30 countries were assessed.
- Study data (including the specific Neoplasia Sub-study) and serious adverse event reports were examined to identify those with no reported previous potential malignancy.
- Patients with incident cases of primary malignancy were ascertained using the same data sources.
- Malignancy status was based on Surveillance, Epidemiology, and End Results (SEER) programme guidelines (6) and World Health Organization (WHO) classification (7).

Calculation of standardised incidence ratios

- SIRs and 95% CIs were calculated as the ratio between the number of cases observed in GeNeSIS and the number of cases expected based on general population reference data:
  - SEER programme data (6) for the USA
  - GLOBOCAN (8) for all other countries
- Follow-up time per patient was calculated from date of first GH dose in GeNeSIS or Visit 1 until the date of the last contact.

3) RESULTS:

Demographics and baseline characteristics of patients with no previous cancer

- A cohort of 19054 patients was identified; demographics and patient characteristics are shown in Table 1.

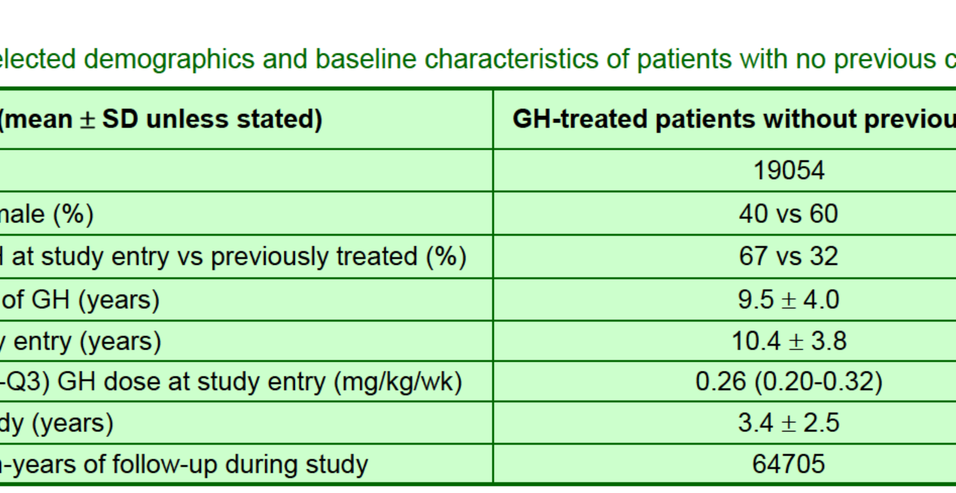
Table 1: Selected demographics and baseline characteristics of patients with no previous cancer

Parameter (mean ± SD unless stated)	GH-treated patients without previous cancer
N	19054
Female vs male (%)	40 vs 60
Naïve to GH at study entry vs previously treated (%)	67 vs 32
Age at start of GH (years)	9.5 ± 4.0
Age at study entry (years)	10.4 ± 3.8
Median (Q1-Q3) GH dose at study entry (mg/kg/wk)	0.26 (0.20-0.32)
Time on study (years)	3.4 ± 2.5
Total person-years of follow-up during study	64705

Abbreviations: GH = growth hormone; Q1-Q3 = interquartile range; SD = standard deviation; vs = versus; wk = week.

- The most common short stature diagnoses were growth hormone deficiency (GHD), idiopathic short stature (ISS), Turner syndrome (TS), and being born small for gestational age (SGA) (Figure 1).

Figure 1: Main short stature diagnoses ,of patients with no previous cancer



* Indicated as not having GHD but enrolled with diagnoses that, according to the structure of the case report form diagnostic module, would routinely be recorded under GHD (predominantly Prader-Willi syndrome).

4) RESULTS: continued

Incident primary cancer cases and standardised incidence ratios

- 13 potentially malignant primary neoplasms from 5 countries were identified (Table 2).
- The overall SIR (95% CI) was 1.02 (0.54–1.75).
- No country-specific SIR was statistically significantly elevated.
- Crude incidence was 20.1 cases per 100,000 person-years.

Table 2: Summary of incident primary cancers and standardised incidence ratios by country and overall

Country[1]	N	Person-years of follow-up	Observed cancer cases	Expected cancer cases	SIR (95% CI)
Canada	656	2758	3	0.76	3.94 (0.81–11.52)
France	1439	5424	2	1.32	1.52 (0.18–5.49)
Germany	2507	12270	5	3.15	1.59 (0.52–3.71)
Japan	2051	5973	1	0.78	1.29 (0.03–7.18)
USA	8465	24660	2	3.83	0.52 (0.06–1.89)
Overall	19054	64705	13	12.71	1.02 (0.54–1.75)

[1] Countries with no incident cases are not listed in the table but are included in the overall SIR.

- The specific reported cancers were:
  - 4 lymphomas (all from Germany; with no previous neoplastic history or identified risk factors)
  - 2 potential intracranial germ cell tumours
  - 2 bone tumours (Ewing's sarcoma and osteosarcoma)
  - 1 case each of gonadoblastoma, neuroendocrine tumour, rectal cancer, soft tissue tumour, and skin cancer
- Some patients had risk factors for tumour development or the tumour was possibly benign (Table 3).
- 1 tumour reported prior to study enrolment was included to maintain a conservative analysis.
- Mean age at reported cancer onset was 13.5 years, and time from start of GH to reported cancer onset ranged from only 5 weeks to approximately 10 years (Table 3).

Table 3: Summary of patient characteristics, cancer type, and relevant history at cancer diagnosis

Country	Short Stature Diagnosis	Age (y)[1]	Time to cancer (y)[2]	Sex	Cancer type	Relevant history / other factors
Canada	TS	16.9	9.0	F	Ewing's sarcoma (pelvic/spinal metastases)[3]	Pathology +ve for *EWSR1* translocation and the chromosome 22q12 location
Canada	Acquired GHD	15.4	3.8	M	Neuroendocrine tumour (pancreatic)	Hamartomas and NF; investigator reports "possible malignant behaviour"
Canada	Congenital GHD	14.4	~10	M	Osteosarcoma	Reported to Neoplasia Sub-study (post GH-start/pre-GeNeSIS start)
France	Acquired GHD	16.0	3.0	M	Rectal cancer	Irradiation for recurrent NF, diagnosed with Gardner syndrome
France	ISS (CDGA)	15.6	0.9	F	Gonadoblastoma (in streak gonad)	46XY mixed gonadal dysgenesis
Germany	SGA (RSS)	9.1	6.0	M	B-cell lymphoma	-
Germany	IGHD	16.1	10.2	F	Burkitt's lymphoma	-
Germany	IGHD	12.1	~8	M	Lymphoma	-
Germany	TS	14.0	5.6	F	Lymphoma	Pathology between a diffuse large-cell B-cell lymphoma and a Burkitt lymphoma)
Germany	Acquired GHD	13.4	1.5	M	Malignant schwannoma	History of WHO Grade 1 astrocytoma (surgery and chemotherapy) and NF
Japan	IGHD	8.2	5 weeks	F	Germinoma (around pituitary)	Hypophysitis diagnosis pre-GH. Tumour diagnosed (MRI) 5 wk after GH start
USA	Acquired GHD	12.4	3.8	M	Germ cell tumour	Possibly a craniopharyngioma (non-malignant) because of cystic structure.
USA	ISS	12.2	0.7	M	Skin cancer (malignant nevi)	-

Abbreviations: +ve = positive; CDGA = constitutional delay of growth and adolescence; F = female; GHD = growth hormone deficiency; IGHD = idiopathic GHD; ISS = idiopathic short stature; M = male; MRI = magnetic resonance imaging; NF = neurofibromatosis; RSS = Russell Silver syndrome; SGA = small for gestational age; TS = Turner syndrome; WHO = World Health Organisation; wk = weeks; y = years.
[1]At reported cancer diagnosis [2]From GH start to cancer diagnosis [3]Fatal during study

5) DISCUSSION

- The overall SIR indicated no increased risk for primary cancers during GeNeSIS participation in GH-treated patients when compared to general population cancer registries.
  - Although the aggregate person-years of follow-up were relatively large, the mean follow-up period per patient was relatively short.
- Cancer induction time was not taken into account: cases diagnosed soon after start of GH treatment in GeNeSIS (naïve patients) are unlikely to be due to the effects of GH treatment.
- Follow-up time is only that in GeNeSIS: those with pre-study GH treatment have had extra time to develop cancer that is not included in the person-years calculation.
- Cases with known (non-malignant) risk factors for cancer were included.

6) CONCLUSIONS

- **There was no increased primary cancer risk during GeNeSIS participation in GH-treated patients without previous cancer history compared to general population cancer registries.**

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