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

- 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 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 Genes ISIS 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 malignant histologies 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 reported previous potential malignancy.
- Patients with incident cases of primary malignancy were ascertained using the same data.
- 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 Genes ISIS 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 Genes ISIS or VisIt until the date of the last contact.

3) RESULTS:

Demographics and baseline characteristics of patients with no previous cancer

- A cohort of 15054 patients was identified; demographics and patient characteristics are shown in Table 1.

4) RESULTS: continued

Incident primary cancer cases and standardised incidence ratios

- 13 potentially malignant neoplasms from 5 countries were identified (Table 2).
- The overall SIR (95% CI) was 1.02 (0.95--1.07).
- 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 | Person-years of follow-up | Observed cancer cases | Expected cancer cases | SIR (95% CI)
--- | --- | --- | --- | ---
Canada | 656 | 2705 | 3 | 0.76 | 3.04 (0.81--11.52)
France | 1435 | 5424 | 2 | 1.52 | 1.52 (0.80--2.58)
Germany | 2507 | 12270 | 1 | 1.59 | 1.59 (0.52--5.37)
Japan | 2051 | 5973 | 1 | 0.78 | 1.29 (0.03--7.18)
USA | 8485 | 24660 | 2 | 3.83 | 0.52 (0.06--1.89)
Overall | 19054 | 64705 | 13 | 12.71 | 1.02 (0.54--1.75)

*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 gobaloblastoma, 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

<table>
<thead>
<tr>
<th>Country</th>
<th>Short stature diagnosis</th>
<th>Age (yr)</th>
<th>Time to cancer diagnosis (yr)</th>
<th>Sex</th>
<th>Cancer type</th>
<th>Relevant history or other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>TS</td>
<td>16</td>
<td>9.0</td>
<td>F</td>
<td>Ewing’s sarcoma (pulmonary metastases)</td>
<td>Pathology review for Ewing’s transformation and the chromosome 22:12 location</td>
</tr>
<tr>
<td>Canada</td>
<td>Acquired GHD</td>
<td>15.4</td>
<td>3.8</td>
<td>M</td>
<td>Neuroendocrine tumour (pancreas)</td>
<td>Hamartomas and NF: investigatory report</td>
</tr>
<tr>
<td>Canada</td>
<td>Congenital GHD</td>
<td>14.4</td>
<td>10.0</td>
<td>M</td>
<td>Osteosarcoma</td>
<td>Reported to Neoplasia Sub-study (post-GH start) and Genes ISIS start</td>
</tr>
<tr>
<td>France</td>
<td>Acquired GHD</td>
<td>16.5</td>
<td>3.0</td>
<td>M</td>
<td>Rectal cancer</td>
<td>Information for NF-diagnosed Gardner syndrome</td>
</tr>
<tr>
<td>France</td>
<td>ISS (CDGA)</td>
<td>15.6</td>
<td>9.0</td>
<td>F</td>
<td>Gobaloblastoma (intra mural)</td>
<td>4SXY mixed gonadal dysgenesis</td>
</tr>
<tr>
<td>Germany</td>
<td>GGA (RSS)</td>
<td>9.1</td>
<td>6.0</td>
<td>M</td>
<td>E-B cell lymphoma</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>IGHD</td>
<td>16.1</td>
<td>10.2</td>
<td>F</td>
<td>Burkitt’s lymphoma</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>IGDH</td>
<td>12.1</td>
<td>9.5</td>
<td>M</td>
<td>Lymphoma</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>TS</td>
<td>14.9</td>
<td>5.6</td>
<td>F</td>
<td>Lymphoma</td>
<td>Pathology between diffuse large-cell B-cell lymphoma and a Burkitt’s lymphoma</td>
</tr>
<tr>
<td>Japan</td>
<td>Acquired GHD</td>
<td>13.4</td>
<td>1.5</td>
<td>M</td>
<td>Malignant schwannoma</td>
<td>History of WHO Grade 2 extraaxial (surgery and chemotherapy) and NF</td>
</tr>
<tr>
<td>Japan</td>
<td>IGHD</td>
<td>8.2</td>
<td>5.0</td>
<td>F</td>
<td>Germ cell tumour</td>
<td>Hypothesised diagnosis pre-GH; Tumour diagnosed (MRI) 5 yrs after GH start</td>
</tr>
<tr>
<td>Japan</td>
<td>Acquired GHD</td>
<td>12.4</td>
<td>3.8</td>
<td>M</td>
<td>Germ cell tumour</td>
<td>Possibly a cambroanphagoma (non-malignant) because of cystic structure</td>
</tr>
<tr>
<td>USA</td>
<td>ISS</td>
<td>12.2</td>
<td>9.7</td>
<td>M</td>
<td>Skin cancer (melanoma nevus)</td>
<td>-</td>
</tr>
</tbody>
</table>

| Abbreviations: TS = primary; CDGA = constitutional delay of growth and adolescence; F = female; GHD = growth hormone deficiency; GHD = idiopathic short stature; ISS = idiopathic short stature; RSS = Russell-Silver syndrome; GGA = growth-gonadal axis; TS = Turner syndrome; RWH = World Health Organization; CMD = cancer mortality; DHR = height; GHD = growth hormone deficiency; N = normal; M = male; F = female; N = normal; M = male; F = female |

5) DISCUSSION

- The overall SIR indicated no increased risk for primary cancers during Genes ISIS 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 Genes ISIS (naive patients) are unlikely to be due to the GH treatment.
- Follow-up time is only that in Genes ISIS; those with pre-study GH treatment have had extra time to develop cancer that was 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 Genes ISIS participation in GH-treated patients without previous cancer history compared to general population cancer registries.

7) REFERENCES