Terapie endocrino-metaboliche e rischio oncologico

GH

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AO Città della Salute e della Scienza di Torino
Molinette - COES
Does growth hormone cause cancer?

- physiology/pathophysiology
- in vitro studies
- animal studies
- epidemiologic studies
- GH excess clinical settings
  - acromegaly
  - unlicensed GH therapy w/o GHD
- GH replacement in GHD

Jenkins PJ et al.; Clin Endocrinol 2006
GH/IGF-1 axis & tumors

endocrine, autocrine, and paracrine actions

• influencing factors:
  – IGF-1 receptor (type 1) density
  – IGF-1/insulin receptor hybrids

Jenkins PJ et al.; Clin Endocrinol 2006
GH/IGF-1 axis & tumors

Pollak MN et al.; Nat Rev Cancer 2004
IGF-1 and insulin receptors

Homology between IR & IGF-IR

Mathieu MC et al; Proc Assoc Am Physicians. 1997

Frasca F et al.; Arch Physiol Bioch 2008
GH/IGF-1 axis & tumors

endocrine, autocrine, and paracrine actions

• influencing factors:
  – IGF-1 receptor (type 1) density
  – IGF-1/insulin receptor hybrids
  – IGF-binding proteins (IGFBP-3, IGFBP-2)
    • regulation of free IGF-1 amount
    • IGF-1-independent actions
  – polymorphisms (IGF-1 gene/GH synthesis pathway)
  – proteases (e.g. PSA), tissue architecture, etc.

Jenkins PJ et al.; Clin Endocrinol 2006
Banerjee I & Clayton PE, Endocrinol Metab Clin N Am 2007
GH/IGF-1 axis & tumors

powerful effects of IGF-1 on:

- cellular proliferation
- apoptosis

across the general population, serum IGF-I levels vary between individuals, and it is postulated that this may impact upon cancer risk
GH/IGF-1 axis & tumors

Pollak MN et al.; Nat Rev Cancer 2004
GH/IGF-1 axis & tumors

powerful effects of IGF-1 on:

• cellular proliferation
• apoptosis
• angiogenesis & lymphangiogenesis
• cell motility
• metastases
• development of resistance to chemotherapeutics

Jenkins PJ et al.; Clin Endocrinol 2006
Pekic S & Popovic V, Eur J Endocrinology 2013
GH/IGF-1 axis & tumors
animal studies

- transfected/silenced mice
  - Yang XF et al., Cancer Res 1996

- Ab against IGF-1R
  - Arteaga CL et al.; J Clin Invest 1989

- selective knockout of hepatic IGF-1 gene
  - Wu Y et al.; Cancer Res 2002
  - Wu Y et al.; Cancer Res 2003

large IGF-1 level variations vs. physiology
GH/IGF-1 axis & tumors
epidemiological studies

- Childhood growth data would predict malignancy in later life
- Birth weight/stature
- Peak height velocity (& breast cancer)
- Final height (& breast, prostate, and CR cancer)
- Leg length
GH/IGF-1 axis & tumors
epidemiological studies

general population

• possible link between GH/IGF-1 levels & the development of a variety of different cancers

• subjects with IGF-1 levels that are in the higher centiles of the normal range would have a significantly increased risk of developing
  – breast, prostate, and colon cancer
  – lung cancer?

Hankinson SE et al.; Lancet 1998
Wolk A et al., J Natl Cancer Inst 1998
taller people are at increased risk of cancer

- large prospective cohort of ~1.3 M middle-aged women w/o previous cancer (follow-up 9.4 y)
- ~97,000 incident cancers (17 sites)

- RR for total cancer for every 10 cm increase in height was 1.16 (95% CI 1.14–1.17; p<0.0001)

- statistically significant increased risk for 10 sites
  - independently of socioeconomic status & geographic area
  - lower in current smokers

- IGF-1 levels in childhood/adulthood?
increased risk of:

• colorectal tumors: 2-7.6x
• thyroid tumors
• breast tumors? prostate cancer?

✓ genetics?
✓ hyperinsulinemia & diabetes role?
### Table 1: Colonoscopy studies in acromegalic patients.

<table>
<thead>
<tr>
<th>Country</th>
<th>Case/control</th>
<th>Mean age—acromegaly</th>
<th>Adenoma prevalence</th>
<th>Comments on controls</th>
<th>Conclusions—prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein et al., 1982</td>
<td>USA</td>
<td>17/—</td>
<td>49</td>
<td>Adenoma prevalence: 5 (29) — Controls: 2 (15)</td>
<td>Increased</td>
</tr>
<tr>
<td>Iturbe et al., 1984</td>
<td>USA</td>
<td>12/—</td>
<td>56</td>
<td>Population cancer rates only</td>
<td>Increased</td>
</tr>
<tr>
<td>Brunner et al., 1990</td>
<td>USA</td>
<td>29/—</td>
<td>NR</td>
<td>Population cancer rates only</td>
<td>Increased</td>
</tr>
<tr>
<td>Ezzat et al., 1991</td>
<td>USA</td>
<td>23</td>
<td>47</td>
<td>One study from literature</td>
<td>Increased</td>
</tr>
<tr>
<td>Ortego et al., 1994</td>
<td>Spain</td>
<td>27/—</td>
<td>49</td>
<td>Compared with literature</td>
<td>Inclusive</td>
</tr>
<tr>
<td>Ladas et al., 1994</td>
<td>Greece</td>
<td>54/—</td>
<td>47</td>
<td>Compared with literature</td>
<td>No increase</td>
</tr>
<tr>
<td>Yasen et al., 1994</td>
<td>NH</td>
<td>49</td>
<td>54</td>
<td>Compared with literature</td>
<td>Increased</td>
</tr>
<tr>
<td>Delhoughes et al., 1995</td>
<td>France</td>
<td>103/138</td>
<td>51</td>
<td>In-house non-acromegalic patients with IBS symptoms</td>
<td>Increased</td>
</tr>
<tr>
<td>Jenkins et al., 1997</td>
<td>UK</td>
<td>127/562</td>
<td>32—80</td>
<td>In-house non-acromegalic symptomatic patients</td>
<td>Increased</td>
</tr>
<tr>
<td>Renehan et al., 2000</td>
<td>UK</td>
<td>115/models</td>
<td>55</td>
<td>Controls modeled from 8 autopsies (n = 3559) and 4 screening colonoscopy (n = 810) studies</td>
<td>No increase</td>
</tr>
<tr>
<td>Martino et al., 2004</td>
<td>Italy</td>
<td>75/75</td>
<td>54</td>
<td>Age-sex-matched patients with IBS bowel symptoms</td>
<td>No increase</td>
</tr>
<tr>
<td>Bhansali et al., 2004</td>
<td>India</td>
<td>60/160</td>
<td>65</td>
<td>Age-sex-matched patients with IBS bowel symptoms</td>
<td>No increase</td>
</tr>
<tr>
<td>Torzola et al., 2005*</td>
<td>Italy</td>
<td>235/233</td>
<td>49</td>
<td>Age-sex-matched patients with IBS bowel symptoms</td>
<td>No increase</td>
</tr>
<tr>
<td>Matsui et al., 2005</td>
<td>Japan</td>
<td>19/76</td>
<td>18</td>
<td>In-house non-acromegalic symptomatic patients</td>
<td>Increased</td>
</tr>
<tr>
<td>Matyas et al., 2006</td>
<td>Poland</td>
<td>51/—</td>
<td>53</td>
<td>Compared against same sample using autofluorescence colonoscopy</td>
<td>‘High prevalence’</td>
</tr>
</tbody>
</table>
acromegaly & CRC

- small patient numbers, unadjusted for major confounding factors (e.g., age and gender)
- endoscopists are not blind (operator bias)
- colonoscopy is technically more difficult in acromegalic patients → more experienced endoscopists may detect more neoplastic lesions.
- hyperplastic & adenomatous polyps described together
- in population-based studies among cohorts of acromegalic patients, invasive CRC rates range from 0.8% to 1.3%.

Renehan AG et al.; Best Pract & Res Clin Endocrinol & Metab 2008
acromegaly & neoplasms

associations of acromegaly with CR and thyroid cancer in population-based studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of cancers</th>
<th>No. of acromegalic</th>
<th>Risk ratio</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>13</td>
<td>1041</td>
<td>3.10</td>
<td>1.70, 5.10</td>
</tr>
<tr>
<td>Ron et al. 1991</td>
<td>12</td>
<td>1364</td>
<td>1.68</td>
<td>0.87, 2.93</td>
</tr>
<tr>
<td>Orme et al. 1998</td>
<td>4</td>
<td>1364</td>
<td>2.60</td>
<td>1.60, 3.80</td>
</tr>
<tr>
<td>Baris et al. 2002</td>
<td>13</td>
<td>1634</td>
<td>2.46</td>
<td>1.79, 3.38</td>
</tr>
<tr>
<td>I² = 11.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Rectal cancer        | 1              | 1041               | 0.40       | 0.00, 2.20          |
| Ron et al. 1991      | 4              | 1364               | 0.86       | 0.23, 2.20          |
| Orme et al. 1998     | 13             | 1634               | 2.50       | 1.30, 4.20          |
| Baris et al. 2002    |                |                    | 1.41       | 0.54, 3.71          |
| I² = 50.2%           |                |                    |            |                     |

| Thyroid cancer       | 1              | 1041               | 4.30       | 0.20, 21.4          |
| Ron et al. 1991      | 1              | 1364               | 2.54       | 0.07, 14.2          |
| Orme et al. 1998     | 3              | 1634               | 3.70       | 1.50, 9.10          |
| Baris et al. 2002    |                |                    | 3.64       | 1.63, 8.11          |
| I² = 0.0%            |                |                    |            |                     |

modest increase

Renehan AG et al.; Best Pract & Res Clin Endocrinol & Metab 2008
GH therapy
1) de-novo cancer in non-cancer patients with GHD

2) tumor recurrence in patients with previously treated cancer and with GHD

3) 2\textsuperscript{nd} neoplasms in survivors of childhood cancer with GHD
1) de-novo cancer in non-cancer patients with GHD
de-novo cancer in non-cancer patients with GHD

GHRT

- long-term
- efficacy
- safety
- cost-effectiveness

Increased fat mass (especially central adiposity)
Decreased lean body mass
Decreased muscle strength
Decreased exercise performance
Decreased cardiac capacity
Decreased bone mineral density and increased risk of fracture
Atherogenic lipid profile
Thin, dry skin
Psychosocial problems and decreased quality of life
  - Fatigue
  - Depression
  - Anxiety
  - Impaired sleep
  - Social isolation

continuation of therapy generally recommended even after completion of linear growth
de-novo cancer in non-cancer patients with GHD

increased malignancy risk

• case-reports
• a minority of series
• SAGhE

not increased malignancy risk

• HypoCCS
• KIMS
• NCGS

Wada E et al.; Jpn J Clin Oncol 1989
Watanabe S et al; J Pediatr Endocrinol 1993
Watanabe S et al; Lancet 1998
Swerdlow AJ et al.; Lancet 2002

Reed ML et al.; Front Endocrinol 2013
Hypopituitary Control and Complication Study (HypoCSS), Lilly™

- IR of events between GH-treated and untreated 2430 GHD adults
- prospective observational study
- mean follow-up 2.3 years
- no significant difference
  - death
  - new cancer
  - intracranial tumor growth/recurrence
  - DM
  - CV events
de-novo cancer in non-cancer patients with GHD

Pfizer™ [formerly Kabi ™] International Metabolic Database (KIMS)

- multicentre, non-interventional study
- mortality & associated factors within GHRT adults
- 13,983 GHD patients; 528 deaths
- mean follow-up 4.9 years
- mortality: slightly higher vs. general pop.
- no increased SMR for deaths from CVDs or malignancies

Gaillard RC et al.; Eur J Endocrinol 2012
de-novo cancer in non-cancer patients with GHD

National Cooperative Growth Study (NCGS), Genentech™

• multicenter post-marketing surveillance study to monitor safety & efficacy of rhGH

• 54,996 children (1985-2006), 900 investigators

• 20 years of GH therapy

• de-novo malignancies: not significantly increased vs. general population
  – leukemia
  – intra/extracranial

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Years of GH exposure</th>
<th>Expected rate per 100,000 yr of exposure</th>
<th>Observed cases</th>
<th>Expected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>11,348</td>
<td>20.4</td>
<td>1</td>
<td>2.32</td>
</tr>
<tr>
<td>5–9</td>
<td>44,585</td>
<td>11.4</td>
<td>6</td>
<td>5.68</td>
</tr>
<tr>
<td>10–14</td>
<td>85,900</td>
<td>12.9</td>
<td>17</td>
<td>11.08</td>
</tr>
<tr>
<td>15–19</td>
<td>36,082</td>
<td>20.0</td>
<td>9</td>
<td>7.22</td>
</tr>
<tr>
<td>20–24</td>
<td>34,9</td>
<td>34.9</td>
<td>1</td>
<td>0.19</td>
</tr>
<tr>
<td>Total</td>
<td>178,464</td>
<td>14.5a</td>
<td>29</td>
<td>25.68</td>
</tr>
</tbody>
</table>

Bell J et al.; J Clin Endocrinol Metab 2010
Safety and appropriateness of Gh treatment in Europe (SAGhE)

- population-based study on long-term safety of rhGH in French children
- 6928 children (1985-1996) with low-risk
- mean follow-up: 17.3 years
- all-cause mortality increased (SMR 1.33) vs. general pop.
  - all-type cancer mortality non increased (CRC, Hodgkin...)
  - bone tumor-related mortality increased (SMR 5.00)
- GH doses >50mcg/kg/day associated with mortality rates
de-novo cancer in non-cancer patients with GHD

Safety and appropriateness of Gh treatment in Europe (SAGhE)

“Overall, our results do not allow the conclusion of the causal role of GH treatment in the findings but highlight the need for additional studies on long-term morbidity and mortality after GH treatment in childhood, in particular when high doses have been used”
1) de-novo cancer in non-cancer patients with GHD

inconclusive evidence of a very modest increase in cancer risk
2) tumor recurrence in patients with previously treated cancer & with GHD
tumor recurrence in patients with previously treated cancer & with GHD

not increased risk

Arslanian SA et al., *Am J Dis Children* 1985
- Rodens KP et al., *Acta Endocrinol* 1987
- Clayton PE et al., *Lancet* 1987
- Ogilvy-Stuart AL et al., *BMJ* 1992
- Swerdlow AJ et al., *J Clin Endocrinol Metab* 2002

### NCGS
- not increased risk of leukemia/brain tumors recurrences

### CCSS
- 13,539 survivors of pediatric tumors
- 361 GH treated pts; follow-up: 6.2 years
- RR of disease recurrence: not increased (0.83; 95% CI 0.37-1.86; *P* = 0.65)
- RR of mortality: not increased (1.21; 95% CI 0.75-1.94; *P* = 0.43)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patient-years on growth hormone treatment</th>
<th>Principal malignancy type(s)</th>
<th>Risk estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogilvy-Stuart et al [105]</td>
<td>53</td>
<td>-</td>
<td>brain tumors</td>
<td>RR 0.8</td>
</tr>
<tr>
<td>Sklar et al [98]</td>
<td>172</td>
<td>-</td>
<td>brain tumors</td>
<td>RR 0.8</td>
</tr>
<tr>
<td>Swerdlow et al [104]</td>
<td>180</td>
<td>-</td>
<td>brain tumors</td>
<td>RR 0.6</td>
</tr>
<tr>
<td>Blethen et al [96]</td>
<td>19,000</td>
<td>47,000</td>
<td>leukemia</td>
<td>no increased risk</td>
</tr>
<tr>
<td>Maneatis et al [97]</td>
<td>33,161</td>
<td>113,000</td>
<td>leukemia nonleukemic neoplasms</td>
<td>SMR 0.7</td>
</tr>
<tr>
<td>Wyatt [95]</td>
<td>~33,000</td>
<td>135,431</td>
<td>nonleukemic neoplasms</td>
<td>SIR 0–1.6</td>
</tr>
</tbody>
</table>
tumor recurrence in patients with previously treated cancer & with GHD

Childhood Cancer Survivor Study (CCSS)

retrospective cohort of 5-yr survivors of childhood cancer diagnosed <21 yr, between 1970 and 1986, and treated in USA/Canada

- currently, overall 5-yr survival rate for childhood cancer: >70%
- most prevalent late effects of cancer therapy: endocrine disorders (40%)
- GHD: up to 30-40%

follow-up: 6.2 yr

Sklar CA et al.; J Clin Endocrinol Metab 2002
tumor recurrence in patients with previously treated cancer & with GHD

Craniopharyngioma

• case-control study
  – GHD caused by craniopharyngioma
  – rhGH > 3 years vs. no therapy

• 56 patients

• mean duration of GHRT: 13.6 years

long-term GHRT did not affect the PFS

Olsson DS et al.; Eur J Endocrinol 2012
2) tumor recurrence in patients with previously treated cancer & with GHD

the general evidence suggests no increased risk
3) 2\textsuperscript{nd} neoplasms in survivors of childhood cancer with GHD
2nd neoplasms in survivors of childhood cancer with GHD

Childhood Cancer Survivor Study (CCSS)

- 13,539 survivors of pediatric tumors
- 361 GH treated pts; follow-up: 6.2 years
- RR of 2nd neoplasms 3.21 (95% CI 1.88-5.46; \( P < 0.0001 \))
- excess of solid tumors in GH-treated survivors of acute leukemia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>RR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute leukemia</td>
<td>4.98 (1.95–12.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CNS tumors</td>
<td>2.34 (0.96–5.70)</td>
<td>0.06</td>
</tr>
<tr>
<td>CNS tumors (meningiomas excluded)</td>
<td>1.46 (0.31–6.79)</td>
<td>0.69</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>1.82 (0.41–8.01)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Sklar CA et al.; *J Clin Endocrinol Metab* 2002
2nd neoplasms in survivors of childhood cancer with GHD

Childhood Cancer Survivor Study (CCSS)

- 14,108 survivors of pediatric tumors
- 361 GH treated pts; follow-up: 8.8 years
- RR of 2nd neoplasms 2.15 (95% CI 1.3-3.5; P < 0.002)
- excess of solid tumors in GH-treated survivors of acute leukemia
- meningiomas: the most common 2nd tumor
- the elevation of risk due to GH use diminish increasing follow-up

Ergun-Longmire E et al.; J Clin Endocrinol Metab 2006
2\textsuperscript{nd} neoplasms in survivors of childhood cancer with GHD

- **NCGS**: increased risk with rhGH in pts with a prior history of malignancy, exp. leukemia and previously irradiated pts
- GH could induce mitogenic activity in cells already predisposed to neoplastic change and hence increase the theoretical risk of developing 2\textsuperscript{nd} neoplasms
- The increased risk of developing 2\textsuperscript{nd} neoplasms in GH-treated childhood cancer survivors is now listed in U.S. labeling for all rhGH products

Bell J et al.; *J Clin Endocrinol Metab* 2010
2nd neoplasms in survivors of childhood cancer with GHD

Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) + Hypopituitary Control and Complication Study (HypoCSS), Lilly™

- retrospective analysis of 2 prospective cohort studies
  - childhood cancer survivors (GeNeSIS)
  - GHD adults (HypoCSS)

- incidence of 2nd tumors: consistent with increased risk

- estimated cumulative incidence of 2nd tumors after 5 yr of follow-up:
  - 6.2% GeNeSIS
  - 4.8% HypoCSS

- most common: meningiomas (nearly all, after CT/RT exposure)

Woodmansee WW et al.; Eur J Endocrinol 2013
2\textsuperscript{nd} neoplasms in survivors of childhood cancer with GHD

retrospective study of 50 CCSs who developed GHD due to cancer therapies from a specialized outpatient clinic

Transition Unit for Childhood Cancer Survivors – Città della Salute e della Scienza Hospital of Turin

- cumulative incidence of 2\textsuperscript{nd} neoplasms between pts treated with rhGH during childhood and pts who did not: \textbf{no difference}
- follow-up: 20 years
- high incidence of 2\textsuperscript{nd} neoplasms: \textbf{28\%!}
- most common 2\textsuperscript{nd} neoplasms: menigioma, basal cell ca.
- elapsed time to the 2\textsuperscript{nd} neoplasm: shorter in GHD-treated pts (17.0 vs. 24.7 yrs)

\textbullet all 2\textsuperscript{nd} neoplasms \textbf{in pts treated with RT!}

Brignardello E et al. (in press)
2\textsuperscript{nd} neoplasms in survivors of childhood cancer with GHD

GH and IGF-1 have a promoting rather than initiating effect on carcinogenesis $\rightarrow$ GH could accelerate the growth of 2\textsuperscript{nd} neoplasms

Key messages:

- GHRT worthy to CCSs during childhood, to obtain normal height w/o increased risk of cancer

- however, 2\textsuperscript{nd} neoplasms seem to arise earlier: close follow-up!

- in adult survivors, the indication for GHRT are less obvious

Brignardello E et al. (in press)
3) 2\textsuperscript{nd} neoplasms in survivors of childhood cancer with GHD

some evidence of a modest increased risk associated with GH usage
Terapie endocrino-metaboliche e rischio oncologico

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