Safety of Growth Hormone Treatment in Patients Previously Treated for Cancer

Wassim Chemaitilly, MD[a,*], Leslie L. Robison, PhD[b]

KEYWORDS

• Growth hormone deficiency • Childhood cancer survivor • Cancer recurrence
• Second neoplasms • Cancer survivors

KEY POINTS

- The use of growth hormone (GH) in cancer survivors raises safety concerns because of the mitogenic and proliferative properties of GH and insulin-like growth factor 1 (IGF-1).
- Treatment with GH in childhood cancer survivors has not been shown to increase the risks of disease recurrence or mortality.
- Treatment with GH may be associated with an increased risk of second neoplasms, but studies are based on a few events.
- Radiation-associated meningiomas are the most common second neoplasms observed in GH-treated individuals.
- Exposure to cranial radiotherapy also predisposes to the development of meningiomas.
- Cancer survivors treated with GH require close monitoring during therapy and long-term follow-up.
- More data are needed on the long-term safety and benefits of GH replacement in deficient adult survivors.

INTRODUCTION

GH deficiency (GHD) is one of the most commonly observed hormonal disorders in brain tumors survivors. Patients with tumor development close to the hypothalamus and/or pituitary and, more commonly, individuals exposed to cranial radiotherapy are particularly at risk of GHD.[1] Contemporary regimens of GH replacement therapy are effective in restoring linear growth and improving the adult height outcomes of

Conflict of interest: Dr Chemaitilly—None; Dr Robison—Consultant for Eli Lilly.

[a] Division of Endocrinology, Department of Pediatric Medicine, St Jude Children's Research Hospital, 262 Danny Thomas Place, MS 737, Memphis, TN 38105-3678, USA; [b] Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, 262 Danny Thomas Place, MS 735, Memphis, TN 38105-3678, USA
* Corresponding author.
E-mail address: wassim.chemaitilly@stjude.org

Endocrinol Metab Clin N Am 41 (2012) 785–792
http://dx.doi.org/10.1016/j.ecl.2012.07.002 **endo.theclinics.com**
0889-8529/12/$ – see front matter © 2012 Elsevier Inc. All rights reserved.

children with GHD.[2,3] Proved benefits in body composition, bone health, and metabolism have extended the indications for GH replacement to adults with GHD over the past decade.[4,5]

Given the mitogenic and proliferative properties of GH and IGF-1, through hepatic secretion stimulated by GH, the potential association between GH replacement therapy and increased long-term risk of developing a malignancy has been the subject of many reports and reviews.[6–9] Associations between treatment with human-derived pituitary GH and an increased risk of de novo leukemia,[10] cancer-related mortality, and colon cancer[11] have been reported, but none of these findings was subsequently confirmed by studies of patients treated with modern regimens using recombinant (DNA-derived) GH.[12,13] Concerns regarding the long-term safety of GH therapy were reignited by a recent report of higher mortality rates in individuals treated with GH during childhood for idiopathic GHD and non-GHD indications compared with the general population.[14] Although the report, compiling data on 6928 children treated with GH between 1985 and 1996, did not show an increase in cancer-related mortality in this population, there was an increase in mortality related to "bone tumors" (standardized mortality ratio 5.00; CI, 1.01–14.63).[14] Despite the lack of compelling evidence in favor of the association between treatment with recombinant GH and increased cancer risk in the general population of GH-deficient individuals, there are safety concerns among cancer survivors that command additional scrutiny given a proved predisposition for cancer and inherently increased risks of second neoplasms and malignancies.[15,16]

The aim of this review is to discuss available data on the safety of GH replacement therapy in cancer survivors, specifically from the perspective of the potential association between GH replacement and higher cancer recurrence and/or second neoplasm risks. Given that for many years GH was exclusively prescribed in children to promote linear growth, the focus is primarily on childhood cancer survivors.

GROWTH HORMONE, IGF-1, AND CANCER RISK

The IGF system includes 3 growth factors: insulin, IGF-1, and IGF-3; 2 receptors: the insulin receptor, which mediates insulin actions, and the IGF-1 receptor (IGF-1R), which mediates the actions of both IGF-1 and IGF-2; and 6 IGF-binding proteins (IGFBPs) with high binding affinity to the IGFs and low binding affinity to insulin. GH is the main systemic stimulus for the hepatic secretion of circulating endocrine IGF-1. GH also stimulates the secretion of IGFBP-3, which, in turn, regulates the action of IGF-1 through the formation of a stable complex that limits the interaction with IGF-1R.[17] Autocrine/paracrine production of GH and IGF-1 also occur at the level of peripheral tissues. Cellular overexpression of GH and GH receptor and changes in the paracrine/autocrine IGF-1–IGF-1R–IGFBP-3 axis were shown to affect cell cycle and to influence tumor growth in different experimental models.

GH overexpression has been shown to increase in vitro proliferation of both normal and cancerous mammary cells, likely in an autocrine fashion and independently from IGF-1.[9] IGF-1 has mitogenic, proangeiogenic, and antiapoptotic properties, hence promoting tumoral cell growth in several in vitro models.[6–9,17] In contrast, IGFBP-3 seems to exert an inhibitory effect on cancer cell growth and to possess proapoptotic properties that limit tumoral expansion.[6–9,17] Transgenic animal models have provided further corroboration of these properties with situations of tissue-targeted GH or IGF-1 overexpression, leading to higher risks of tumor development, tumor progression, and metastasis. Conversely, tumor growth is inhibited or reversed in models with tissue targeted inhibition of GH and IGF-1 and in models with targeted overexpression of IGFBPs, as summarized in the review by Clayton and colleagues.[6]

The association between cancer risk and increased systemic, endocrine secretion of GH and IGF-1 was mainly studied using 2 approaches: (1) assessment of cancer risk in individuals with acromegaly and (2) measurements of the IGF-1 and IGFBP-3 plasma levels in individuals with different malignancies. There are multiple reports of increased cancer risk in individuals with acromegaly, the more compelling findings related to higher risks of colon cancer, colonic neoplasia, and thyroid cancer.[6] In the general population, weak associations were reported between elevated plasma levels of IGF-1 and increased risks of breast, prostate, and colorectal cancers in several prospective epidemiologic studies.[6,18] These associations do, however, reinforce the need for careful monitoring of IGF-1 levels during GH replacement therapy and bring to attention the particular situation of individuals with GHD who also belong to high-risk groups, such as cancer survivors.[19]

LONG-TERM SAFETY OF GH REPLACEMENT IN CHILDHOOD CANCER SURVIVORS

Childhood cancer survivors are at a significantly higher risk of developing multiple subsequent neoplasms during the course of their lifetime. In a report from the Childhood Cancer Survivor Study (CCSS), a multicenter retrospective cohort of more than 14,000 individuals recruited among 26 institutions in North America, Armstrong and colleagues[16] showed that 9.3% of enrolled subjects (1382 survivors out of 14,358) had developed a second neoplasm. Second neoplasms included, by order of frequency, nonmelanoma skin cancer, breast neoplasms, meningiomas, thyroid cancer, soft tissue sarcomas, and central nervous system malignancies. Even more strikingly, among individuals who had developed second neoplasms, 27.9% went on to further develop additional new neoplasms over the following 20 years.[16] Considering the young age of patients followed in this cohort (the median age at the time of the study was 32 years), genetic predisposition and therapy-related tissue injuries are likely to significantly increase the risk of subsequent tumors and malignancies. Multiple studies have attempted to investigate whether past treatment with GH further increases this risk, including 2 reports from the CCSS.

Treatment with GH and Cancer Recurrence

Several studies concur on the lack of significant association between past treatment with GH and recurrence of the same primary cancer. Reporting on the cumulative incidence of leukemia relapse and second malignancies in 910 survivors of childhood acute lymphoblastic leukemia (ALL), including 47 treated with GH replacement, Leung and colleagues[20] did not find significant differences between GH and non–GH-treated patients after 7 and 11 years of follow-up. In a report on 31 patients treated with GH (24 childhood brain tumor survivors and 7 leukemia survivors exposed to cranial radiotherapy), Clayton and colleagues[21] did not find relapse rates that significantly differed from those observed in non–GH-treated patients. Similar findings were reported in survivors of childhood brain tumors by several consecutive studies.[22] In a report on 207 children treated for various brain tumors, including 47 treated with GH, Ogilvy-Stuart and colleagues[23] did not identify an increased risk of recurrence in children treated with GH (relative risk [RR] 1.01; 95% CI, 0.36–2.83). In a multicenter study of 1071 children diagnosed with brain tumors (patients with craniopharyngioma were not included in this study), including 108 treated with GH, Swerdlow and colleagues[24] also reported that past treatment with GH did not increase the risk of tumor recurrence (RR 0.7; 95% CI, 0.5–1.1). Data collected from large postmarketing surveillance registries, such as Pfizer International Growth Database (KIGS) and the National Cooperative Growth Study (NCGS), with, respectively, more than 50,000

and 19,000 individuals treated with GH, were not suggestive of a higher risk of tumor or cancer recurrence. These studies were limited, however, by lack of non–GH-treated comparison groups.[25,26] In the KIGS registry report, Darendeliler and colleagues[25] compared the observed frequency of tumor recurrence by tumor type to available data in the literature. In patients treated with GH, recurrence rates were 9.8% in individuals with glial tumors (n = 400), 8.8% in those with ependymoma (n = 113), 4.4% in individuals with medulloblastoma (n = 655), and 4.0% in individuals with germinoma (n = 297). These numbers were reported as reassuring when compared with data available on non–GH-treated individuals in other studies, referring in particular to the article by Swerdlow and colleagues.[24,25] In the NCGS report, Blethen and colleagues[26] reported recurrence rates of 7.2% in GH-treated individuals with primitive neuroectodermal tumors (n = 194) and 18.1% in those with low-grade glioma (n = 194). These rates were described as not "excessive" but no further comparisons were provided in the report. In the first CCSS report on the risk of disease recurrence and second neoplasms, Sklar and colleagues[27] did not find a significantly increased risk of cancer recurrence in individuals treated with GH when compared with non–GH-treated survivors. They reported an RR of disease recurrence of 0.83 (95% CI, 0.37–1.86) in individuals treated with GH (n = 361) among 13,539 survivors enrolled in the CCSS at the time.[27] In a more recent single-center retrospective study of 110 survivors of childhood (n = 41) and adult (n = 69) cancer treated with cranial radiotherapy and 110 matched non–GH-treated controls (individuals were matched for radiotherapy dose, age at primary diagnosis, and duration of follow-up), Mackenzie and colleagues[28] did not find significant differences in recurrence rates between the comparison groups (5.5% in the GH-treated group vs 7.3% in controls, $P = .78$).

Treatment with GH and Second Neoplasms

The initial report from the CCSS by Sklar and colleagues[27] identified an increased risk of second neoplasms in childhood cancer survivors treated with GH when compared with those not treated with GH. In this cohort of 13,222 participants, including 354 patients treated with GH, data regarding second neoplasm occurrence were available. Among individuals treated with GH, 15 developed second neoplasms, including 7 while on GH. All observed second neoplasms in GH-treated individuals were solid tumors and all except 1 involved sites exposed to external radiation. Second neoplasms diagnoses included meningioma (n = 6), osteosarcoma (n = 3), soft tissue sarcoma (n = 2), brain astrocytoma (n = 1), brain glioma (n = 1), mucoepidermoid carcinoma of the parotid (n = 1), and adenocarcinoma of the colon (n = 1). Among survivors not treated with GH, 344 developed second neoplasms. After adjustment for confounding factors, including age at diagnosis, gender, radiation, and alkylating agent effects, exposure to GH significantly increased the risk of second neoplasms (RR 3.21; 95% CI, 1.88–5.46, $P<.0001$). There was a relative excess of individuals with a primary diagnosis of ALL among GH-treated survivors who developed second neoplasms. When the analysis was restricted to malignant second neoplasms only, treatment with GH was no longer associated with higher risks of second neoplasms. Treatment with GH was not associated with an increased risk of death in this study.[27]

As accrual within the CCSS continued and additional long-term follow-up data became available, an updated report, specifically on the risk of second neoplasms and treatment with GH, was published 4 years later.[29] The expanded CCSS cohort included 14,108 childhood cancer survivors, 361 treated with GH. The findings reported by Ergun-Longmire and colleagues[29] continued to demonstrate that treatment with GH was associated with an increased risk of second neoplasms. The investigators reported 20 cases of second neoplasms in survivors treated with GH, all solid

tumors. Diagnoses included meningioma (n = 9), osteosarcoma (n = 3), soft tissue sarcoma (n = 2), brain glioma (n = 2), brain astrocytoma (n = 1), papillary thyroid carcinoma (n = 1), mucoepidermoid carcinoma of parotid (n = 1), and colon adenocarcinoma (n = 1). Among survivors not treated with GH, 555 developed second neoplasms. After adjustment for confounding factors, including age at diagnosis, gender, radiation, and alkylating agent effects, treatment with GH remained independently associated with a higher risk of developing a second neoplasm, although the magnitude of the risk was somewhat lower than the initial analysis (RR 2.15; 95% CI, 1.33–3.47; $P = .002$). When results were stratified by the initial diagnosis of cancer, no diagnostic category seemed associated with a higher risk of developing second neoplasms. The updated report included data on GH dose and duration of therapy and neither was associated with the risk of developing a second neoplasm. Meningioma was the most common diagnosis among second neoplasms observed in individuals treated with GH; all individuals who developed it were exposed to cranial radiotherapy, itself a known risk factor for meningioma.[30] The latency period for developing a meningioma was shorter in individuals treated with GH than in those who developed meningiomas but were not treated with GH (n = 62), 12.2 years versus 19 years ($P<.01$). Treatment with GH was not associated with an increased risk of death in this study.[29]

The CCSS reports on the risk of second neoplasms in childhood cancer survivors treated with GH had a lasting impact on clinical practice and patient counseling. The decrease in the RR with longer follow-up and the possibility of ascertainment bias related to a closer monitoring of individuals treated with GH have nevertheless led some investigators to question the findings in these reports.[28] In a recent article by Mackenzie and colleagues[28] on 110 survivors of childhood and adult cancer treated with cranial radiotherapy and 110 matched non–GH-treated controls and followed in a single institution for a median of 14.5 years, individuals treated with GH did not have a higher risk of developing second neoplasms than those not treated with GH. In this study, 5 individuals treated with GH developed second neoplasms (4 meningioma and 1 malignant nerve sheath tumor) versus 3 individuals not treated with GH (2 meningioma and 1 oligodendroglioma). Individuals were matched for radiotherapy dose, age at primary diagnosis, and duration of follow-up. The mean latency period for the diagnosis of meningioma in this cohort was 22.5 ± 6.3 years and was not found to differ significantly between individuals treated with GH and others. When considering the 41 matched pairs for childhood cancer survivors, 5 secondary tumors occurred among survivors versus 2 among the controls (a 2.5-fold difference). This is similar to the magnitude of difference reported by the CCSS.[29]

SAFETY OF ADULT GH REPLACEMENT REGIMENS IN SURVIVORS OF CANCER

With the recent expansion of GH replacement therapy indications to adults with GHD, specific data on the long-term safety of this therapy when administered to adult cancer survivors remain scarce. In an article on the neuroimaging surveillance of 45 brain tumor survivors treated with adult GH replacement therapy over a period of 6.7 ± 3.6 years, Jostel and colleagues[31] reported detecting the appearance of second neoplasms in 5 individuals (all were meningioma cases) during the course of therapy. The investigators also reported observing the progression of meningiomas detected before GH replacement therapy (n = 4) and of one residual primary tumor. Meningiomas occurred on average 22.8 years after exposure to cranial radiotherapy and although they did not relate an increased risk of brain tumor recurrence due to GH therapy, the investigators recommended a systematic neuroimaging surveillance of

such individuals, including baseline scans before the initiation of GH replacement and repeat studies at least once after 12 to 18 months of treatment.[31] With the primary aim of reporting on the risk of primary cancers in GH-treated adult hypopituitary patients by analyzing a cohort of 6840 GH-treated and 940 non–GH-treated individuals and by using expected case count reference data for standardized incidence ratio (SIR) calculations, Child and colleagues[32] provide some information on the occurrence of second malignancies on a subset of individuals with a previous diagnosis of cancer who were enrolled in their study. The mean follow-up duration in this study was 3.7 years per GH-treated patient. In total, 138 patients treated as adults with GH developed a cancer versus 32 non–GH-treated individuals. Although the study did not show an overall higher risk of developing a de novo cancer in individuals treated with GH in both the general (SIR 0.88; 95% CI, 0.74–1.04) and United States (SIR 0.94; 95% CI, 0.73–1.18) cohorts, there was a higher than expected incidence of newly diagnosed cancers in individuals 35 years and younger enrolled in the United States cohort (SIR 3.79; CI, 1.39–8.26) based on 6 observed cancers versus an expected reference count of 1.58. The investigators noted that 5 of these 6 patients had a previously diagnosed malignancy (this was a second cancer) and 4 of 6 individuals had childhood-onset GHD. These observations reflect the known relative vulnerability of childhood cancer survivors to second cancers[16] when compared with individuals with similar ages in the general population and call for continued caution in their risk assessment.

SUMMARY

Treatment with GH replacement does not seem to increase the risk of disease recurrence and mortality in survivors of childhood cancers. An increased risk of second neoplasms has been reported in survivors treated with GH when compared with those not receiving GH replacement. This risk seems to involve primarily a higher incidence of meningiomas in GH-replaced individuals who were treated with cranial radiotherapy. It remains unclear what the true magnitude of risk may be for GH exposure given the small sample sizes and potential for residual confounding by radiation therapy exposure. Longer-term follow-up is necessary to confirm if this higher RR persists or changes over time. The expansion of GH indications beyond the years of childhood has brought about the need for close monitoring and prospective safety data, especially in childhood cancer survivors, given their known higher risks for subsequent neoplasms and long-term health concerns.

REFERENCES

1. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. Endocr Relat Cancer 2010;17:R141–59.
2. Adan L, Sainte-Rose C, Souberbielle JC, et al. Adult height after growth hormone (GH) treatment for GH deficiency due to cranial irradiation. Med Pediatr Oncol 2000;34:14–9.
3. Gleeson HK, Stoeter R, Ogilvy-Stuart AL, et al. Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumours receiving GH replacement. J Clin Endocrinol Metab 2003;88:3682–9.
4. Mukherjee A, Tolhurst-Cleaver S, Ryder WD, et al. The characteristics of quality of life impairment in adult growth hormone (GH)-deficient survivors of cancer and their response to GH replacement therapy. J Clin Endocrinol Metab 2005;90:1542–9.
5. Murray RD, Darzy KH, Gleeson HK, et al. GH deficient survivors of childhood cancer: GH replacement during adult life. J Clin Endocrinol Metab 2002;87:129–35.

6. Clayton PE, Banerjee I, Murray PG, et al. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Nat Rev Endocrinol 2011;7:11–24.
7. Jenkins PJ, Mukherjee A, Shalet SM. Does growth hormone cause cancer? Clin Endocrinol 2006;64:115–21.
8. Ogilvy-Stuart AL, Gleeson H. Cancer risk following growth hormone use in childhood. Implications for current practice. Drug Saf 2004;27:369–82.
9. Cohen P, Clemmons DR, Rosenfeld RG. Does the GH-IGF axis play a role in cancer pathogenesis? Growth Horm IGF Res 2000;10:297–305.
10. Fradkin JE, Mills JL, Schonberger LB, et al. Risk of leukemia after treatment with pituitary growth hormone. JAMA 1993;270:2829–32.
11. Swerdlow AJ, Higgins CD, Adlard P, et al. Risk of cancer in patients treated with human pituitary growth horone in the UK, 1959-85: a cohort study. Lancet 2002; 360:273–7.
12. Allen DB, Chen Rundle A, Graves DA, et al. Risk of leukemia in children treated with human growth horone: review and reanalysis. J Pediatr 1997;131:S32–6.
13. Tuffli GA, Johanson A, Chen Rundle A, et al. Lack of increased risk for extracranial, non leukemic neoplasms in recipients of recombinant deoxyribonucleic acid growth hormone. J Clin Endocrinol Metab 1995;80:1416–22.
14. Carel JC, Ecosse E, Landier F, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report on the French SAGhE study. J Clin Endocrinol Metab 2012;97:416–25.
15. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 2001;93:618–29.
16. Armstrong GT, Liu W, Leisenring W, et al. Occurrence of multiple subsequent neoplasms in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2011;29:3056–64.
17. LeRoith D, Butler AA. Insulin-like growth factors in pediatric health and disease. J Clin Endocrinol Metab 1999;84:4355–61.
18. Renehan AG, Zwahlen M, Minder C, et al. Insulin-like growth factor (IGF)-I, IGF binding protein-3 and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346–53.
19. Rosenfeld RG, Cohen P, Robison LL, et al. Long-term surveillance of growth hormone therapy. J Clin Endocrinol Metab 2012;97:68–72.
20. Leung W, Rose SR, Zhou Y, et al. Outcomes of growth hormone replacement therapy in survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 2002;13:2959–64.
21. Clayton PE, Shalet SM, Gattamaneni HR, et al. Does growth hormone cause relapse of brain tumours? Lancet 1987;1(8535):711–3.
22. Bogarin R, Steinbok P. Growth hormone treatment and risk of recurrence or progression of brain tumors in children: a review. Childs Nerv Syst 2009;25: 273–9.
23. Ogilvy-Stuart AL, Ryder WDJ, Gattamaneni HR, et al. Growth hormone and tumour recurrence. BMJ 1992;304:1601–5.
24. Swerdlow AJ, Reddingius RE, Higgins CD, et al. Growth hormone treatment of children with brain tumors and risk of tumor recurrence. J Clin Endocrinol Metab 2000;85:4444–9.
25. Darendeliler F, Karagiannis G, Wilton P, et al. Recurrence of brain tumours in patients treated with growth hormone: analysis of KIGS (Pfizer International Growth Database). Acta Paediatr 2006;95:1284–90.

26. Blethen SL, Allen DB, Graves D, et al. Safety of recombinant deoxyribonucleic acid derived growth hormone: the National Cooperative Growth Study experience. J Clin Endocrinol Metab 1996;81:1704–10.
27. Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the childhood cancer survivor study. J Clin Endocrinol Metab 2002;87: 3136–41.
28. Mackenzie S, Craven T, Gattamaneni HR, et al. Long-term safety of growth hormone replacement after CNS irradiation. J Clin Endocrinol Metab 2011;96: 2756–61.
29. Ergun-Longmire B, Mertens AC, Mitby P, et al. Growth hormone and risk of second neoplasms in the childhood cancer survivor study. J Clin Endocrinol Metab 2006;91:3494–8.
30. Paulino AC, Ahmed IM, Mai WY, et al. The influence of pretreatment characteristics and radiotherapy parameters on time interval to development of radiation-associated meningioma. Int J Radiat Oncol Biol Phys 2009;75:1408–14.
31. Jostel A, Mukherjee A, Hulse PA, et al. Adult growth hormone replacement therapy and neuroimaging surveillance in brain tumour survivors. Clin Endocrinol 2005;62:698–705.
32. Child CJ, Zimmermann AG, Woodmansee WW, et al. Assessment of primary cancers in GH-treated adult hypopituitary patients: an analysis from the hypopituitary control and complications study. Eur J Endocrinol 2011;165:217–23.