Safety of Growth Hormone Treatment in Patients Previously Treated for Cancer

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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

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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]

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