Growth hormone treatment and risk of malignancy

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ABSTRACT

Growth hormone (GH) treatment has been widely used for the children with GH deficiency as survival rate of pediatric patients with malignancies is increased. GH and insulin-like growth factor-I have mitogenic and anti-apoptotic activity, therefore there has been theoretical risk and concern that GH treatment may be associated with tumor development. The authors review the relationship of GH treatment and cancer risk in the aspects of de novo malignancy, recurrence and secondary neoplasm. Although the results of numerous researches are not consistent, this review of various clinical and epidemiological studies demonstrates that there is no clear evidence and causal relationship between GH treatment and tumor development. Nonetheless, a small number of studies report that childhood cancer survivors who receive GH treatment have a small increased risk of de novo cancer and second malignant neoplasm. Therefore, regular check-up and careful examination of the development of cancer should be needed in those who receive GH treatment. Continued surveillance for an extended period is essential to monitor long-term safety.

Key Words: Growth hormone, Malignancy, Cancer, Recurrence, Secondary neoplasm, Insulin-like growth factor-I

Introduction

Growth hormone (GH) has been administered to the children with GH deficiency using extracts from human pituitary glands since late 1950s[1]. GH is now produced by recombinant DNA technology and is prescribed for a wide variety of disorders in late 1980s. As use of synthetic human recombinant GH increase, there has been a focus of safety issues for several decades[2]. Recently, Carel et al.[3] analyzed a French population-based registry of 6,928 children who started GH treatment between 1985 and 1996. The researchers insisted that the mortality rates were increased in children treated with recombinant GH. However, all type cancer-related mortality was not increased, and it was due to bone tumors or cerebral hemorrhage. This showed the controversy associated with GH treatment and risk of malignancy.

Survival rates of pediatric patients with malignancies are increasing due to improved treatment modalities. Likewise, interest for long-term quality of life is increasing including final height of a patient with GH deficiency after cancer treatment[4]. The patients who have GH deficiency after completion of therapy against tumor are recommended with GH to increase height velocity and improve quality of life[5].

However, GH has mitogenic activity in its own[6]. There have been theoretical and clinical concerns that GH may play a part in tumor recurrence[7,8]. GH treatment may have the possibility to increase an individual's risk of developing cancer, particularly in the case of cancer survivors, by increasing the risk of recurrence or the secondary malignancy[9]. Therefore, controversies and debates have been existed that GH treatment might have a causal relationship with tumor recurrence.

It is recognized that GH and insulin-like growth factor-I (IGF-I) have mitogenic and anti-apoptotic activity from in vitro and in vivo studies and there is a probability that GH treatment may be associated with tumor development[7,8]. Higher serum level of IGF-I could be associated with increased cancer risk, and concern has been raised regarding its potential role as a cancer initiation factor after GH treatment[10]. Some epidemiological studies have showed the correlation between high serum level of IGF-I and cancers, including carcinomas of prostate, lung, breast and colon[11,12]. GH receptors have been expressed on normal and transformed human white cells, and in vitro studies have shown that GH may cause transformation of normal cells and proliferation of leukemic cells[9,13]. Most of the physiological effects of IGF-I are mediated through the type 1 IGF receptor, which is over-expressed in many different types of cancers[14]. Although the results of all studies are not completely consistent, high concentration of IGF-I may be linked with increased risk of cancer development[15].

As above, there is a concern that GH treatment may be associated with tumor development, while GH treatment has been shown to be safe generally. It is important to investigate the relationship between GH treatment and risk of cancer. The authors review the clinical and epidemiological studies that have examined cancer risk in patients treated with GH in the aspects of de novo malignancy, recurrence and secondary neoplasm.

GH treatment and de novo malignancy

Leukemia

A possible correlation between GH therapy and increased risk of leukemia was reported in Japan[16]. However, the investigators carried out a follow-up analysis of the cohort and they could not find close association between GH therapy and leukemia when subjects with known risk factors for leukemia were excluded[17]. Another study, the National Hormone Pituitary Program in the United States between 1963 and 1985 investigated that there were 3 cases of leukemia in 59,736 patient-years of GH treatment. The rate was not significantly higher than the 1.6 cases expected for an age, ethnicity, and sex matched population[18]. The Genentech's National Cooperative Growth Study (NCGS) which enrolled more than 40,000 GH recipients during 20 years follow-up showed that the leukemia risk was comparable to that of general population excluding subjects with known risk factors for leukemia[19]. Another study from the NCGS reported 3 cases of de novo leukemia compared with 5.6 of expected in age-matched general population[20].

Solid tumors

There was concern that elevated endogenous levels of growth hormone and IGF-I might be associated with increased risk of certain solid tumors. Swerdlow et al.[21] studied cancer incidence and mortality in 1,848 patients in the UK who were treated with human pituitary growth hormone during childhood and early adulthood between 1959 and 1985. The incidence and mortality of colorectal cancer and the mortality of Hodgkin's disease were increased after exclusion of patients with high risk of cancer originally. However, it was argued because the regimen of GH therapy at

that time were different from those used currently[8]. All patients received standard GH doses given twice or three times a week, and serum IGF-I levels were not monitored.

Tyden et al.[22] reported two cases of de novo development of cancer in living donor kidney transplants, although de novo development of cancer in renal transplants might be rare. However, according to the analysis from the Kabi International Growth Study (KIGS) and NCGS databases, only two cases of renal cell carcinoma in those who did not have renal disease were found among the 43,000 patients in the NCGS and 42,000 in the KIGS registries[23]. The number of malignancies seemed disproportionately high for the relatively small number of children who had chronic renal failure and who were receiving GH treatment[8,23].

Tuffli et al.[24] reported that the number of extracranial, non-leukemic neoplasms from 12,209 individuals who were treated with the recombinant GH was not increased compared with expected cases. Ten new cases of malignancies were noted, and it was not greater than expected, indicating that GH is not implicated in the occurrence of solid tumors. Another report from NCGS showed that there was no evidence of an increase in the incidence of de novo intracranial tumors in children treated with GH[25]. Bell et al.[20] reported that de novo intracranial and extracranial malignancies were not significantly increased in patients without risk factors from the recent analysis of the NCGS registry (29 confirmed versus 26 expected). One of the most recent report from the KIGS compared the incidence of cancer in the cohort with that in the general population by using the standardized incidence ratio (SIR)[26]. A total of 32 new malignant neoplasms were reported in 58,603 patients, versus the 25.3 expected [SIR, 1.26; 95% confidence interval (CI), 0.86-1.78]. GH

treatment in patients showed no statistical significant difference compared with the expected number of cases in this study.

GH treatment and recurrence of malignancy

Leukemia

Survivors of childhood leukemia are at risk of developing complications including growth failure, which may require GH treatment[8]. The patients with GH deficiency are common because total body irradiation increases risk of growth failure. However, GH deficiency also can be developed from the regimens using only chemotherapy[27]. There were concerns that children treated with GH after therapy against leukemia may be at a higher risk of recurrence.

Leung et al.[28] studied 47 patients who had received GH replacement therapy among 910 patients treated for acute lymphoblastic leukemia, and examined recurrence rates at 7 years and 11 years after continuous hematologic remission. There was no statistical evidence that GH therapy was associated with leukemia relapse or development of second malignancy.

The NCGS has monitored the safety of recombinant human GH since 1985. There were 3 new cases of leukemia in children without known risk factors for developing leukemia and 5 cases in children with known risk factors, however, there was no evidence of an increased recurrence of leukemia[29]. Follow-up report showed no evidence of increased incidence of leukemia among patients without previous risk factors[30]. Another investigator analyzed 47,000 patients representing

165,000 patient years from the NCGS, and demonstrated reassuring evidence that leukemia (de novo or relapse), extracranial nonleukemic neoplasm and central nervous system (CNS) tumor recurrence were not associated with GH therapy[31].

Sklar et al.[32] investigated 122 acute leukemia survivors from among 13,539 subjects enrolled in the Childhood Cancer Survivor Study (CCSS), a cohort of 5-yr survivors of childhood cancer, and the relative risk of recurrence was not increased in comparison with 4,545 children not treated with GH.

Brain tumors

GH deficiency is a common disease in patients with hypothalamic–pituitary tumors, caused by mass itself or by surgical or irradiation therapy to hypothalamo-pituitary axis[9]. It also can be developed in those who have other tumors distant from the hypothalamic–pituitary axis, because cerebrospinal irradiation is often needed to treat them[33].

Arslanian et al.[34] reported the outcome of GH therapy in 34 children with brain tumors in whom hypopituitarism developed in 1985. Twenty-four of 34 patients with brain tumors and hypopituitarism received GH therapy. Eight (33%) of 24 had tumor recurrence, compared with three (30%) of ten who did not receive GH. Clayton et al.[35] reported similar result that the late relapse rate of medulloblastoma and glioma was not altered by GH therapy, and it might not increase the relapse rate of brain tumors.

Medulloblastoma is one of the most highly malignant childhood brain tumors. Survivors from

meduloblastoma are increasing as progress has been made in the treatment of the tumor[36]. From a retrospective analysis of 34 children treated with GH for medulloblastoma over 3 years, Chae et al.[37] reported no recurred patient in the study. Another retrospective review included 170 patients treated with GH among 545 children with medulloblastoma[38]. This review demonstrated that GH treatment was underutilized in survivors of medulloblastoma, however, it was not associated with disease relapse.

Craniopharyngioma is relatively common brain tumor derived from pituitary gland embryonic tissue in children[39]. Due to the morbidities associated with damage to the pituitary and hypothalamus from surgical removal and irradiation against craniopharyngioma, GH treatment is commonly needed after therapy of the tumor[40]. The recurrence rate of craniopharyngioma was 0.045/treatment year in 488 patients who were enrolled in the KIGS from 1988 to 1996, and the investigators concluded that GH treatment might be safe and effective in children with craniopharyngioma[41]. In the NCGS report, children receiving GH after treatment of craniopharyngioma had a recurrence rate of 6.4%, considerably lower than the estimates of 20-25% in another report[25,42].

Swerdlow et al.[43] investigated 180 children with brain tumors treated with GH, and 891 children without GH during 1965-1996. The relative risk of first recurrence in GH-treated patients, adjusted for potentially confounding prognostic variables, was decreased (0.6; 95% CI, 0.4-0.9). The relative risk of mortality was also decreased (0.5; 95% CI, 0.3-0.8). There was no significant trend in relative risk of recurrence with cumulative time for which GH treatment had been given or with

time elapsed since GH treatment started. Another research had shown that recurrence of hypothalamo-pituitary tumor was considered as low in GH-treated patients by surveillance imaging[44]. Only one patient among 100 consecutive patients showed the evidence of slight intrasellar tissue enlargement from pituitary imaging at 6 months. GH replacement was continued, and there was no further change between 6 and 12 months, though the follow-up duration was short.

GH treatment and risk of secondary malignancy

Childhood cancer survivors might be at increased risk for secondary malignancies compared with general population[45]. Assessing the risk of second and subsequent malignancies during long term follow-up is very important.

Meadows et al.[46] investigated 14,358 cohort members in the CCSS and analyzed SIRs for second malignant neoplasm. The 30-year cumulative incidence of second malignant neoplasm was 9.3% and the risk of subsequent neoplasms remains elevated for more than 20 years of follow-up for all primary childhood cancer diagnosis. Another report from the CCSS showed that the risk of sarcoma was more than 9-fold higher among childhood cancer survivors than the general population[47]. Ergun-Longmire et al.[48] analyzed the cohort and reported that the rate of GH-treated survivors developing secondary neoplasms was 2.1 fold higher compared with non-GH-treated survivors, however, the risk appeared to be decreased as follow-up time extended. Carel et al.[49] suggested that children treated with GH following childhood cancer treatment might not have a greater number of

relapses, but there might be a higher incidence of secondary tumors in the early years of GH therapy from large cohort follow-up studies.

However, there are numbers of reassuring data. Neglia et al.[50] analyzed 13,581 children diagnosed with common cancers before age of 21 and surviving at least 5 years from retrospective cohort of U.S. and Canadian institutions. Twenty years after the childhood cancer diagnosis, the estimated cumulative incidence of second malignancy was 3.2%, and only 1.88 excess malignancies occurred during follow-up. Sklar et al.[32] studied 172 brain tumor survivors from among 13,539 survivors enrolled in the CCSS. The relative risk of disease recurrence was 0.83 (95% CI, 0.37-1.86) for GH-treated survivors and it was not increased for any of the major cancer diagnoses.

Most recently, Patterson et al.[51] analyzed 12,098 pediatric cancer survivors from the CCSS and reported the incidence of meningioma, glioma, and other solid tumors of CNS. The adjusted rate in GH-treated patients compared with untreated survivors for development of any CNS tumor was 1.0 (95% CI, 0.6-1.8). There was no statistically significant increased overall risk of the occurrence of solid tumor of CNS associated with GH exposure.

Circulating concentrations of IGF-I might be associated with an increased risk of common cancers, however the association remained unclear[52]. There were few large cohort studies about GH dosage, IGF-I levels and risk of tumor recurrence. A meta-analysis and systematic review showed that high concentrations of IGF-I were associated with an increased risk of prostate cancer and premenopausal breast cancer, but the associations were modest[52]. Nonetheless, monitoring IGF-I levels within normal range might be important and IGF-I based dosing by titrating GH doses to

target IGF-I level could be proposed in high risk group[49].

Conclusion

It is well recognized about the benefits of GH treatment for growth and metabolism in children with GH deficiency, and replacement therapy with GH is recommended[53]. Despite theoretical concerns about the effect of GH on tumor development, this review of various clinical and epidemiological studies demonstrates that there is no clear evidence and causal relationship between GH treatment in patients with GH deficiency and tumor development. Nonetheless, a small number of studies have reported that childhood cancer survivors who have received GH treatment have a small increased risk of de novo cancer and second malignant neoplasm. Therefore, regular check-up and careful examination for the development of cancer should be needed in those who receive GH treatment. Continued surveillance for an extended period is essential to monitor further assessment.

Disclosure

The authors have no conflicts of interest to disclose.

Tabel 1. Major recent studies of growth hormone treatment and malignancy risk from large data registry

	Year of publication	Data registry	No of Patients	No of observed cases	No of expected cases	SIR (95% CI)	Type of observed malignancy
Patterson et al.[51]	2014	CCSS	14,358	16		1.0 (0.6 –1.8)	Secondary CNS malignancy
Wilton et al.[26]	2010	KIGS	58,603	32	25.3	1.26 (0.86-1.78)	De novo malignancy
Bell et al.[20]	2010	NCGS	54,996	29	26	1.12 (0.75-1.61)	De novo non-leukemic malignancy
				3	5.6	0.54 (0.11-1.58)	De novo leukemia
Wyatt D.[31]	2004	NCGS	47,000	16	15.3		Recurred non-leukemic malignancy
Maneatis et al.[30]	2000	NCGS	33,161	20		0.73 (0.20-1.86)	Reccurred Leukemia
				35		0.44 (0.24-0.74)	Recurred nonleukemic malignancy

No, Number: SIR, Standardized Incidence Ratio; CI, Confidence Interval; CNS, Central Nervous System; CCSS, the Childhood Cancer Survivor Study; KIGS, the Kabi International Growth Study; NCGS, the National Cooperative Growth Study

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