

COMMENTARY

Growth Hormone and the Risk of Malignancy[†]

Blanche P. Alter, MD, MPH*

The possible association between growth hormone therapy and malignancy was first proposed in a 1988 report of five Japanese patients who developed leukemia after growth hormone exposure [1]. Since then, nearly 60 cases have been reported, in which 50 developed leukemia, and 10 had lymphomas or solid tumors (most reports summarized in Watanabe et al., Fradkin et al., and Blethen et al. [2–4]). Several of those with leukemia had prior conditions that were thought to increase the risk of secondary leukemia, including Fanconi Anemia, Bloom Syndrome, Down Syndrome, and brain tumors which had been treated with radiation therapy. The Lawson Wilkins Pediatric Endocrine Society and the Growth Hormone Research Society concluded that there is no evidence that the risk of leukemia is increased in growth hormone-deficient patients without other underlying conditions who receive growth hormone treatment. However, these organizations also provided a cautionary note, stating “*Certain patient groups, who occasionally receive GH treatment, carry an intrinsic risk of developing malignancies including those with neurofibromatosis type 1, Down’s and Bloom’s syndromes, and Fanconi’s anemia. Although there is no evidence that GH replacement poses an increased cancer risk, we recommend that such children will be carefully monitored with regard to tumor formation*” [5]. In relation to patients with syndromes with a malignant diathesis, the 2003 guidelines from the American Association of Clinical Endocrinologists states “*the high risk of malignant tumor or leukemia has prompted many pediatric endocrinologists to recommend that GH not be used because occurrence of a malignant condition might then be linked (appropriately or not) to the GH*” [6]. In addition, Rapaport et al. hypothesized that GH deficiency itself might be associated with an increased risk of leukemia [7].

It is difficult to determine whether there is a risk of leukemia related to treatment with GH, because of the small number of reported cases. The standardized incidence ratio was estimated to be as high as 9.4 in Japan [8], and between 2 and 5 in the USA [3,9,10]; the higher values were statistically significant due to the inclusion of patients with underlying leukemia susceptibility disorders of the types mentioned above. It was also noted that patients with acromegaly may be at increased risk of leukemia [11]. In addition to the potential risk of leukemia, the use of growth hormone was reported to be asso-

ciated with an increase in second malignancies, primarily osteosarcomas, in patients who received GH following treatment for leukemia [12]. Finally, an increased incidence of colon cancer and Hodgkin disease was observed in the UK pituitary growth hormone cohort [13]. All of these studies were limited in their ability to definitively address this question due to small numbers of cases with cancer.

The Endocrine community appears to be reassured that GH therapy per se does not lead to malignancy [5]. However hematologists and oncologists may need to remain alert to this possible association. Our patients are, by definition, among those in the high-risk categories, for whom the available evidence is less reassuring. They may have already had cancer, such as brain tumors or leukemia, for which they received radiation and/or chemotherapy. Alternatively, they may have primary disorders with known high risks of cancer. These include conditions with defects in responses to DNA damage, such as Fanconi Anemia, as well as other bone marrow failure syndromes, including Diamond-Blackfan Anemia, dyskeratosis congenita, and Shwachman-Diamond Syndrome [14,15].

More than 100 cases of leukemia have been reported in patients with Fanconi Anemia, as well as a similar number who had solid tumors, primarily squamous cell carcinomas of the head and neck, as well as gynecological tumors [14]. Two of the FA patients with leukemia had been treated with GH [16,17]. At least 10 patients with Diamond-Blackfan Anemia are known to have developed leukemia, as well as 2 with myelodysplastic syndrome, and 17 patients had solid tumors. The latter group included 1 with colon cancer, and 5 with osteogenic sarcomas; these cancer types were also associated with GH use in the general population [12,13]. In addition, 2 of the DBA patients with osteogenic sarcomas had received GH. Patients

Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Department of Health and Human Services, Rockville, Maryland

*Correspondence to: Blanche P. Alter, Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Executive Plaza South, Room 7020, Rockville, MD 20852-7231. E-mail: alterb@mail.nih.gov

Received 2 February 2004; Accepted 5 May 2004

Published 2004 Wiley-Liss, Inc.

[†]This article is a U.S. Government work and, as such, is in the public domain in the United States of America.
DOI 10.1002/pbc.20110

with dyskeratosis congenita also have a high risk of leukemia and solid tumors, while patients with Shwachman-Diamond Syndrome are at high risk of leukemia (and many of the SD patients are also short).

Children with “idiopathic” short stature are those in whom provocative endocrine testing does not demonstrate GH deficiency. Nevertheless, there are studies in which such children were treated with GH, and although they do appear to show initial growth acceleration, it is not apparent that they ultimately achieve a greater adult height than in untreated controls [18]. Reports of the use of GH in small numbers of FA or DBA patients have also indicated that there is an improvement in short term growth velocity, unrelated to whether GH deficiency was diagnosed, but none of these patients had reached their adult heights, and thus the long-term efficacy could not be determined [19,20].

It is worth pointing out that associations identified by case reports or case series do not prove causality. There are clearly insufficient numbers, and no prospective cohorts or retrospective case-control studies that would provide better insights into this problem. However, there is some biologic plausibility, since growth hormone treatment leads to increased levels of insulin-like growth factor (IGF-1), which itself has been implicated in cancer risk [21].

GH deficiency is a real problem for some FA and some DBA patients, due to pituitary stalk interruption or other endocrine etiologies [22–25]. However, these are the same patients who are at high risk of leukemia and other malignancies, and in whom the association of GH and subsequent leukemia has been observed. There are no data to prove that the intrinsic risk of leukemia is further exacerbated by GH treatment, particularly if the dose of GH is at the level of physiologic replacement. Nevertheless, this possibility requires serious consideration by the physicians and the families involved, and absence of data should not necessarily be construed to mean absence of an effect.

REFERENCES

1. Watanabe S, Tsunematsu Y, Fujimoto J, et al. Leukaemia in patients treated with growth hormone. *Lancet* 1988;i:1159–1160.
2. Watanabe S, Mizuno S, Oshima L-H, et al. Leukemia and other malignancies among GH users. *J Pediatr Endocrinol* 1993;6:99–108.
3. Fradkin JE, Mills JL, Schonberger LB, et al. Risk of leukemia after treatment with pituitary growth hormone. *JAMA* 1993;270:2829–2832.
4. Blethen SL, Allen DB, Graves D, et al. Extensive personal experience safety of recombinant deoxyribonucleic acid-derived growth hormone: The National Cooperative Growth Study Experience. *J Clin Endocrinol Metab* 1996;81:1704–1710.
5. Critical evaluation of the safety of recombinant human growth hormone administration: Statement from the Growth Hormone Research Society. *J Clin Endocrinol Metab* 2001;86:1868–1870.
6. Gharib H, Cook DM, Saenger PH, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 Update. *Endocr Pract* 2003;9:64–76.
7. Rapaport R, Oberfield SE, Robison L, et al. Relationship of growth hormone deficiency and leukemia. *J Pediatr* 1995;126:759–761.
8. Ogawa M, Mori O, Kamijo T, et al. The occurrence of acute lymphoblastic leukemia shortly after the cessation of human growth hormone therapy. *Jpn J Clin Oncol* 1988;18:255–260.
9. Antony GJ. Report of the International Workshop on Growth Hormone and Leukemia. *Lawson Wilkins Pediatric Endocrine Society* 1988; May 5, #1988.
10. Allen DB, Rundle AC, Graves DA, et al. Risk of leukemia in children treated with human growth hormone: Review and reanalysis. *J Pediatr* 1997;131:S32–S36.
11. Au WY, Chow WS, Lam KSL, et al. Acute leukaemia in acromegaly patients. *Br J Haematol* 2000;110:871–873.
12. Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer with growth hormone: A report from the childhood cancer survivor study. *J Clin Endocrinol Metab* 2002;87:3136–3141.
13. Swerdlow AJ, Higgins CD, Adlard P, et al. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959–85: A cohort study. *Lancet* 2002;360:273–277.
14. Alter BP. Cancer in Fanconi anemia, 1927–2001. *Cancer* 2003;97:425–440.
15. Alter BP. Inherited bone marrow failure syndromes. In: Nathan DG, Orkin SH, Look AT, Ginsburg D, editors. *Nathan and Oski's Hematology of Infancy and Childhood*, 6th edition. Philadelphia PA: WB Saunders; 2003. pp 280–365.
16. Standen GR, Hughes IA, Geddes AD, et al. Myelodysplastic syndrome with trisomy 8 in an adolescent with Fanconi anaemia and selective IgA deficiency. *Am J Hematol* 1989;31:280–283.
17. Endo M, Kaneko Y, Shikano T, et al. Possible association of human growth hormone treatment with an occurrence of acute myeloblastic leukemia with an inversion of chromosome 3 in a child of pituitary dwarfism. *Med Ped Oncol* 1988;16:45–47.
18. Radetti G, Buzi F, Cassar W, et al. Growth hormone secretory pattern and response to treatment in children with short stature followed to adult height. *Clin Endocrinol (Oxf)* 2003;59:27–33.
19. Becker RE, Maurer H, Bowyer FP, et al. Growth hormone deficiency (GHD) in Diamond-Blackfan anemia (DBA). *Pediatr Res* 1991;29:74A.
20. Lanes R, Muller A, Palacios A. Multiple endocrine abnormalities in a child with Blackfan-Diamond anemia and hemochromatosis. Significant improvement of growth velocity and predicted adult height following growth hormone treatment despite liver damage. *J Pediatr Endocrinol Metab* 2000;13:325–328.
21. 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;363:1346–1353.
22. Dupuis-Girod S, Gluckman E, Souberbielle J-C, et al. Growth hormone deficiency caused by pituitary stalk interruption in Fanconi's anemia. *J Pediatr* 2001;138:129–133.
23. Leblanc T, Gluckman E, Brauner R. Growth hormone deficiency caused by pituitary stalk interruption in Diamond-Blackfan anemia. *J Pediatr* 2003;14:358.
24. Massa GG, Heinrichs C, Vamos E, et al. Hypergonadotrophic hypogonadism in a boy with Fanconi anemia with growth hormone deficiency and pituitary stalk interruption. *J Pediatr* 2002;140:277.
25. Wajnrajch MP, Gertner JM, Huma Z, et al. Evaluation of growth and hormonal status in patients referred to the International Fanconi Anemia Registry. *Pediatrics* 2001;107:744–754.