LEADING ARTICLE

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Cancer Risk Following Growth Hormone Use in Childhood

Implications for Current Practice

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Abstract

The therapeutic use of growth hormone (GH) has caused concern, as it is anabolic and mitogenic, and its effector hormone, insulin-like growth factor (IGF)-I is anti-apoptotic. As both hormones can cause proliferation of normal and malignant cells, the possibility that GH therapy may induce cancer, increase the risk of tumour recurrence in those previously treated for a malignancy, or increase the risk of cancer in those with a predisposition, has resulted in concerns over its use. There are theoretical and epidemiological reasons that suggest GH and IGF-I may be important in tumour formation and proliferation. Malignant tumours have been induced in animals exposed to supraphysiological doses of GH, whereas hypophysectomy appears to protect animals from carcinogen-induced neoplasms. *In vitro*, proliferation and transformation of normal haemopoetic and leukaemic cells occurs with supraphysiological doses of GH, but not with physiological levels. IGF, IGF binding proteins (IGFBP) and IGFBP proteases influence the proliferation of cancer cells *in vitro*; however, GH is probably not involved in this process. Epidemiological studies have suggested an association between levels of IGF-I and cancer, and an inverse relationship between IGFBP-3 and cancer; however, these associations have been inconsistent. A number of studies have been undertaken to determine the risk of the development of cancer in children treated with GH, either *de novo*, or the recurrence of cancer in those previously treated for a malignancy. Despite early concerns following a report of a cluster of cases of leukaemia in recipients of GH, there appears to be no increased risk for the development of leukaemia in those treated with GH unless there is an underlying predisposition. Even in children with a primary diagnosis of cancer, subsequent GH use does not appear to increase the risk of tumour recurrence. However, a recent follow-up of pituitary GH recipients has suggested an increase in colorectal cancer. In addition, follow-up of oncology patients has suggested an increase in second neoplasms in those who also received GH therapy. These studies emphasise the importance of continued surveillance both internationally with established databases and also nationally through single-centre studies.

Growth hormone (GH) has been used as replacement therapy for GH deficiency in children for more than 40 years and, more recently, it has been used in adults. In both children and adults there are proven

benefits. GH has also been used in pharmacological doses to promote growth in children with non-GH-deficient short stature conditions. However, the oncogenic potential of GH has resulted in caution over its use. This review examines the published evidence that GH therapy in childhood might be linked to subsequent cancer risk. The implications from the data for the use of GH, particularly in children with a previous history of malignancy are discussed.

1. Animal Models of Cancer and the Growth Hormone (GH)-Insulin-Like Growth Factor (IGF) Axis

It was from studies in hypophysectomised animals that a relationship between GH and tumour development was first suspected. GH administered in supraphysiological doses to female rats induced neoplastic changes in several organs including lymphosarcomas of the lung, adrenocortical and adrenomedullary carcinomas, ovarian tumours and breast tumours.[1] In contrast, hypophysectomised rats had a lower incidence of carcinogen- and viral-induced tumours and leukaemia, which was reversed after treatment with a crude pituitary extract of 'purified' GH.[2,3] Eighty-three percent of non-hypophysectomised newborn rats developed virus-induced T-cell leukaemia compared with none of the hypophysectomised rats.[4]

To determine whether GH has any intrinsic mitogenic action *in vivo*, the expression of the c-myc proto-oncogene and insulin-like growth factor (IGF)-I was examined in the liver and kidney after GH administration in hypophysectomised rats.[5] Maximal expression of c-myc messenger RNA (mRNA) levels occurred in both tissues by 1 hour after a single injection of GH (100μg/100g bodyweight). By comparison, peak expression of IGF-I mRNA transcripts occurred 6–12 hours after GH administration. Furthermore, administration of recombinant IGF-I to hypophysectomised rats (50μg/100g bodyweight) failed to increase c-myc expression in either the liver or kidney, suggesting that GH itself, rather than IGF-I, initiates the mitogenic response in the liver and kidney following GH administration in hypophysectomised rats.[5]

GH administration to animals after hypophysectomy has prevented thymic involution and splenic follicular atrophy,[6] and corrected reduced ^{3}H-thymidine incorporation into DNA of thymocytes and splenocytes.[7] GH antiserum led to thymic atrophy and involution of lymphoid tissue in the spleen in mice.

Although these studies point to a role for the pituitary in exerting some effects on normally and abnormally growing cells *in vitro* and modulating the occurrence and growth of tumours in experimental animals, they fail to define the role of GH in this process. Hypophysectomy ablates the source of many hormones, of which GH is only one, thus suppression or regression of tumour growth in hypophysectomised animals can only suggest that GH is involved. Nonetheless, it was such information that resulted in management of metastatic carcinoma by hypophysectomy. It was proposed at the time that the effects of GH were mediated through the induction of tumourigenic factors that could accelerate the growth of spontaneous tumours.

More recent studies on human GH transgenic mice demonstrated the development of mammary tumours.[8] However, it is likely that this mechanism is via an effect of GH on the prolactin receptor,[9] as bovine GH (which does not activate the prolactin receptor) transgenic mice were not associated with breast tumours despite elevated IGF-I levels.[10]

Animal models in which the GH-IGF axis has been manipulated in the presence of tumour xenografts, suggests GH-IGF-I does influence the growth of established tumours, with slower growth in the presence of GH deficiency or the use of growth hormone-releasing hormone antagonists or somatostatin analogues.[11-13]

The findings, however, are not consistent, with no effect of IGF-I infusion on rhabdomyosarcoma xenograph[14] and evidence that IGF-I may actually be beneficial by reducing cancer cachexia.[15] Infusions of IGF binding protein-3 (IGFBP-3) inhibit the growth of cancer xenographs in a mouse model.[16]

Rat models inoculated with a spontaneously metastasising mammary adenocarcinoma and receiving GH in combination with somatostatin and insulin were significantly heavier and had evidence of inhibition of tumour growth kinetics.[17] Rats with prostate tumour implants had evidence of inhibition of pulmonary metastases when treated with GH.[18]

While some of these animal models support the GH product recommendations that active tumours should be a contraindication to use of GH therapy, GH may in fact have a beneficial role in reducing cancer cachexia and benefiting survival.

2. *In Vitro* Models of Cancer and the GH-IGF Axis

Both GH and IGF-I have stimulatory effects on the haemopoetic system *in vivo* and *in vitro*. Receptors for GH are present in cultured circulating human lymphocytes. IGF-I regulates both hormone function and cell proliferation via various autocrine, paracrine and endocrine pathways. The effects of IGF-I and IGF-II on cancer cells are mediated via the type-1 IGF receptor[19] and are present on myeloid and B-cell leukaemic cells.[20,21]

GH increases the transformation of normal human peripheral blood lymphocytes in cell culture and causes lymphocyte blastogenesis.[22,23] Both GH and IGF-I stimulate the proliferation and transformation of normal and leukaemic human lymphocytes *in vitro* when used in supraphysiological doses,[4,24,25] which can also lead to a 2-fold increase in colony numbers.[24] GH is mitogenic to leukaemic cells from children with acute lymphoblastic leukaemia (ALL) or acute non-lymphoblastic leukaemia at concentrations of 150–250 μg/L when used in combination with conditioning medium.[25] However, when used in a concentration of <50 μg/L (which is more representative of physiological levels), no increase in either colony numbers of human ALL cells or increase in DNA synthesis (examined by measuring ^{3}H-thymidine incorporation) was found.[24] Nanogram concentrations of human GH can potentiate T-cell colony growth from normal cultures and from a patient with a T-cell variant of hairy cell leukaemia, indicating a direct rather than an IGF-I-mediated role for GH in human lymphoid cells.[23] However, physiological levels of human GH do not influence colony formation in MOLT-4 (a cell line derived from an adolescent with ALL), nor affect thymidine incorporation into lymphoblasts from children with ALL.

Thus, although proliferation and transformation of normal and leukaemic cells *in vitro* may occur in the presence of GH, this is only with supraphysiological doses.

A potent mitogenic effect of IGF-I on a number of breast cancer cell lines has been documented.[26] Immunoreactive IGF-I has also been shown to be increased in human lung and colon carcinomas compared with adjacent normal tissue. Specific IGF-I receptors have also been characterised on human T-lymphoblasts, neurogliomas and colon carcinomas.

IGF function is modulated by the IGFBP and proteases and these are therefore also implicated in cell growth and differentiation. Local IGFBP-3 levels might be important in the pathogenesis of cancer. *In vitro*, IGFBP-3 has inhibitory effects on cancer cell growth.[27] IGFBP-3 induces apoptosis in a dose-dependent manner via an IGF/IGF receptor-independent pathway in breast and prostate cancer cells *in vitro*.[28]

Prostate-specific antigen is an IGFBP-3 protease, and elevated levels have been associated with reduced IGFBP-3 and with stage of prostatic cancer.[29]

Therefore, *in vitro*, IGF, IGFBP and IGFBP proteases influence the proliferation of cancer cells. However, GH is probably not involved in these cellular events *in vitro* and, *in vivo*, non-IGF-dependent effects have not been established. Consequently, in adults receiving GH replacement, monitoring IGF-I and maintaining levels within the normal range is accepted practice. Normative data in children are now more readily available. Serum IGF-I and IGFBP-3 levels are being more frequently monitored in children on GH therapy[30] and in the future this should become commonplace. At present, in children serum IGF-I levels are a marker of GH replacement and are useful to compare with clinical endpoints; however, it is unclear with our

present knowledge whether it should result in dose alteration, particularly in conditions where supraphysiological GH doses are employed.

3. Epidemiological Cancer Data and the GH-IGF-IGF Binding Protein-3 Axis

Several epidemiological studies have suggested an association between levels of IGF-I and cancer. Case-controlled studies and prospective studies report that IGF-I levels in the upper normal range may be associated with an increased risk of developing prostate cancer,[31,32] lung cancer[33] and, in premenopausal women, breast cancer.[34] The IGF-I level may be elevated up to 7 years before the tumour becomes clinically apparent.[34,35] A high IGF-I level and low IGFBP-3 level may be associated with an increased risk of colon cancer. In contrast, high IGFBP-3 levels are associated with a reduced cancer risk. However, these associations have not been consistent in all studies, for example the relationship between IGF-I and prostate cancer,[36,37] and IGF-I and breast cancer.[38] While IGF-I or IGFBP-3 alone have not been shown to be significantly related to colon cancer risk, the combination of high IGF-I and low IGFBP-3 was associated with a 4-fold increased risk.[39]

In acromegaly, in which there are pathologically sustained high levels of GH, IGF-I and IGFBP-3, an increased incidence of colonic polyps and adenocarcinomas have been reported.[40-46] However, the association with colonic cancer has not been consistent.[47-49] There are also anecdotal reports of an association between acromegaly and other tumours: adenocarcinoma of the breast,[44] adenomas and papillary carcinomas of the thyroid gland,[50] parathyroid adenomas, thymomas, carcinomas of the cervix and ovary, adenocarcinomas of the uterus, renal cell carcinomas, meningiomas, neuromas, bone cancer and multiple myeloma.[45,50,51] In many of these studies the numbers are small, and the studies retrospective and uncontrolled and hence open to bias. The largest study, which has included previously published data, found no increase in incidence of cancer (including colonic cancer) in patients with acromegaly.[52] The mortality rate, however, was higher in the acromegalic population than in the normal population, suggesting an effect of GH-IGF-I on established tumours.[53] To conclude, there is no convincing evidence of an association between acromegaly and specific carcinomas, apart possibly from colonic tumours. The GH levels in people with acromegaly greatly exceed the degree of GH exposure of those treated with replacement doses of GH therapy. However, a prospective study in healthy men without acromegaly has suggested a relationship between GH levels and mortality from cancer.[54]

4. GH, Childhood Leukaemia and Other Cancers

The clinical setting that has generated concern involves the development of leukaemia *de novo* in children receiving GH therapy for idiopathic GH deficiency.[55-59] A cluster was first reported from Japan in 1987.[56] A worldwide search for other such cases has revealed 15, 14 of whom started with GH after 1973; leukaemia was induced 0.2–11 years after the start of treatment.[60] The dosages of GH ranged from 4.5–18 IU/m^2/week. Seven of the 14 children had an additional leukaemia risk (Fanconi anaemia [n = 1], previous cyclophosphamide and azathioprine therapy [n = 1], radiation [n = 4], myelodysplasia [n = 1]), and a further two had received GH for only 2 and 3.5 months, respectively, making an aetiological link unlikely. When a link between GH treatment and leukaemia is considered on a worldwide basis, there is no striking relationship. The incidence of leukaemia in GH-treated patients is as expected in an aged-matched population in the US, Australia, Canada and Europe (the latter only if those with additional risk factors and brief treatment periods are excluded). The Lawson Wilkins Pediatric Endocrine Society and the Human Growth Foundation of the United States convened an international workshop in 1988[61] to review all cases of leukaemia after GH therapy, and the estimated risk of leukaemia was calculated to be 1 per 21 000 patient-years, representing a 2-fold increase over the expected rate. The incidence of leukaemia in Japan after treatment with GH was calculated as 1

per 6000 patient-years, while in other countries the estimates varied between 1 per 12 000 and 1 per 35 000 patient-years. An explanation for the cluster in Japan may be related to factors other than GH itself.[61]

A study of 6284 recipients of pituitary GH in the US between 1963 and 1985 sought to determine the risk of developing leukaemia or lymphoma.[62] Eighty-four percent of the cohort were contacted, and a positive history of malignancy confirmed by review of clinical records. Deaths in the cohort were monitored through the National Death Index, and medical records and/or death certificates were reviewed in 94% of patients. The denominator for expected number of cases of leukaemia or lymphoma for an age-, sex- and race-matched population was taken from the Surveillance, Epidemiology and End Results programme between 1982 and 1986[62] (a period when 44% of the defined person-years of risk occurred).

There were six cases of leukaemia. Four patients had been treated for craniopharyngioma and three of these had received cranial irradiation. One patient had received previous cranial irradiation for an astrocytoma and one patient with fetal alcohol syndrome was treated with GH as part of the therapy for panhypopituitarism. Three of these cases had been ascertained from the original analysis. The other three were collected from passive reporting of occurrence of leukaemia, or detection through the National Death Index in the 2.5 years after the original contact and interviewing period, and hence may denote an under-representation in cases of leukaemia, particularly if non-fatal. There were an estimated 83 917 person-years of risk and an expected 2.26 cases of leukaemia, which gave an observed to expected ratio of 2.6 : 1 (95% CI 1.2, 5.2). The patients who developed leukaemia had received GH for a mean of 3.5 years, whereas the mean duration in the entire cohort was 2.9 years.

Five patients developed lymphoma: one had been treated for a craniopharyngioma without radiotherapy, three had idiopathic GH deficiency, and one had Turner's syndrome. The five cases did not represent a significant excess over the expected (4.5) number of cases.[62]

The association of leukaemia after treatment of craniopharyngioma has not been reported elsewhere. Clayton et al.[63] found no association between the use of GH after treatment of craniopharyngioma and tumour recurrence and did not report any cases of leukaemia in 23 children who had received GH.

By May 1990, at a subsequent meeting of the Lawson Wilkins Pediatric Endocrine Society, the incidence of leukaemia in patients treated with GH but without additional risk factors was estimated to be 1 per 19 000 patient-years, i.e. a slightly increased risk compared with the general paediatric population. Cases of acute myeloid leukaemia, acute non-lymphoblastic leukaemia and chronic myeloid leukaemia were analysed in children treated with GH between 1988 and 1995, when ascertainment was likely to be complete. The incidence, 1 per 41 100 patient-years, is comparable to the expected rate for the 0–15 years age group (1 per 30 000), and the same as that expected for the 5–19 years age group (1 per 42 700 to 1 per 45 200), which is probably more representative for the GH-treated children.

In 1996, updated figures of *de novo* leukaemia were compiled by Dr Gunnarsson of Pharmacia and Upjohn from data provided by several pharmaceutical manufacturers of GH and from the literature.[64] Leukaemia, pre-leukaemia or myelodysplastic syndrome has been reported in 56 patients with GH deficiency. Forty-seven of these patients had received treatment with GH; the other nine had not received exogenous GH treatment. Twenty-nine were treated for idiopathic GH deficiency. Of these, three had Fanconi's anaemia, and minor or multiple malformations were present in four patients. In 12 patients, the underlying cause of GH deficiency was a craniopharyngioma or radiation-induced damage. The other six children were treated with GH therapy for idiopathic short stature (n = 2), short stature associated with Bloom's syndrome (n = 1), Down's syndrome (n = 2) and unknown diagnosis (n = 1).[64]

The ratios of the different leukaemia types: ALL (n = 24), acute non-lymphoblastic leukaemia (n = 15), chronic myeloid leukaemia (n = 3), and pre-leukaemia or myelodysplastic syndrome (n = 5), were similar to those expected in the childhood population, although others have disagreed with this.[65] Twenty-two of these children had risk factors for the development of leukaemia.

The recent data from the National Cooperative Growth Study data in the US and Canada have suggested that the incidence of leukaemia in GH-treated patients without additional risk factors was comparable to that in the age-matched children.[66]

The updated data have been published from the Foundation for Growth Science in Japan that has monitored safety of GH since 1975.[67] More than 32 000 children were treated with GH from 1975 until the end of 1997. *De novo* leukaemia was diagnosed in 14 patients – six with ALL, seven with acute myelocytic leukaemia and two with chronic myelocytic leukaemia. Six patients had predisposing risk factors for leukaemia including Fanconi's anaemia, previous chemotherapy or radiotherapy, and pancytopenia. Nine patients developed leukaemia while on GH therapy and five after completion of treatment. The incidence of leukaemia in patients without risk factors was 3.0 per 100 000 patient-years (date from the first dose of GH treatment to date of last dose of GH therapy). The incidence of leukaemia in those without risk factors from the first dose of GH until the end of 1997 was 3.9 per 100 000 patient-years. This is similar to the incidence in Japanese children aged 0–15 years (2.9–4.0 per 100 000 patient-years. Although these data suggest no increase in leukaemia in those treated with GH who were without other risk factors, the upper 95% CIs of the standard incidence ratio (number of cases observed to number of cases expected) exceeded one, so complete reassurance cannot be given.[67]

To further complicate the picture is the suggestion that GH deficiency itself may predispose a child to an increased risk of developing leukaemia.[68]

To conclude, the data to date do not suggest a significant increase in leukaemia risk in recipients of GH therapy who do not have a predisposing genetic or haematological condition. However, the cluster of cases from Japan remains unexplained.

Tuffli and colleagues sought to determine if there was an increase in non-leukaemic, extracranial neoplasms in recipients of GH.[69] Data were predominantly from the National Cooperative Growth Study (NCGS) [16 500 patients] with an additional 3000 non-NCGS patients reported to Genentech's Medical Information and Drug Experience department. Patients were excluded from the analysis if they had an additional risk factor for the development of an extracranial neoplasm (CNS tumour, cranial irradiation, leukaemia, histiocytosis, craniopharyngioma, renal disease, Bloom's syndrome, Down's syndrome or mixed gonadal dysgenesis). Thus there were 12 209 evaluable patients. Cancer incidence rates for the general population were taken from the National Institute's Surveillance, Epidemiology and End Results Programme. Risk calculations (standard mortality ratios [SMR]) were made separately for sex and 5-year age groups. Girls with Turner's syndrome were also analysed separately. Of the 18 cases of newly diagnosed, non-leukaemic extracranial neoplasms reported to Genentech, ten had no evidence of pre-existing cancer or exposure to irradiation. For each of the subgroups, the SMR was statistically indistinguishable from one, suggesting no increased risk for the development of a non-leukaemic extracranial neoplasm.

The longest follow-up data are available from an analysis of cancer incidence and mortality in the 1848 recipients of pituitary GH received between 1959 and 1985.[70] Person-years at risk of death from cancer was calculated by sex and 5-year age group starting from the date of first treatment with GH until the end of 2000. Analysis of cancer risk was calculated from the date of first treatment or from the beginning of 1971 (when the data were entered onto the NHS Central Register) and ended at date of cancer incidence, death, loss to follow-up or the end of 1995. Expected numbers of cancers were taken from the Office for National Statistics and the Information Services Division and General Register Office for Scotland. Non-melanoma skin cancers were

excluded as national cancer registration was incomplete. CNS tumours were also excluded, as many of the initial diagnoses included CNS tumours or a CNS tumour could not be excluded as the cause of idiopathic GH deficiency. Deaths from cancers that were the reason for the start of GH therapy were excluded from the mortality analyses. Thirty-nine percent of patients were aged <10 years and 60% were aged 10–19 years at first GH treatment. Fifty-three percent had idiopathic GH deficiency, 26% had intracranial neoplasms and the other cases included 22 with leukaemia or lymphoma, four with chromosome fragility and two with glycogen storage disease. Two hundred and forty-one patients died and 28 were lost to follow-up. There was an average of 16.1 years of follow-up per patient (total 29 817 years) for the cancer incidence analysis and an average of 21.2 years per patient follow-up (total 39 178 years) for the mortality analyses.

There were 12 cancers and ten deaths attributable to cancer in the patients. Patients treated with pituitary GH had a significantly increased risk of mortality from cancer overall (SMR 2.8, 95% CI 1.3, 5.1), colorectal cancer (SMR 10.8, 95% CI 1.3, 38.8; two cases) and Hodgkin's disease (SMR 11.4, 95% CI 1.4, 41.3; two cases). Even after exclusion of patients whose initial diagnosis put them at high risk of cancer (previous radiotherapy or chemotherapy, chromosome fragility or glycogen storage disease), the significance and size of risks of colorectal cancer incidence and mortality, and mortality from Hodgkin's disease were increased. Both deaths from colon cancer were at a young age (23 and 37 years) and in one patient there was an unclear possibility of polyposis coli. There were no cases of leukaemia in the GH-treated patients.

Once again, the numbers are small and 95% CIs wide. In addition, there are no data as to whether these children went on to receive synthetic GH. Although this will not have affected the analysis based on first or ever treatment, the duration of GH therapy may not be accurate. The data on the risk of colorectal cancer is of concern and requires further investigation in other cohorts. It is unknown whether modern GH dose regimens with synthetic GH are associated with the same increased risk of colorectal cancer.[70]

5. GH and Tumour Recurrence in Children

There are several malignancies that can render a child GH deficient, either as a result of the tumour impinging on the hypothalamic-pituitary axis or secondary to treatment with radiotherapy encompassing the hypothalamic-pituitary axis. The former includes craniopharyngiomas, germinomas, teratomas and histiocytosis. The latter includes leukaemia, and tumours distinct from the hypothalamic-pituitary axis (medulloblastomas, astrocytomas, ependymomas and nasal rhabdomyosarcomas). The concern has been that GH therapy might induce tumour recurrence, or increase the incidence of a second malignancy.

A few clinical studies have sought to assess the influence of GH therapy on tumour recurrence. Arslanian et al. reported on 34 children with brain tumours sited in the pituitary region or distant from it.[71] The predominant tumour type was craniopharyngioma (n = 18). The most common childhood brain tumour, the medulloblastoma, accounted for only two patients. Twenty-five children were GH deficient before treatment with surgery, with or without radiotherapy, and 32 were GH deficient after treatment. Twenty-four patients received GH 0.1 IU/kg three times a week, of whom eight had a tumour recurrence, five within the first 7 months of treatment. Three of ten children who did not receive GH therapy had recurrences. Those with recurrences grew significantly slower than those without recurrences during the first year of GH therapy. Although these results suggested that GH was not influencing tumour recurrence, concern was raised by the close temporal relationship between recurrence and initiation of GH in five cases.

In a similar study, Rodens et al.[72] reviewed tumour recurrence in 80 brain tumour patients, 50% of whom had a craniopharyngioma. Five of 31 patients who received GH therapy had tumour recurrences compared with 18 recurrences in 31 GH-deficient patients who did not receive GH therapy.

One-third of 18 patients who were not GH deficient developed tumour recurrence. In these two studies it is difficult to extrapolate significant conclusions from treatment and control groups comprised of heterogeneous tumour types with different growth and recurrence rates. This was addressed by Clayton et al.[73] who studied tumour recurrence rates in 24 children with brain tumours distant from the hypothalamic-pituitary axis and six with ALL who had received GH therapy. The recurrence rates in those treated with GH and those who did not receive GH were compared. The findings on small numbers suggested GH therapy does not increase tumour recurrence rates in medulloblastoma, glioma and ALL.

An analysis of deaths in recipients of pituitary GH in the UK cited brain tumour recurrence as one of the most common causes, but there was no comparative group who had not received GH to complement the study population. Therefore, it could not be established whether the use of GH was contributory to tumour recurrence.[74]

Several studies have now sought to determine tumour recurrence rates in children treated with GH after tumour therapy compared with an untreated group. In Manchester, we analysed tumour recurrence rates between children treated with GH for radiation-induced GH deficiency and an untreated population.[75] We also reviewed the computed tomograms (CT) in the children with brain tumours treated with GH performed at the time of GH commencement and subsequently to determine if children with abnormal CNS radiology at the outset are at special risk for a clinically apparent relapse following GH administration.

Fifty-three of 207 children with a primary diagnosis of a brain tumour and 15 of 161 with a primary diagnosis of ALL were treated with GH at least 2 years after completion of radiotherapy. For those children with a diagnosis of a brain tumour, Cox regression model was used to compare children who did or did not receive GH at the time of each recurrence, taking into account other co-variates thought to influence relapse-free survival (diagnosis, sex, age at diagnosis, and whether or not chemotherapy was included in the primary treatment). The Cox model is a multivariate method of survival analysis, which allows comparison of the risk of an event between groups adjusting for potential confounders. The method models the relative hazard over time of an adverse event comparing groups and assumes that the relative hazard is the same throughout the period of follow-up, the proportional hazards assumption. It has the advantage over logistic regression that it takes into account variable periods of follow-up and censoring.

Five children treated with GH had a recurrence of their brain tumour whereas 42 children who did not receive GH relapsed. Adjusting for variables other than GH that might affect tumour recurrence, the estimated relative risk of tumour recurrence was 0.82 (95% CI 0.28, 2.37) for GH recipients. In each tumour category, there was no association between the use of GH and subsequent tumour recurrence.

Forty-four children with brain tumours had CT scans around the time that GH was started. Nineteen of these scans were abnormal with ten showing residual tumour, and the remainder, non-enhancing low attenuation or cystic lesions in the area of the original tumour. The five children who had a clinical recurrence of their brain tumour had CT scans at the time of GH commencement. One had evidence of residual tumour, and one had a low-density non-enhancing lesion. In all five children, subsequent relapse was confirmed on CT scan. None of the other children who remained clinically relapse-free and had received follow-up scans had a deterioration in scan appearance.[75]

No child with ALL who had been relapse-free at the time of GH commencement subsequently relapsed. Eleven of 146 children (7%) not receiving GH relapsed and a further three died from other related causes. No child receiving GH developed a second primary tumour and no child treated for a brain tumour and subsequently with GH developed leukaemia.[75]

Some of these patients are a subset of a larger study of 180 children with brain tumours who were treated with GH between 1965 and 1996 at the three largest oncology centres in the UK. Also followed

were 891 children treated with radiotherapy for brain tumours but who did not receive GH therapy.[76] The relapse rate between GH-treated and -untreated patients was compared using Cox regression analysis adjusting for the confounding variables: sex, age at tumour diagnosis, tumour histology, calendar period of diagnosis, the use of adjuvant chemotherapy, hospital of tumour treatment. The person-time at risk was calculated from the date of first GH treatment to the date of last clinical contact. Thirty-five first recurrences occurred in the GH-treated children and 434 in the GH-untreated children. The relative risk of first recurrence in GH-treated compared with -untreated patients adjusted for potential confounding variables was decreased (0.5; 95% CI 0.4, 0.9) as was the relative risk of mortality (0.5; 95% CI 0.3, 0.8). There was no significant trend in recurrence risk with cumulative time of GH treatment or with time lapsed from treatment commencement. The relative risk of mortality significantly increased with time since first GH treatment.

These data from the largest study of person-years of treatment with GH and with a follow-up period of 6.4 years on average (with 31 patients followed for >10 years), suggest that recurrence rates are not substantially increased after GH therapy. However, the period from 5 years from GH commencement requires further surveillance as the CIs were wider and there was a significant rising trend in mortality in the GH-treated group.[76]

The impact of GH therapy on medulloblastoma relapse rates was assessed in 11 neuro-oncology centres in North America.[77] One hundred and seventy of the 545 patients who were under 15 years of age at diagnosis received GH therapy. Cox regression model and a landmark analysis was used to assess the relative risk of tumour relapse in surviving patients with time of commencement of GH therapy taken as a time-dependent co-variate. There was no statistical evidence that GH therapy affected tumour recurrence or progression in either those who were aged <3 years at diagnosis or those aged 3–10 years at diagnosis, with some suggestion that those treated with GH had a better outcome. This probably reflects selection bias in that children who survived, or were clinically tumour free, would be likely to be considered for GH therapy. There was a wide diversity between centres in the time from diagnosis to commencement of GH therapy, which ranged from 1.6–6.2 years from diagnosis in those aged <10 years of age at diagnosis.

A larger and more detailed study of 72 children with leukaemia (68 with ALL and four with acute myeloid leukaemia) treated with GH for radiation-induced GH deficiency for a total of 149 patient-years of GH, has been undertaken at the Hospital for Sick Children, Great Ormond Street, London (A. Leiper, personal communication).[78] Thirty-two children were in first remission of ALL, 17 in second or subsequent remission, and 23 were receiving GH therapy following bone marrow transplantation. Statistical analysis allowed comparison to be made with children with the same diagnosis and treatment but who did not receive GH therapy for both the group in first remission and the group treated with GH after bone marrow transplantation. This took into account variation in chemotherapy protocol and other prognostic factors: age, white cell count at diagnosis, immunophenotype, sex and the diminishing risk of relapse with increasing time from the end of chemotherapy. Statistical analysis was not possible in the group who received GH after a second or subsequent relapse because of the heterogeneity of the type of relapse. One of 32 patients in first remission, five of 17 in second or subsequent remission and two of 23 post-bone marrow transplant patients relapsed after GH therapy. Exclusion of bias by taking into account prognostic factors and the naturally diminishing risk of relapse with increasing time from cessation of chemotherapy demonstrated no increased risk in the GH-treated children compared with those who did not receive GH.

Leukaemia recurrence rates and second tumours were reviewed in 47 patients with a primary diagnosis of ALL who were treated with GH for GH deficiency and who had now reached final height. They were compared with 544 control patients, diagnosed with ALL during the same period but who

had not received GH.[79] No GH-treated patients had a leukaemia relapse. One had a sweat duct carcinoma of the scalp, and one had myelodysplastic syndrome. There were eight leukaemia relapses and 16 second malignancies in the control group. Data were analysed using a time-dependent variable and a landmark method whereby the data were censored at the time of initiation of GH therapy and an approximate median time (7 years) and maximum time (11 years) for commencement of GH therapy from complete remission chosen. There was no statistical evidence that GH-replacement therapy was associated with relapse of ALL or second malignancy

The risk of disease recurrence and second neoplasms in survivors of childhood cancer was determined from the childhood cancer survivor study.[80] This included 5-year survivors who were diagnosed with cancer before 21 years of age between 1970 and 1986. This study includes a sizeable number of survivors of cancer other than brain tumours. Comparison of recurrence rates between those who were and were not treated with GH was made. Data on the risk of recurrence were available for 12 039 patients, of whom 297 were treated with GH. One hundred and seventy-two of the 297 treated with GH had a diagnosis of a brain tumour. Using a time-dependent Cox model, the relative risk of recurrence was 0.83 (95% CI 0.37, 1.86; p = 0.65) for GH-treated survivors. The relative risk was not increased for any of the major cancer diagnoses.

Data were available for 13 222 patients, including 354 treated with GH, to assess the risk of development of a second neoplasm.[80] Fifteen children treated with GH subsequently developed second neoplasms. All were solid neoplasms, with no cases of secondary leukaemias. All except one neoplasm was within the field of previous irradiation. Second neoplasms were diagnosed in 344 patients not treated with GH. After adjusting for other factors associated with the development of a second neoplasm (age at diagnosis, sex, radiation, alkylating agents), the relative risk of a second neoplasm in GH-treated patients compared with those not treated with GH was 3.21 (95% CI 1.88, 5.46; p < 0.0001). The increased relative risk of a second neoplasm was primarily accounted for by an excess in those initially treated for leukaemia. The excess of second neoplasms in GH-treated patients initially treated for a CNS tumour was because of benign meningiomas. When the analysis was restricted to malignant tumours, treatment with GH no longer showed an effect. There was a striking association between GH use and osteogenic sarcomas (three cases) as a second tumour in patients with previous treatment for leukaemia or lymphoma, compared with only two cases of osteogenic sarcoma in over 4500 patients with leukaemia or lymphoma not treated with GH.[80]

The authors comment that a probable association between GH therapy and the development of osteogenic sarcoma has been reported in Diamond-Blackfan anaemia.[81] In addition, both meningioma and osteogenic sarcoma cell growth can be altered *in vitro* by GH and IGF-I.[82,83] The authors urge caution with the interpretation of these results, pointing out that the number of events is small and the CIs wide. Being a retrospective study, there may have been unrecognised biases in the selection of patients who received GH. If the results prove to be correct, the number of excess tumours that would occur as a result of GH therapy would be 3–4 per 1000 person-years at 15 years from diagnosis.[80]

6. The Theoretical Risk of Malignancy in Other Children Receiving GH Therapy

6.1 Supraphysiological Doses of GH

Children with chronic renal failure have high endogenous levels of GH although they continue to grow poorly.[84,85] Therefore, treatment of growth failure with GH in this situation, which is not a GH deficiency state, is pharmacological rather than replacement therapy. Even after transplantation, when GH levels are often low, high-dose replacement with GH has been employed. The demonstration of enhanced proliferation and transformation of haemopoetic cells *in vitro* has been in the presence of supraphysiological doses of GH. However, high-dose GH replacement has been used in other clinical situations, such as treatment of bony dyspla-

sias,[86,87] Turner's syndrome,[88,89] and intrauterine growth retardation,[90,91] and although this may theoretically put the child at increased risk for the development of leukaemia, there is no published evidence that it does so.

6.2 Immunosuppression

Immunosuppressive drugs are utilised after organ transplantation to maintain graft function. The increased risk for the development of leukaemia following the use of cytotoxic drugs is discussed in section 5. Immunosuppressive therapy in organ homograft recipients is associated with an increased incidence of malignancy in adults. There is a 4–6% incidence of *de novo* cancers in organ homograft recipients who were apparently free of cancer before and at the time of transplantation.[92,93] Similarly, although it is extremely difficult to transplant malignant cells into healthy humans,[94,95] in the immunosuppressed, cancer cells will survive, multiply and metastasise.[94,96,97] Despite the apparent concerns when the body's normal immunosurveillance mechanisms may be impaired, there are no reports of an increase in tumours in childhood recipients of transplants, even when GH therapy has subsequently been used.[98]

7. Conclusions

GH therapy has proven benefits. There are epidemiological data that link GH and IGF-I levels to subsequent tumour development. A variety of malignant tumours have been induced in animals exposed to supraphysiological doses of GH, whereas hypophysectomised animals appear protected from carcinogen-induced neoplasms. GH and IGF-I have been shown to stimulate both proliferation and transformation of normal and leukaemic human lymphocytes *in vitro* only when used in supraphysiological doses. The therapeutic use of GH causes concern because of its oncogenic potential. Despite these fears, there appears to be no increased risk of leukaemia in GH-deficient children treated with GH who do not have pre-existing risk factors. Tumour development has not been reported in children treated with GH after renal transplantation and conditions where the child is not GH deficient, although supraphysiological doses may have been used. Despite the theoretical arguments, there is no evidence of an increased risk of tumour recurrence following GH therapy in replacement dosage in children previously treated for a malignancy. However, recent data have shown a possible increase in new cancers in patients treated with GH – either primary malignancies in those who had not had a malignancy before, or second neoplasms in those who had. Although the data do not suggest a large risk, they emphasise the importance of continued surveillance. We would also recommend that GH therapy should not be used for non-licensed indications outside of clinical trials.

Surveillance should continue both internationally with established databases, and also nationally through single-centre studies. Cancer survivors, whether treated with GH in childhood or not, are at increased risk of both a recurrence of primary tumour and second malignancies as a consequence of cancer therapy. They should therefore remain under lifelong follow-up by a physician with knowledge of the late effects of cancer therapy to aid early detection. The increasing clinical practice of measuring serum IGF-I and IGFBP-3 levels may provide a useful marker should malignancies be detected, although the late presentation of many malignancies may make the association with abnormal serum levels of IGF-I and IGFBP-3 levels in childhood difficult. In the future, after additional clinical studies, serum IGF-I levels may enable GH dose titration in children to minimise the theoretical risks associated with over-treatment with GH in the GH-deficient child without compromising the known benefits of GH replacement.

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