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Recent Status in the Occurrence of Leukemia in Growth Hormone-Treated Patients in Japan

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ABSTRACT

The Foundation for Growth Science in Japan has monitored the safety and efficacy of GH treatment in GH-deficient patients since 1975. Data were collected from more than 32,000 patients up to December 31, 1997. New leukemia was observed in 14 patients and myelodysplastic syndrome (MDS) in one patient. The types of leukemia were acute lymphocytic leukemia (n = 6; 40%), acute myelocytic leukemia or MDS (n = 7; 47%), and chronic myelocytic leukemia (n = 2; 13%). Leukemia developed in 9 patients during GH treatment and in 6 after the cessation of GH treatment. Six patients had known risk factors for leukemia, such as Fanconi's anemia and previous radiation or chemotherapy. Patient-years of GH therapy was defined as the time from the first dose of GH to the date of the last visit during GH therapy, and patient-years of risk was defined as the time from the first dose of GH to December 31, 1997. The incidence of leukemia of patient-years of GH therapy and patient-years of risk in GH-treated patients without risk factors was 3.0/100,000 and 3.9/100,000, respectively, a figure similar to the incidence in the general population aged 0–15 yr.

We conclude that the incidence of leukemia in GH-treated patients without risk factors is not greater than that in the general population aged 0–15 yr, and a possible increased occurrence of leukemia with GH treatment appears to be limited to patients with risk factors. (*J Clin Endocrinol Metab* **84:** 1961–1965, 1999)

IN 1988 Watanabe *et al.* (1) reported leukemia in patients treated with GH. Although GH treatment has generally been considered safe, there has been much discussion as to whether GH treatment increases the risk of developing leukemia. Several studies of the occurrence of leukemia in children treated with GH have been reported (2–10). Recently, Allen *et al.* (3) reported that the incidence of leukemia in GH-treated patients without risk factors for leukemia was comparable to that in the general population of age-matched children by using data from the National Cooperative Growth Study in the United States and Canada. Moreover, according to the most recent published review of international reports of new leukemia in GH-treated patients, the incidence of new leukemia in non-Japanese patients without known risk factors who were treated with GH was not greater than that in the general population aged 0–15 yr (2). Any increased occurrence of leukemia appeared to be limited to those patients with known risk factors (2, 3, 8, 10). In Japan, 13 cases with new leukemia among GH-treated patients were reported in 1994 (9). In this article we present an analysis of current data on the relationship between GH therapy and leukemia in Japanese GH-treated patients up to 1997.

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Materials and Methods

Data collection

The Foundation for Growth Science in Japan was developed in 1975 to monitor the safety and efficacy of GH treatment. The GH treatment study committee was established within the Foundation for Growth Science in Japan for the analysis of the occurrence of leukemia in GH-treated patients in Japan. Data for this analysis were collected from more than 32,000 patients who received GH therapy from 1975 to December 31, 1997.

Data analysis

Two different types of patient-years were calculated: patient-years of GH therapy and patient-years of risk. Patient-years of GH therapy was defined as the sum of the time from the first dose of GH to either the last dose of GH (if GH therapy had been discontinued) or the date of the last visit (if GH therapy was still being given) (3). Patient-years of risk was defined as the sum of the time from the first dose of GH to the cut-off date of December 31, 1997, which included both the time of GH treatment and the time after treatment, up to the cut-off date (3). For a correct assessment of the relative risk associated with GH use, patient-years of risk after the cessation of GH should be included (3).

The standard incidence ratio (SIR), defined as the ratio of the number of cases observed to the number of cases expected, was calculated, and 95% confidence intervals (CI) for the SIR were determined (11).

Results

The clinical and hormonal data of 15 patients with new leukemia or myelodysplastic syndrome (MDS) among Japanese GH users are presented in Table 1. These consisted of 6 patients with acute lymphocytic leukemia (ALL; 40%), 7 with acute myelocytic leukemia (AML) or MDS (47%), and 2 with chronic myelocytic leukemia (CML; 13%). In 6 patients, strong known risk factors for leukemia, such as Fanconi's anemia, previous radiation or chemotherapy, *etc.*, were present. Leukemia developed in 9 patients during GH treatment and in 6 after the cessation of GH treatment. Of 9 patients without risk factors for leukemia, 3 patients were diagnosed as having leukemia 3.8, 4.8, and 9.8 yr after the cessation of GH therapy (cases 15, 6, and 5), and 2 patients received GH therapy for only 0.3 and 0.5 yr before the diagnosis of leukemia (cases 10 and 12). The duration of GH treatment, the administered doses of GH, and the source of GH (pituitary-derived, recombinant human (h) met-GH, and authentic recombinant hGH) were not related to the occurrence of leukemia.

In Japan an annual incidence of leukemia in children aged 0–15 yr per 10^5 is 2.9–4.0 (12, 13). With patient-years of GH therapy as the denominators, the SIR values are as follows: total patients, 1.61–2.14 (95% CI, 0.62–3.75; 9 cases observed *vs.* 4.2–5.6 expected); patients without risk factors, 0.75–1.00 (95% CI, 0.20–2.57; 4 cases observed *vs.* 3.99–5.32 expected); and patients with risk factors, 17.86–23.81 (95% CI, 4.48–48.77; 5 cases observed *vs.* 0.21–0.28 expected). With patient-year of risk as the denominator, the SIR values are as follows: total patients, 1.54–2.05 (95% CI, 0.78–3.21; 15 cases observed *vs.* 7.32–9.76 expected), patients without risk factors, 0.97–1.29 (95% CI, 0.44–2.45; 9 cases observed *vs.* 6.96–9.28 expected); and patients with risk factors, 12.50–16.67 (95% CI, 3.36–32.41; 6 cases observed *vs.* 0.36–0.48 expected). These results suggest that there is no increased risk of leukemia in GH-treated patients without risk factors, but with the upper 95% confidence limit being much greater than 1.0, caution should be exercised in making a definitive conclusion (3).

Discussion

The most recent published review of international reports of new leukemia in GH-treated patients including Japanese patients found 46 cases (31 male patients); the predominant types were ALL (n = 21; 46%), acute nonlymphocytic leukemia (ANLL; n = 12; 26%), and AML or pre-AML (n = 6; 13%) (2). In our study, 6 of 15 patients with leukemia had ALL (40%), 7 had AML or MDS (47%), and 2 had CML (13%). In Japan, AML was previously classed as ANLL. Leukemia is one of the most common childhood malignancies, occurring in approximately 1 in 2000 children under the age of 15 yr (3, 14). ALL accounts for 75–85% of these cases, ANLL for 15–20%, and CML for 3% (3, 14). These data suggest that if there is an excess of leukemia in patients treated with GH, it is only a risk for AML, ANLL, or MDS not for ALL (2, 3, 6).

The reasons for an increased risk for developing AML, ANLL, or MDS in GH-treated patients cannot be fully explained, but the following possibility is suggested. Ascribing the occurrence of leukemia in GH-treated patients to GH treatment is complex, because the etiology of short stature must also be considered. For example, Fanconi's anemia is known to be associated with both an increased risk for leukemia, especially AML and MDS, (>50% by age 40 yr), and for GH deficiency (15, 16). It is possible that some cases of leukemia observed in children with GH deficiency are due to unrecognized Fanconi's anemia presenting as short stature without skeletal or hematological abnormalities in childhood (7, 15). Therefore, some GH-treated patients may have had unrecognized Fanconi's anemia, but died before definitive diagnostic studies could be performed (7, 15). In our study, 7 of 15 patients (47%) had AML or MDS, suggesting the inadvertent inclusion of short children with unrecognized Fanconi's anemia.

If GH therapy could induce leukemia, one would expect a high leukemia relapse rate in GH-treated patients with GH deficiency due to cranial irradiation for leukemia. In the National Cooperative Growth Study more than 200 patients who had leukemia before GH therapy were enrolled, and 4 of 200 (2%) patients relapsed for the first time while receiving GH, with an average interval after the initial diagnosis of 6 yr (7). In the Pharmacia & Upjohn, Inc., International Growth Database, the recurrence of leukemia was reported in 4 of 343 patients (1.2%) 8.6–13.4 yr after the initial diagnosis. Two of these patients had discontinued GH therapy 4 and 18 months, respectively, before the recurrent event (6). Children treated for ALL have a relapse rate of 10%/yr for the first 2 yr and 25–30% within the first 5 yr. Relapse after 5 yr of remission occurs in about 1–2% of patients/yr (17). Therefore, the reported relapse rate of leukemia in GH-treated patients after the remission of leukemia was within the expected range, and GH therapy did not increase leukemia relapse.

The question of whether GH deficiency that is not caused by Fanconi's anemia, neoplasia, irradiation, or chemotherapy might be a risk factor for developing leukemia remains open. Several cases of leukemia were reported in GH-deficient patients who did not receive treatment with GH and had no other potential cause of their leukemia (4, 18, 19). Moreover, leukemia developed in our three patients without risk factors 3.8, 4.8, and 9.8 yr after the cessation of GH therapy. Leukemia developing many years after the cessation of GH therapy may suggest a causal relationship between GH deficiency itself and leukemia. However, the reporting of leukemia occurring many years after the cessation of GH therapy is probably not complete, and it is not known when the effect of exogenous use of GH becomes negligible for developing leukemia after the cessation of GH therapy. To estimate this, the incidence of leukemia in GH-treated idiopathic GH-deficient patients has to be compared with that in GH-untreated idiopathic GH-deficient patients, but it is not possible to estimate this figure in children with untreated GH deficiency because most children who are diagnosed with GH deficiency will be treated with GH. Blethen (8) reported that the possibility of GH deficiency itself as a risk factor for developing leukemia is probably small in GH-deficient patients without risk factors for leukemia.

It is also of interest to consider whether long periods of GH hypersecretion could cause leukemia. Acromegaly is associated with an increased incidence of colonic carcinomas, but there is no evidence to suggest an increased risk of hema-

TABLE 1. Clinical and hormonal data

Case no.	Ref. no.	Sex	GH therapy					Leukemia				
			Age start (yr)	Duration (yr)	Source of GH	Total dose (IU)	GH secretion	Type	Age at diagnosis (yr)	GH therapy when leukemia diagnosed	Time from the cessation of GH therapy to diagnosis (yr)	Known risk factors
1	9, 21	M	14.0	6.3	p[a]	12,000	I[b]	ALL	21.3	No	0.9	
2	9, 22	M	2.5	2.8	p	464	I	ALL	5.3	Yes		Fanconi's anemia
3	9, 23	M	15.5	2.4	p	380	I	ALL	17.8	Yes		Germinoma, radiation therapy
4	9, 24	M	14.8	3.5	p/m[c]	2,374	I	ALL	18.3	Yes		
5	9	M	12.1	5.2	p	4,480	I	ALL	27.1	No	9.8	
6		M	12.8	2.5	m/r[d]	816	I	ALL	20.2	No	4.8	
7	9, 25	F	9.1	2.8	p	1,000	I	AML	11.8	Yes		
8	9	F	15.3	1.0	m	624	II	AML(MDS)[e]	17.0	No	0.8	Turner syndrome, teratoma, embryonal carcinoma, chemotherapy
9		M	6.6	11.2	p	4,380	I	AML	17.8	Yes		
10	9, 26	F	7.7	0.3	r[d]	170	I	AML	8.0	Yes		
11	9, 27	M	12.8	0.2	r	570	II[f]	AML	12.9	Yes		Pancytopenia
12	9	M	18.4	0.5	r	510	III[g]	AML	20.0	No	0.9	
13	28	M	6.7	1.7	r	710	II	MDS	8.4	Yes		Neuroblastoma, radiation therapy, chemotherapy
14	9, 29	M	14.3	1.0	m	3,025	I	CML	15.3	Yes		Craniopharyngioma, radiation therapy
15	9	F	13.8	1.8	p	1,564	III	CML	18.8	No	3.8	

[a] Pituitary-derived GH.
[b] All peak GH values were 5 ng/mL or less in more than two provocative tests.
[c] Recombinant met-hGH.
[d] Authentic recombinant hGH.
[e] Review of blood smears suggested that AML could develop from myelodysplastic syndrome.
[f] All peak GH values were 10 ng/mL or less in more than two provocative tests, except I.
[g] The peak GH value was more than 10 ng/mL in at least one provocative test.

TABLE 2. Leukemia in GH-treated patients

Country	Annual incidence of leukemia in children aged 0–15 yr 10^5	No. of patients with leukemia	Patient-yrs of GH therapy[a]	No. of cases/patient-yrs of GH therapy/10^5	Patient-yrs of risk[a]	No. of cases/ patient-yrs of risk/10^5
International reports (~1995) (2)	3.3	46[b] (total)				
		13[b] (non-Japanese without risk factors)	>300,000	3.3–4.3[c]		
US and Canada (1985–1995) (3)	3.3	11[b] (total)			136,582	8.1
		3[b] (without risk factors)			119,846	2.5
		8[b] (with risk factors)			16,736	47.8
		6[d] (total)	76,735	7.8		
		2[d] (without risk factors)	67,773	3.0		
		4[d] (with risk factors)	8,962	44.6		
Europe (1988–1992) (4)	3.6	10[d] (total)	138,000–148,000	6.8–7.2		
		6[d] (without risk factors)		4.1–4.3		
Shalet *et al.* (1988–1995) (5)	3.3	17[d] (total)	370,000	4.6		
		9[d] (without risk factors)	—[e]	2.4		
KIGS[f] (1987–1996) (6)		1[d] (without risk factors)	49,919	2.0		
Japan (1975–1997)	2.9–4.0 (12, 13)	15[b] (total)			244,000	6.1
		9[b] (without risk factors)			232,000	3.9
		6[b] (with risk factors)			12,000	50.0
		9[d] (total)	140,000	6.4		
		4[d] (without risk factors)	133,000	3.0		
		5[d] (with risk factors)	7,000	71.4		

[a] The definitions are shown in *Materials and Methods*.
[b] Leukemia was diagnosed during GH therapy or after the cessation of GH therapy.
[c] Ten to 13 new cases of leukemia/300,000 patient-yrs would have been expected.
[d] Leukemia was diagnosed during GH therapy.
[e] The number of patient-years of GH therapy in patients without risk factors was not reported.
[f] Pharmacia and Upjohn International Growth Database.

tological malignancy (20). GH-secreting adenomas occur predominantly in adults rather than children, and the condition has usually been present for approximately 10 yr before the diagnosis. The sustained pathologically high levels of GH vastly exceed the duration and degree of GH exposure in GH-deficient children receiving GH replacement. Therefore, in the analysis of the oncogenic potential of GH replacement in GH-deficient children, acromegaly is a poor paradigm (5).

Although the presence of a dose-response relationship is not necessary to indicate that a statistical association reflects a cause and effect association, it does add weight to that conclusion if present (8). There is no suggestion that longer periods of GH treatment are associated with more frequent development of leukemia (8), and in our study the administered doses of GH and the duration of GH therapy period were not related to the incidence of leukemia. In addition, the GH doses typically used in Japan (0.05–0.2 mg/kg·week) were lower than those currently used in the U.S. (mean ± SE, 0.26 ± 0.07 mg/kg·week) (8), and it is not known whether a very short time of GH therapy may influence the occurrence of leukemia. Stahnke (4) considered that a very short period of GH therapy (0.2–0.6 yr) rendered a less probable relationship between GH administration and the occurrence of leukemia. In our study, two patients without known risk factors were diagnosed as having leukemia only 0.3 and 0.5 yr after the commencement of GH therapy.

Attempts have been made to assess whether the reported cases of leukemia in patients treated with GH represent an increased incidence of leukemia compared with that in the general population (2–10). This requires making two assumptions: first, that GH deficiency itself confers no additional risk of developing leukemia, and second, that the proportion of patients with an increased risk for leukemia is the same in the GH-deficient population as it is in the general population (8). Excluding patients with known risk factors, such as Fanconi's anemia, radiation, and chemotherapy, provides an incidence similar to that for the age group 0–15 yr (Table 2). In our study the incidence of leukemia was comparable to that in the general population under 15 yr of age in Japan (12, 13).

In conclusion, the incidence of leukemia in GH-treated patients without known risk factors is not greater than that in the general population aged 0–15 yr in Japan, as reported in the U.S., Canada, and Europe. However, it is not yet known whether the incidence of leukemia in patients with risk factors is altered by GH therapy. Continued surveillance is necessary.

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