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Second Primary Malignancies in Lymphoma Patients

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Abstract

We evaluated the occurrence and the type of second malignancies among 74 patients with Hodgkin's disease (HD) and 407 patients with non-Hodgkin's lymphoma (NHL) who were treated at the National Cancer Center Hospital for more than one year.

Fifteen patients developed a second malignancy. In 10 of these patients the second cancer was gastric cancer, but no cases of acute nonlymphocytic leukemia were encountered.

The observed number of second cancers in females among the HD patients was significantly ($p < 0.005$) greater than the expected incidence based upon the number of age-adjusted person-years both for all cancers and for stomach cancer. However, no significant differences between males and females in the NHL patients were found. Furthermore, no significant differences were seen in any of the groups between the observed and expected numbers of second malignancies according to the treatment.

Introduction

The treatment for malignant lymphoma has changed substantially over the last 20 years. Survival has improved and delayed complications of treatment are now being pointed out and investigated (Glicksman and Pajak, 1982). One of these, the occurrence of second malignancies, has been attracting the attention of many investigators.

Reports of an increasing incidence of multiple primary neoplasms in patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) have been published from many cancer centers and cooperative study groups (Rosenberg *et al.*, 1961; Berg, 1967; Arseneau *et al.*, 1972; Canellos *et al.*, 1975; Brody, 1977; Libshitz *et al.*, 1978; Toland *et al.*, 1978; Zarrabi *et al.*, 1979; Baccarani *et al.*, 1980; Valagussa *et al.*, 1980; Zarrabi, 1980; Boivin and Hutchison, 1981; MacDougall *et al.*, 1981; Greene *et al.*, 1983).

The development of second neoplasms is of special interest, because of the suggestion that they may be related to the treatment of the primary cancer. We undertook this study to determine the risk of development of second malignancies in patients treated for HD and NHL by current therapeutic methods.

Materials and Methods

The records of a total of 651 adult pa-

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tients with malignant lymphoma, treated at the National Cancer Center Hospital over a 22-year period (May 1962 to December 1983) were reviewed retrospectively with the aim of establishing the frequency of occurrence and characteristics of second neoplasms.

We have excluded the following:

1) One hundred and seventy patients who were followed for or who survived for less than one year. We thought it necessary to leave an arbitrary time between the diagnosis of the lymphoma and the second malignancy, in order to have a strong case concerning the relationship between the disease and its treatment regarding the development of the second malignancy.

2) Three cases unsuspected during life but diagnosed at autopsy. We thought it necessary to avoid the obvious bias because the percentage of latent cancers detected at autopsy was much greater in patients dying of lymphoma than in those dying in the general population.

The observed incidence of second malignancies was compared by using the Poisson distribution with the expected incidence based upon the number of age- and sex-adjusted person-years (The Research Group for Population-Based Cancer Registration in Japan, 1981). As the probability of a second malignancy developing is small, the number can be expected to follow the Poisson distribution.

Results

We analyzed 74 patients with HD and 407 patients with NHL who were followed up or who survived for a total of 455 person-years and 2,126 person-years, respectively (Table 1).

Table 2 shows the clinical characteristics of the 15 lymphoma patients who devel-

Table 1
Characteristics of 481 Lymphoid Malignancies and the 15 Double Primary Malignancies

	Total		HD		NHL	
	All cases	Double primary cases	All cases	Double primary cases	All cases	Double primary cases
No. of cases (alive/dead)						
Males	314 (112/202)	9 (1/8)	53 (26/27)	1 (0/1)	261 (86/175)	8 (1/7)
Females	167 (77/90)	6 (2/4)	21 (10/11)	3 (1/2)	146 (67/79)	3 (1/2)
Total	481 (189/292)	15 (3/12)	74 (36/38)	4 (1/3)	407 (153/254)	11 (2/9)
Mean age at onset of lymphoma (years)						
Males	48.8	58.7	41.5	(59)	50.3	58.6
Females	47.4	60.3	42.3-($p<0.05$)-71.3		48.1	49.3
Total	48.3-($p<0.05$)-59.3		41.7	68.3	49.5	56.1
Median age at onset of lymphoma (years)						
Males	50	59	42	(59)	51	59
Females	46	60	41	73	48	54
Total	49	59	41	61	50	55
Range of age at onset of lymphoma (years)						
Males	15–84	36–75	15–76	(59)	16–84	36–75
Females	17–80	34–80	18–80	61–80	17–80	34–60
Total	15–84	34–80	15–80	59–80	16–84	34–75

Table 2
Characteristics of the 15 Patients with Second Malignancy

Patient	Age/Sex	Type of lymphoma	Histology	Site	Clinical stage	Treatment			Interval	Type of 2nd malignancy	Survival after diagnosis of 2nd malignancy	Cause of death
						Operation	Chemotherapy	Radiotherapy				
SY	61/F	HD	LP	Node	I		+		10 y	Stomach (adeno)[a]	4 mo+	(alive)
TS	59/M	HD	MC	Node	I		+		7 y	Stomach (adeno)[a]	2 y 11 mo	pneumonia
TI	73/F	HD	NS	Node	I			+	1 y 10 mo	Stomach (adeno)[a]	8 mo	ML
KY	80/F	HD	MC	Orbita	II		+		1 y 3 mo	Stomach (adeno)	3 mo	CA
RH	36/M	NHL	d-PDL	Small intestine	II	+		+	20 y	Stomach (adeno)	1 y	CA
SK	60/F	NHL	d-PDL	Stomach	I	+			13 y	Bile duct (?)	3 mo	CA
HS	47/M	NHL	d-H	Node	II		+	+	9 y 11 mo	Stomach (adeno)[a]	1 y 2 mo	ML
TS	55/M	NHL	d-H	Tonsil	I		+	+	8 y 7 mo	Liver (hepatoma)	9 mo	CA
SK	59/M	NHL	d-H	Node	II		+		8 y 6 mo	Lung (adeno)	1 y 9 mo	CA
YS	34/F	NHL	d-H	Tonsil	II		+	+	5 y 3 mo	Stomach (adeno)[a]	2 y 3 mo+	(alive)
KH	61/M	NHL	d-H	Node	I		+	+	4 y 9 mo	Stomach (adeno)[a]	5 y 7 mo	CA[b]
JT	65/M	NHL	d-PDL	Node	II		+	+	4 y 7 mo	Prostate (adeno)	8 mo	CA
TT	54/F	NHL	d-H	Tonsil	I			+	3 y 7 mo	Stomach (adeno)	9 mo	CA
NT	71/M	NHL	d-H	Node	III		+		3 y 4 mo	Stomach (adeno)	2 y 5 mo	ML+CA
ST	75/M	NHL	d-Mix	Node	III		+		1 y 6 mo	Colon (adeno)	3 mo+	(alive)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma, LP: lymphocytic predominance, MC: mixed cellularity, NS: nodular sclerosis, d-PDL: diffuse poorly differentiated lymphocytic, d-H: diffuse histiocytic, d-Mix: diffuse mixed lymphocytic-histiocytic, adeno: adenocarcinoma, ML: malignant lymphoma, CA: cancer.

a) early gastric cancer.

b) gastric cancer developed in the residual stomach (3rd malignancy).

oped second primary cancers. Second malignancies developed 1 year and 3 months to 20 years after HD or NHL was diagnosed. Of the 15 patients, nine were males and six were females. The second malignancies included 10 gastric cancers, one hepatoma, one bile duct cancer, one colon cancer, one lung cancer and one prostate cancer. No cases of acute leukemia were encountered. The mean age at onset of lymphoma was 68.3 years for the four HD patients who developed second cancer and it was significantly ($p < 0.05$) higher than the 41.7 years for all 74 HD patients. On the other hand, the mean age at onset was 56.1 years for the 11 NHL patients who developed second cancer and it was not significantly higher than the 49.5 years for all 407 NHL patients.

The observed number of second cancers was compared with the expected number in HD and NHL, respectively (Table 3).

The observed/expected ratio in females in the HD patients was significantly ($p < 0.005$) high for both total cancers and stomach cancer. However, a significant difference between the observed and expected number of cases of second cancer was not found in male patients. On the other hand, no significant differences in the observed and expected number of cases of second cancer in the NHL patients were found between males and females.

The observed number of second primary cancers was compared with the expected number according to the treatment. The patients were divided into four groups: chemotherapy (CT) alone, radiotherapy (RT) alone, both CT and RT, and surgery without CT/RT. The number and person-years of HD and NHL patients in each group are given in Table 4. No significant differences were seen in any of the groups except the RT group of HD patients between the observed number of second cancers and the expected number, according to the treatment.

Discussion

Metachronous second primary neoplasms among patients with lymphoid malignancy have been suspected of being associated with the intensive therapeutic management of lymphoid malignancy. Various reports on HD suggest that patients who have been treated with extensive radiotherapy (Arseneau *et al.*, 1972; Canellos *et al.*, 1975), combination chemotherapy (Brody *et al.*, 1977; Toland *et al.*, 1978) or both radio-

Table 3
Second Malignancies Occurring after Lymphoid Malignancies (by Histology and Sex)

Histology		No. of cases	P-Y	All cancers			Stomach cancer		
				O	E	O/E	O	E	O/E
HD	Males	53	329	1	1.08	0.9	1	0.47	2.1
	Females	21	126	3	0.32	9.4**	3	0.10	30.0***
	Total	74	455	4	1.40	2.9	4	0.57	7.0**
NHL	Males	261	1277	8	7.82	1.0	4	3.35	1.2
	Females	146	849	3	3.08	1.0	2	0.94	2.1
	Total	407	2126	11	10.90	1.0	6	4.29	1.4
Total		481	2581	15	12.30	1.2	10	4.86	2.1*

P-Y: person-years, O: observed cases, E: expected cases.
* $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$

Table 4
Second Malignancies Occurring after Lymphoid Malignancies (by Treatment)

Treatment	HD					NHL					All cases				
	No. of cases	P-Y	O	E	O/E	No. of cases	P-Y	O	E	O/E	No. of cases	P-Y	O	E	O/E
Chemotherapy (CT)	28	170	3	0.84	3.57*	132	599	3	2.86	1.05	160	769	6	3.70	1.62
Radiotherapy (RT)	2	8	1	0.03	33.33**	70	592	2	3.34	0.60	72	600	3	3.37	0.89
CT+RT	43	271	0	0.53	0	190	836	5	4.06	1.23	233	1107	5	4.59	1.09
Operation	1	6	0	0.001	0	15	99	1	0.64	1.56	16	105	1	0.64	1.56

P-Y: person-years, O: observed cases, E: expected cases.
* $p = 0.053$, ** $p < 0.05$

therapy and chemotherapy (Arseneau *et al.*, 1972; Canellos *et al.*, 1975; Toland *et al.*, 1978) develop second malignancies in excess of the number of malignancies expected on the basis of indirect comparisons using population-based incidence data.

Acute nonlymphocytic leukemia (ANLL) is often the most frequent type of second malignancy encountered in patients with intensively treated HD (Larsen and Brincker, 1977; Neufeld *et al.*, 1978; Toland *et al.*, 1978; Baccarani *et al.*, 1980; Pedersen-Bjergard and Larsen, 1982). In this study, however, several differences were observed in comparison with previous reports. Firstly, no ANLL developed in HD patients. According to the data of a cooperative study in Japan (Nagura *et al.*, 1985), there was no cases of ANLL among six HD patients who developed a second malignancy, as in our study. Secondly, in all four HD patients who developed a second malignancy the second cancer was gastric cancer and the observed number was significantly greater than the expected number. However, if three cases of early gastric cancer were excluded from the second cancer because they were found incidentally and the patients were diagnosed as cancer patients, no significant difference was found between the observed and expected numbers of second cancers in the HD female group. Although it is important to discuss whether or not early subclinical cancers should be included as a second malignancy, they are included in the present study because they have been diagnosed clinically during the follow-up survey and the patients have been operated on. According to the report of Brodey *et al.* (1977) of 22 HD patients who developed second malignancy, ANLL and gastric cancer were observed in three and two patients, respectively. The most common solid tumors were breast cancer (3 cases), colon cancer (2 cases), skin cancer (2 cases) and laryngeal cancer (2 cases).

It was noted especially in our study on HD patients that the mean age at onset of

lymphoma in the patients with associated second cancer was significantly greater than that in all patients including those with double primary malignancies. This may be a reflection of the fact that the risk of developing malignancy is increased in the older age group.

Our findings did not show a positive correlation between the risk of a second malignancy and the therapeutic method. This may be due to the facts that the number of cases analyzed was smaller than in other studies and that the mean observed period was a relatively short 6 years.

In the contrast with HD, the occurrence of second malignancies in patients with NHL has varied widely. Although the risk of developing ANLL in patients treated for NHL is greater than the predicted number (Zarrabi *et al.*, 1979; Zarrabi, 1980; Greene *et al.*, 1983), the risk of a solid tumor as a second neoplasm has not been adequately estimated. Zarrabi (1980), MacDougall *et al.* (1981) and Greene *et al.* (1983) failed to detect an increased risk of second solid tumors in NHL. However, a significant increase in the incidence of skin cancer (Berg, 1967), colon cancer (Rosenberg *et al.*, 1961) and lung cancer (Libshitz *et al.*, 1978) has been reported.

In our study, NHL patients did not develop ANLL and these findings are similar to those of Canadian study (MacDougall *et al.*, 1981). On the other hand, in the study by Nagura *et al.* (1985), in five of 14 NHL patients who developed second malignancy the second malignancy was ANLL. The difference between our study and theirs regarding the risk of a secondary ANLL is pronounced, but the cause is not known at present.

Although we did not find a significant difference between the observed and expected numbers of second primary cancers in patients with NHL, it is noteworthy that in six out of 11 cases gastric cancers developed after diagnosis of NHL and three of these were diagnosed histologically as early gastric cancer.

According to Zarrabi's review (1980) of 90 NHL patients who developed metachronous second neoplasms, only one patient had gastric cancer. The most common solid tumors were lung cancer (23 cases), basal or squamous cell cancer of the skin (11 cases), colon or rectal cancer (10 cases), bladder cancer (6 cases) and breast cancer (6 cases). The difference in cancer types between our cases and theirs is probably owing to the difference in cancer incidence among races. Moreover, the occurrence of gastric cancer seemed not to be significantly influenced by a difference in treatment.

To understand the relationship between malignant lymphoma and the occurrence of a second malignancy, we must take into account the following three factors: 1) the constitutional tendency to develop cancer, 2) immunosuppressive and/or carcinogenic effects of radiotherapy and/or chemotherapy, 3) impairment of cellular immunity in patients with lymphoma. At the present time, however, we can not find sufficient evidence of a discrepancy between Japanese and Western cases relating to the risk of a second malignancy on the basis of these three factors.

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