Risk of Second Cancer in Patients With Hairy Cell Leukemia: Long-Term Follow-Up

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Purpose: **The purpose of the present study was to assess the risk of second cancers in patients with hairy cell leukemia (HCL).**

Patients and Methods: **We investigated the incidence of additional cancers in those patients registered in the nationwide registry of the Italian Cooperative Group for the Study of HCL, asking the cooperating centers for additional information on initial and subsequent therapies and on time and type of second malignancies, if they developed. Here we report the final results of this survey, consisting of 54 cases of second malignancies (excluding nine cases of epithelial skin cancer) which developed in 54 patients of 1,022 with adequate follow-up.**

Results: **The cumulative risk of development of a second cancer was 5%, 10%, and 14% at 5, 10, and 15 years, respectively. The incidence of second malignancies was not significantly higher than the expected rate (standardized incidence ratio [SIR], 1.01; 95% confidence interval [CI], 0.74 to 1.33; *P* = 1.0). However, the SIR of non-Hodgkin's lymphoma in the entire cohort was 5.3 (95% CI, 1.9 to 11.5). Second malignancies occurred in eight (4.7%) of 386 patients who never received interferon (IFN), nine (5.9%) of 495 patients treated with IFN at the time of diagnosis, and seven (6.9%) of 102 patients who received IFN as second-line therapy. These differences were not statistically significant. Analysis of the separate calendar periods did not reveal any particular trends with respect to variations in SIR.**

Conclusion: **The present study does not support the suspicion that patients with HCL are at increased risk of additional second malignancies, although the incidence of lymphoid neoplasms was significantly higher than expected. In addition, our data indicate that IFN therapy did not exert an oncogenic effect in such patients.**

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HAIRY CELL LEUKEMIA (HCL) is a rare chronic B-cell disorder which comprises approximately 1% of all lymphoproliferative malignancies.[1,2] The prognosis of the disease dramatically improved about 30 years ago with the introduction of splenectomy as initial therapy.[3-5] Since that time, prognosis has further improved with the demonstration of the efficacy of interferon-alfa 2a, 2b, or Ly (IFN),[6-11] deoxycoformycin (DCF),[12-16] and 2-chlorodeoxyadenosine (2-CdA)[17-22] in controlling the course of the disease. With current therapies, the life expectancy of HCL patients approaches that of the general population.[23]

Ever since the first report on HCL (initially referred to as leukemic reticuloendotheliosis) by Bouroncle et al[24] in 1958, an apparent association with other malignancies has been remarked on.[25-31] This has led to the commonly held belief that HCL patients may have an intrinsic susceptibility for the development of a second malignancy. Nevertheless, an increased rate of second malignancies after HCL has yet to be demonstrated. As noted by Bernstein,[2] frequent appearance of a second malignancy may merely reflect the greater long-term survival after HCL with respect to most other forms of cancer, or may also stem from impairments to the immune function (decreased natural killer and T-cell activity) that have been widely reported[25,26,28,29,32-36] among HCL patients. The role of therapy, and particularly of IFN, in the development of second primary malignancies is also controversial. Whereas Kampmeier et al[28] reported significantly more second malignancies among patients treated with IFN, Troussard et al[29] and, more recently, Kurzrock et al[30] were unable to confirm the association and recommended larger studies.

To investigate these two issues, we looked for the incidence of second malignancies among the patients registered in the nationwide registry of the Italian Cooperative Group for the Study of HCL. This registry probably

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comprises the largest series of HCL patients yet collected. For the purpose of this study, we reviewed 1,136 records of patients diagnosed before December 1996, obtaining complete information from the cooperating centers on initial and subsequent therapies and on timing and type of any second malignancies in 1,022 of them.

PATIENTS AND METHODS

Between January 1981 and December 1996, a total of 1,136 patients were recorded in the Italian Registry of HCL. Of these, 252 patients had been recognized from retrospective analysis of clinical and pathology medical records collected at the time of institution of the registry in 1981; 884 patients were subsequently registered at diagnosis during the period from January 1981 through December 1996. All patients were pooled in a preliminary working file. Because of incomplete data, 114 patients were excluded from the subsequent analysis. Thus, a total of 1,022 patients were included in the study. Patients' clinical and biologic characteristics at the time of diagnosis are summarized in Table 1. To investigate whether there was an excess of second tumors in HCL patients, we conducted an active survey. The cooperating centers all provided complete written information on date of second malignancy, nature of the tumor, HCL status at the time of second cancer, initial and subsequent therapy for HCL, and patient follow-up.

A second malignancy was defined as any invasive neoplasm, other than epithelial (squamous or basal) skin cancer, occurring more than 3 months after the diagnosis of HCL. Concurrent malignancies were considered to be those diagnosed in a period ranging from 3 months before to 3 months after diagnosis of HCL. Preceding malignancies were those detected more than 3 months before diagnosis of HCL. Standardized incidence ratios (SIRs) were calculated by determining the ratio of the observed to the expected number of individuals with second malignancies in the 1978 to 1999 period. The expected number of subjects with second invasive malignancies was determined by using 5-year age-, sex-, and calendar-period-specific incidence rates estimated for the Italian population.[37] Calendar periods were 1978 to 1982, 1983 to 1987, 1988 to 1992, and 1993 to 1999. To obtain an estimate of cancer incidence in the whole nation, we calculated the mean between cancer rates in northern Italy (by averaging rates released by the Varese, Modena, and Parma Cancer Registries), central Italy (Latina Cancer Registry), and southern Italy (Ragusa Cancer Registry). For calculation of SIRs, person-years at risk were calculated from time of diagnosis of HCL to the date of the second cancer diagnosis or the date of the last contact. We computed the SIRs of second malignancies in the entire cohort and in two subgroups of interest, namely patients who never received IFN and those treated with IFN alone at the time of diagnosis of HCL. We also conducted analyses specific for age group, calendar period, and length of follow-up.

The 95% confidence intervals (CIs) and *P* values for the SIRs were determined by assuming a Poisson distribution for the observed number of second cancers. A two-sided test was used to test the equality of the observed and expected number of cancers. Survival analyses and the cumulative probability of second malignancy were calculated by the method of Kaplan and Meier. The Cox proportional hazards model was used to estimate the effect of suspected factors on subsequent risk of second malignancy.

Table 1. Patient Characteristics

	No. of Patients	%
Age, years		
Median	54	
Range	23-84	
Sex		
Male	826	81
Female	196	19
Infections		
Yes	196	23
No	665	77
Blood transfusions		
Yes	134	16
No	702	84
Spleen size*		
Not palpable	305	32
1-4 cm	220	23
5-10 cm	256	26
> 10 cm	185	19
Liver size*		
Not palpable	465	50
1-2 cm	209	23
2-4 cm	171	18
> 4 cm	85	9
Lymphadenopathy		
Yes	80	8
No	942	92
Hemoglobin		
< 8.6 g/dL	272	32
8.6-12 g/dL	417	48
> 12 g/dL	175	20
Leukocytes†		
≤ 1,000 × 10^9/L	31	4
1,001-3,500 × 10^9/L	469	58
3,501-10,000 × 10^9/L	206	26
> 10,000 × 10^9/L	98	12
Neutrophils†		
≤ 500 × 10^9/L	347	41
501-1,500 × 10^9/L	350	41
> 1,500 × 10^9/L	151	18
Monocytes†		
Not detectable	537	62
1-150 × 10^9/L	245	28
151-500 × 10^9/L	65	8
> 500 × 10^9/L	16	2
Hairy cells†		
Not detectable	283	32
1-500 × 10^9/L	273	31
501-5,000 × 10^9/L	154	17
> 5,000 × 10^9/L	179	20
Jansen's stage		
I	324	42
II	212	27
III	237	31

*Under costal margin.
†Peripheral-blood findings.

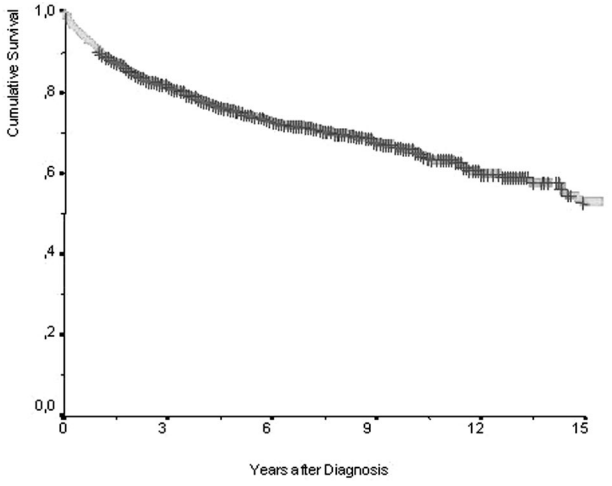

Fig 1. Overall survival of 1,022 HCL patients: the mean follow-up time after diagnosis was 73 months.

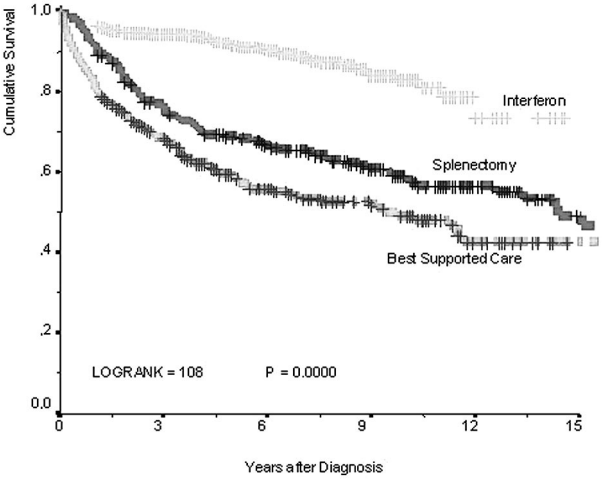

Fig 2. Overall survival of HCL patients according to initial therapy.

RESULTS

Treatment and Survival

Initial therapy consisted of best-supportive care or single-agent chemotherapy in 272 patients, splenectomy in 216, IFN in 495, and purine analogs in the remaining 39 patients. Overall, 425 patients never received IFN (including 146 of those who underwent splenectomy), 495 received IFN as induction therapy at diagnosis, and 102 received IFN as second or further treatment (70 of whom were initially treated with splenectomy).

At the time of analysis, 271 patients had died, 647 were alive, and 104 patients were lost to follow-up. The mean follow-up time after diagnosis was 73 months (86 months for living patients and 81 for those lost to follow-up). The median follow-up of patients diagnosed before 1985 and never treated with IFN was 63 months (95 for living patients) as compared with 73 months (76 for living patients) for those initially treated with IFN. The overall survival of all patients is shown in Fig 1. Survival according to initial therapy is shown in Fig 2.

Second Malignancies

Overall, 63 second malignancies were recorded (Table 2). Nine cases of epithelial skin cancer were not considered in the analysis. No patient had more than one malignancy in addition to HCL. One patient had had a preceding malignancy (infiltrating cervical cancer 30 months before HCL). Four patients had concurrent malignancies (diagnosed in a period ranging from 3 months before to 3 months after diagnosis of HCL), and 49 patients (4.8%) had a second malignancy at a median time of 64 months (range, 7 to 206 months) after the diagnosis of HCL. A summary of clinical features of patients with HCL and second tumors is reported in Table 3.

The 49 metachronous malignancies occurred at a median age of 60.4 years (61.4 years in men and 58.2 years in women). The median age of diagnosis of HCL was 56.6 years (57.3 in men and 52.8 in women) among patients who later developed second malignancies, as compared with

Table 2. Frequency of Second Malignancies in Patients With HCL Recorded at the Italian Cooperative Group HCL Registry

Site	No. of Cases
Lung	11
Gastrointestinal tract	
Stomach	2
Colon	6
Rectum	2
Skin (carcinoma)	9
Genitourinary system	
Bladder	4
Kidney	3
Prostate	2
Non-Hodgkin's lymphoma	7
Breast, female	5
Leukemia and other myeloproliferative disorders	3
Gynecologic	
Cervix	2
Ovary	1
Soft tissue	2
Thyroid	1
Oral cavity	1
Larynx	1
Liver	1
Total	63

Table 3. Clinical Features of Patients With HCL and Second Neoplasm

Case No.	Age at Dx (years)	Sex	Time From Dx to Second Cancer (months)	Site of Second Cancer	Initial HCL Therapy	HCL Second-Line Therapy	Status	HCL Status at Last Observation	Survival From Dx of HCL (months)	Survival After Dx of Second Cancer (months)
Prior malignancy										
1	82	F	−30	Cervix	Unknown	Unknown	Dead	PD	46	76
Concurrent malignancy										
2	35	M	2	NHL	Splenectomy	None	Dead	Unknown	10	8
3	63	M	3	Colon	Splenectomy	Unknown	Dead	Minimal	18	14
4	71	M	0	Bladder	None	None	Dead	PD	16	16
5	46	M	0	Kidney	Splenectomy	IFN	Alive	Minimal	18	18
Later malignancy										
6	46	M	128	NHL	Splenectomy	IFN	Dead	PR	129	1
7	50	F	10	Colon	Splenectomy	CLB	Dead	PR	11	1
8	54	M	49	Lung (NSCLC)	None	Unknown	Dead	SD	61	12
9	60	M	29	Rectum	Splenectomy	—	Dead	SD	41	12
10	44	F	206	Ovaries	Splenectomy	IFN	Dead	PR	221	15
11	54	F	22	NHL	None	None	Dead	PD	24	2
12	62	F	77	NHL	Splenectomy	Unknown	Dead	PD	86	9
13	47	M	130	Polycythemia vera	Splenectomy	IFN	Alive	CR	203	73
14	29	F	101	Breast	Splenectomy	None	Alive	CR	179	78
15	40	M	102	Lung (NSCLC)	Splenectomy	None	Dead	CR	114	12
16	50	M	138	Lung (NSCLC)	None	None	Lost to FU	PR	138	0
17	47	M	84	Soft tissue sarcoma	Splenectomy	None	Dead	PR	88	4
18	46	M	130	NHL	IFN	Unknown	Alive	PR	143	13
19	59	F	40	Breast	IFN	IFN	Dead	PR	76	36
20	66	M	97	Lung (NSCLC)	None	None	Dead	SD	110	13
21	57	F	82	Mesothelioma	IFN	DCF	Dead	PR	88	6
22	62	M	77	Rectum	IFN	Splenectomy	Dead	PR	83	5
23	59	M	101	Kidney	IFN	None	Alive	CR	101	0
24	62	M	57	Bladder	IFN	IFN	Alive	PR	151	94
25	60	M	107	Colon	IFN	None	Dead	PR	107	0
26	58	M	45	Mesothelioma	IFN	Splenectomy	Dead	PR	48	3
27	59	F	18	Colon	IFN	Splenectomy	Dead	Minimal	18	0
28	76	M	25	Prostate	IFN	None	Dead	PR	27	2
29	74	M	24	Colon	IFN	None	Alive	PR	87	63
30	62	M	63	Lung (NSCLC)	IFN	2-CdA	Dead	CR	66	3
31	68	M	53	Stomach	IFN	Unknown	Lost to FU	PR	83	30
32	58	M	20	Acute leukemia	IFN	None	Alive	PR	34	14
33	71	M	7	Bladder	IFN	None	Dead	Minimal	7	0
34	51	F	21	Breast	IFN	Splenectomy	Alive	PR	79	58
35	65	M	97	Stomach	IFN	2-CdA	Dead	PD	98	1
36	52	M	108	Oral cavity	None	None	Dead	CR	113	5
37	50	M	55	Prostate	IFN	None	Alive	PD	112	57
38	54	M	45	Colon	IFN	None	Dead	CR	50	5
39	59	F	18	Soft tissue sarcoma	IFN	DCF	Alive	CR	125	107
40	50	F	41	Thyroid	Splenectomy	IFN	Alive	PR	157	116
41	48	M	114	Liver	Splenectomy	IFN	Alive	PR	120	6
42	50	M	55	Bladder	Splenectomy	IFN	Alive	PR	75	20
43	57	M	109	Lung (NSCLC)	IFN	None	Alive	CR	109	0
44	57	F	59	Cervix	IFN	2-CdA	Alive	CR	93	34
45	77	F	36	NHL	None	None	Dead	SD	40	4
46	44	F	88	Breast	IFN	Splenectomy	Alive	CR	126	38
47	47	M	46	Larynx	IFN	2-CdA	Alive	CR	80	34
48	50	M	96	Lung (NSCLC)	IFN	Splenectomy	Dead	CR	102	6
49	43	F	12	Polycythemia vera	IFN	None	Alive	CR	18	6
50	75	M	14	Lung (NSCLC)	IFN	None	Dead	PR	21	7
51	51	M	84	NHL	Splenectomy	None	Alive	CR	109	25
52	30	F	142	Breast	Splenectomy	None	Alive	PR	209	67
53	64	M	13	Lung (NSCLC)	IFN	None	Dead	PR	17	4
54	77	M	4	Kidney	IFN	None	Dead	SD	6	2

Abbreviations: NHL, non-Hodgkin's lymphoma; NSCLC, non–small-cell lung cancer; CLB, chlorambucil; PD, progressive disease; PR, partial response; SD, stable disease; CR, complete response; FU, follow-up.

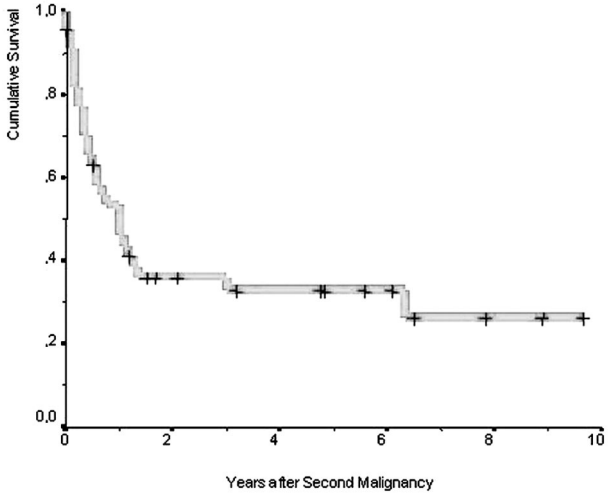

Fig 3. Cumulative survival of 49 HCL patients after the diagnosis of second neoplasm: the cumulative 5-year survival rate after the diagnosis of second cancers was 39%.

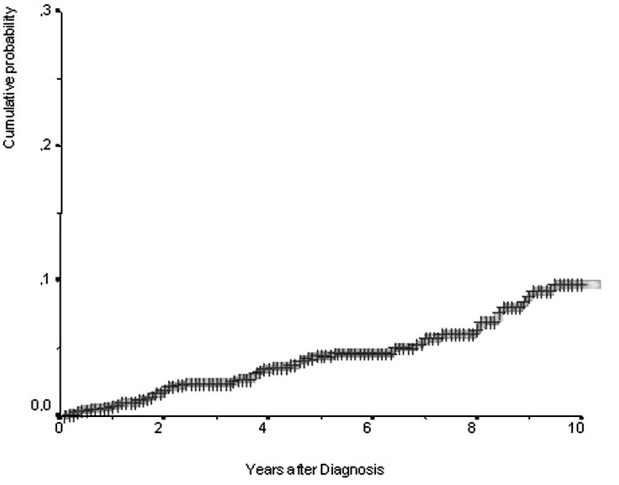

Fig 4. Cumulative risk of second malignancy in HCL patients: the overall 5-, 10-, and 15-year cumulative probabilities of developing a second cancer were 5%, 10%, and 14%. respectively.

53.7 years (54.1 in men and 52.1 in women) among subjects who remained free of second malignancies at the end of the follow-up period.

There were 18 second neoplasms (4.7%) in the group of 386 HCL patients who never received IFN, 29 (5.9%) in the group of 495 HCL patients treated with IFN at time of diagnosis, and seven (6.9%) in the group of 102 patients who received IFN as second-line therapy. The rate of second malignancies was similar in the three groups, and statistical analysis revealed nonsignificant differences ($P = .89$).

Thirty-one patients died of a second malignancy 1 to 78 months from its diagnosis. The median time to death was 11 months. The cumulative 5-year survival rate after the diagnosis of a second malignancy was 39% (Fig 3). Interestingly, no patient died of HCL after the diagnosis of a second malignancy. The cumulative risk of developing a second malignancy is shown in Fig 4. The overall 5-, 10-, and 15-year cumulative probabilities of developing another cancer were 5%, 10%, and 14%, respectively. Among the 386 patients who never received IFN, the 5- and 10-year cumulative probabilities of developing a second cancer were 5% and 12%, respectively, as compared with 5% and 11%, respectively, in the 495 patients initially treated with IFN at the time of diagnosis (Fig 5).

Risks of Second Primary Cancer

The follow-up of the 1,022 cohort members for whom there were complete data was based on a total of 5,571 person-years. The incidence of second malignancies in the entire cohort was not significantly higher than the expected rate (SIR, 1.01; 95% CI, 0.74 to 1.33; $P = 1.0$). Analysis of the separate calendar periods did not reveal any particular trends with respect to variations in SIR (Table 4). Stratification of the duration of follow-up did not reveal any particular variation in the risk of occurrence of second malignancy with respect to time from diagnosis (Table 5).

The incidence of second malignancy in patients treated with IFN at the time of diagnosis was not significantly different from the incidence in those never treated with IFN. In particular, the SIR of second malignancy was 1.12 (95% CI, 0.75 to 1.61) for patients who received IFN at diagnosis, as compared with 1.02 (95% CI, 0.56 to 1.70) for those

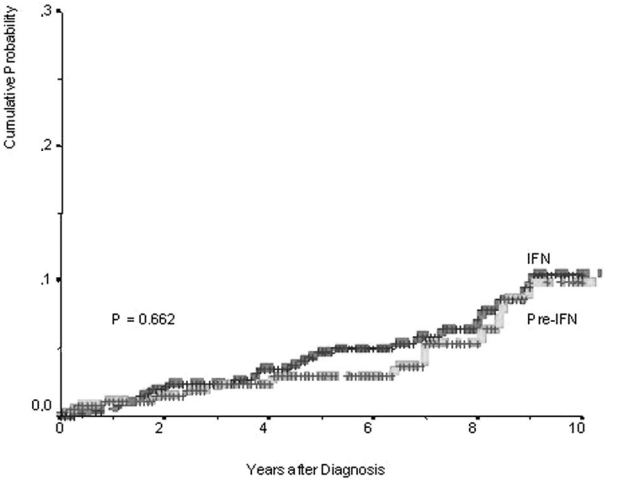

Fig 5. Cumulative probability of second cancer in HCL patients treated or not with IFN.

Table 4. SIR of Second Malignancy in a Cohort of 952 Patients With HCL According to Calendar Period, Italy, 1978-1999

Period of Analysis	OC	EC	SIR	95% CI
1978-1982	4	3.99	1.00	0.27-2.57
1983-1987	7	7.85	0.89	0.36-1.84
1988-1992	18	17.28	1.04	0.62-1.65
1993-1999	20	19.61	1.02	0.62-1.58

Abbreviations: OC, observed cases; EC, expected cases.

never treated with IFN. Stratifications according to age, calendar period, and length of follow-up did not reveal any significant differences between the two groups.

A multiple regression analysis performed according to the Cox model, limited to subjects treated with IFN from the time of diagnosis or never treated with IFN, showed that the risk of any second malignancy was higher in women than in men and was directly correlated with age at diagnosis of HCL (Table 6). No association was found between risk of second malignancy and use of IFN.

Six (12.2%) of the 49 second malignancies diagnosed during the follow-up were non-Hodgkin's lymphomas (NHLs). In terms of sex distribution, the NHLs occurred in three (0.39%) of 826 men and three (1.60%) of 196 women. They presented at 8.6, 10.7, and 10.8 years from diagnosis of HCL in men and at 1.8, 3.0, and 6.4 years from diagnosis in women. With respect to IFN treatment, four cases occurred in patients never treated with IFN, one in a patient treated with IFN because of disease progression after splenectomy, and one in a patient who received IFN as first-line treatment. Overall, the SIR of NHL in the entire cohort was 5.3 (95% CI, 1.9 to 11.5). Analysis of the separate calendar periods did not reveal any particular trends in NHL with respect to variations in SIR. However, a relationship emerged between incidence of NHL and time from diagnosis of HCL. Four out of six cases of NHL occurred in the 55- to 59-year-old age group, yielding a SIR of 27.3 (95% CI, 7.4 to 69.9). The SIR of NHL among patients never treated with IFN was 13.2 (95% CI, 3.6 to 33.7), as compared with 1.6 (95% CI, 0.04 to 9.06) among those treated with IFN from the time of diagnosis.

DISCUSSION

The present study was designed to investigate the incidence of additional cancers in what, to the best of our knowledge, is the largest series of HCL patients yet to be collected. The series comprises 1,022 patients from the Italian Cooperative Group for the Study of HCL, treated sequentially according to the different approaches over a period of 16 years. Specifically, this study is based on the comparison of a stable, geographically defined population of HCL patients with a matched control group derived from the mean rates provided by major cancer centers in the north, center, and south of Italy.[37] After a median follow-up of 6.1 years (7.2 years for living patients), we found that 54 of 1,022 HCL patients had another cancer diagnosis, and 49 of them developed a second malignancy at least 4 months after the diagnosis of HCL.

Table 5. SIR of Second Malignancy in a Cohort of 952 Patients With HCL According to Length of Follow-Up, Italy, 1978-1999

Length of Follow-Up	OC	EC	SIR	95% CI
0-4 years	28	28.46	0.98	0.65-1.42
5-9 years	15	15.09	0.99	0.56-1.64
≥ 10 years	6	5.18	1.16	0.43-2.52

Table 6. Cox Proportional Hazards Model of Risk of Second Malignancy According to Selected Risk Factors in a Cohort of Patients With HCL, Italy, 1978-1999*

Variable	Hazard Ratio†	*P*	95% CI
Sex	1.94	.043	1.02-3.68
Age at HCL diagnosis	1.03	.017	1.01-1.06
IFN therapy	1.25	.508	0.65-2.38

* Analysis limited to the 483 HCL patients regularly treated with IFN and to the 330 patients who were never administered IFN.

† Hazard ratio in multivariate analysis for: men *v* women, 1-year increase in age at diagnosis of HCL, and regular therapy with IFN *v* no IFN therapy.

The clinical suspicion that HCL patients are more prone to second malignancies than other survivors of cancer has never been conclusively demonstrated. Several studies have evaluated the risk of secondary malignancies in patients with HCL.

In an epidemiologic study based on incidence data collected from 1972 to 1987 by the Cancer Surveillance Program among residents in Los Angeles County, Bernstein et al[2] found that 30 out of 208 HCL patients had another cancer diagnosis. They estimated that HCL patients were more than twice as likely to have multiple primary cancer diagnoses as other cancer patients. Since the majority of the other cancers occurred before (27%) or concurrent with (40%) the HCL diagnosis, the authors suspected that patients who develop HCL may have impaired immune function. Our study does not confirm these findings. In our experience, most cases occurred after the diagnosis of HCL.

However, in this respect, a number of further studies have clearly elucidated some details of this peculiar impairment, particularly at the level of T-cell function: decrease of memory T helper cells,[38] abnormal activation of spleen T lymphocytes that seem to behave like tumor-infiltrating ones,[39] and selection of oligoclonal T-cell populations showing a very restricted and skewed T-cell repertoire.[40] These features, together with an inadequate antigen presentation process due to monocytopenia and with the lack of

CD28 on T cells, could explain at least in part the overall lack of responsiveness shown by HCL patients' T lymphocytes[41] as well as anecdotal reports of T-cell leukemia[42] and lymphoproliferative disorders of granular lymphocytes[43] developed after HCL treatment.

In a review of the records of 172 patients with HCL seen at the University of Chicago over a 10-year period,[25] 15 patients were found to have a second malignancy, suggesting a possible role of monocytopenia in the pathogenesis of the second malignancy. About 10 years later, Kampmeier et al[28] from the same institution reported an unexpectedly high incidence of second malignancies (13 cases) in a small group of 69 HCL patients treated with IFN, suggesting that IFN therapy could have some direct oncogenic effect. Au et al[26] investigated a group of 117 patients referred for treatment to the British Columbia Cancer Agency between 1976 and 1996 and found 26 additional malignancies diagnosed after HCL. This represented a statistically significant increased risk of second cancer (relative risk, 2.6; 95% CI, 1.8 to 3.6, $P < .001$), apparently more related to HCL tumor burden than to genetic predisposition or treatment effect.

On the contrary, Troussard et al[29] did not find an excess of second malignancies in a group of 97 patients treated with IFN. They found eight second malignancies diagnosed at least 6 months after the diagnosis of HCL and the observed-expected ratio of 1.53 (95% CI, 0.62 to 3.16) was not statistically significant ($P = .36$). In a large study based on 350 patients treated at the University of Texas M.D. Anderson Cancer Center between 1968 and 1995, Kurzrock et al[30] found that 26 patients (7.4%) developed a second malignancy, and statistical analysis failed to find a significant increase in the incidence of second neoplasms (observed-expected ratio, 1.34; $P = .08$).

Finally, recently Cheson et al[21] reported 52 second cancers in a cohort of 928 HCL patients treated between 1992 and 1993 with 2-CdA according to the group C phase II open study of the National Cancer Institute and followed up for a median time of 52 months. They suspected a potential increased risk for secondary malignancies, but specific analyses were not reported.

Our present study revealed no trend toward an increase of second malignancies among HCL patients as compared with the expected rate derived from the control population of cancer patients (SIR, 1.01; 95% CI, 0.74 to 1.33; $P = 1.0$), nor were any significant SIR variations found in relation to the duration of the follow-up among the various calendar periods studied. Given the large size of our study population, we have also been able to study the possible oncogenic effect of IFN therapy in HCL patients. Among the 494 patients treated with IFN from the time of diagnosis and the 102 patients who received the drug as second-line therapy, we recorded second malignancy rates of 5.9% and 6.9%, respectively. These rather similar rates were not significantly higher than the 4.7% of second malignancies found in the subset of 386 patients who never received IFN. Statistical analysis revealed a nonsignificant increase in the incidence of a second neoplasm evaluating both the global cohort and according to the period of analysis, and comparing incidence in the cohorts of patients treated or not with IFN.

When we analyzed the second malignancies according to their histologic type, the largest group (12.2%) was found to be lymphomas. In particular, all six cases presented in the form of aggressive NHL (at a median interval from diagnosis of HCL of 84 months). Previous reports have observed a significant excess of the lymphoma subgroup of second malignancies.[30] Here again, our study provides no concrete evidence for the existence of an adverse role of IFN (only two out of six patients who developed NHL had been treated with this drug).

Unlike patients with Hodgkin's disease and NHL, who are at increased risk of acute leukemia after splenectomy, among the 216 HCL patients treated with splenectomy, no cases of acute leukemia were recorded. This surprising lack of increased risk of developing secondary leukemia could be explained by the fact that patients with HCL underwent splenectomy at an older age than patients with Hodgkin's disease or NHLs. The relevance of immune surveillance by the spleen is probably different at different ages.

Given the low number of patients in the present study treated with purine analogs at the time of diagnosis, we did not perform any subset analysis for exploring a possible oncogenic effect of these drugs in our patients. Although the investigators involved in the large group C treatment protocol expressed some concern about the risk of second tumors after therapy with 2-CdA or DCF,[21] recently Flinn et al[16] have concluded that subsequent malignancies do not seem to be increased with DCF treatment.

In conclusion, the analysis of the present large cohort of HCL patients does not confirm the suspicion that patients with HCL are at increased risk of additional second malignancies nor an oncogenic effect of IFN therapy, although a longer follow-up evaluation of patients treated with 2-CdA or DCF is required in order to better assess the oncogenic potential of both agents.

APPENDIX

The appendix is available online at www.jco.org.

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