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A population-based study of hairy cell leukemia in Israel

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Paltiel O, Adler B, Barchana M, Dann EJ. A population-based study of hairy cell leukemia in Israel.

Abstract: *Objectives:* Few population-based data exist on the incidence and prognosis of hairy cell leukemia (HCL). Our objectives were to study the effect of socio-demographic factors on this rare disease and the risk of second malignancies occurring in HCL patients. *Methods:* We measured crude and age-adjusted incidence rates of HCL based on reporting to the Israel Cancer Registry (ICR) 1991–2001. Using Kaplan–Meier and multivariate analysis, we assessed survival by gender, ethnicity and geographic region. We ascertained additional primary tumors reported in this population and calculated standardized incidence ratios (SIRs) for tumors reported after the diagnosis of HCL. *Results:* The ICR registered 147 cases of HCL among males and 34 in females between 1991 and 2001. Age-adjusted incidence rates were 1.62/10^6/yr for women and 7.97/10^6/yr for men, with rates 1.5 times higher in Jewish than in non-Jewish (mainly Arab) men. Mean overall survival also differed by ethnicity. In a multivariate model, increasing age at diagnosis ($P < 0.001$), as well as Arab origin ($P = 0.008$) were associated with poorer survival but gender did not significantly affect the survival after controlling for age and ethnicity. Other primary malignancies were reported in 20 (11%) individuals, with a predominance of genito-urinary tumors (65%) among males. Secondary genito-urinary tumors were significantly increased above the expected population rates (SIR 3.23, 95% confidence interval: 1.39–6.36, $P = 0.008$). *Conclusions:* In the Israeli population, age and ethnicity were associated with prognosis of HCL. Variations in disease characteristics, stage of disease at diagnosis or differential access to treatment may contribute to these findings. Patients with HCL appear to be at increased risk for genito-urinary malignancies.

Key words: hairy cell leukemia; epidemiology; cancer registry; second malignancy

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Hairy cell leukemia (HCL) is a rare lymphoproliferative disorder of B-cell origin. Its prognosis and excellent response to single chemotherapeutic agents sets this entity apart from other indolent B-cell disorders. In the era of treatment with nucleoside analogs, long-term survival above 90% can be expected (1–3). Despite its excellent prognosis, the disease has a measurable impact on health, insurability and lifestyle (4). Little is known about the epidemiology and prognosis of this disorder among different ethnic groups.

Nucleoside analogs (notably cladribine – 2CDA) have been available for the treatment of HCL in Israel since the early 1990s. We performed a nationwide descriptive epidemiologic study of this disorder in order to determine whether there are socio-demographic differences in incidence and survival, and to analyze the prevalence of second malignancies in this population. Israeli society is multiethnic with a Jewish majority composed of immigrants and Israeli-born citizens and a non-Jewish (mainly Muslim Arab) minority comprising about 20% of the population.

Methods

We studied all cases with a diagnosis of HCL (ICD-9 2042, OR ICD-O morphology code 99403) as reported to the Israel Cancer Registry (ICR) from January 1991 to December 2001. Reports to the Registry originate from various sources including pathology departments, death certificates, hospital

discharge records and visits to Oncology Departments. The ICR was established in 1960 and since 1981 cancer notification has been obligatory by law (5). Cancer reporting to the Registry is considered to be about 94% complete according to quality control surveys.

Statistical analysis

Using data from the Israel Population yearbook (6), near the midpoint of the study (1996) we estimated crude and age-standardized incidence rates for both sexes, by ethnic origin and region. Rates were standardized using the distribution of age in the population above the age of 18 yr according to 15 yr categories.

We measured the overall survival of patients with HCL from date of diagnosis to death or June 30, 2003 using univariate Kaplan–Meier analysis. Differences in survival functions were compared using the log-rank test. We then constructed Cox proportional hazard models to assess the survival of HCL patients controlling for age, sex, ethnicity and region. Age at diagnosis of HCL was entered as a continuous variable, sex and ethnicity (Arab vs. Jewish) as dichotomies and geographic region in four categories. Only variables with a P-value of < 0.05 were retained in the model. Two-sided P-values of < 0.05 were considered statistically significant. All statistical analyzes were performed using SPSS Version 12 (SPSS Inc., Chicago, IL, USA).

Finally, we examined the second primary malignancies in this population reported to the Cancer Registry. We calculated standardized incidence ratios (SIRs) and their 95% confidence intervals for second malignancies occurring after the diagnosis of HCL, both overall and by specific sites, by comparing the observed number of cases to those expected based on Israeli population rates in 1995, by age and sex. Clinical data including details of treatment and disease presentation and relapse were not available.

Ethical issues

The statistical analysis was performed using unidentified data. The study was approved by the legal adviser of the Ministry of Health and was exempt from requiring individual informed consent.

Results

During the study period, there were 181 cases of HCL reported in Israel, of which 81% occurred in men and 19% in women. The age-adjusted annual incidence rate for the 11-yr study period was 1.62 per million for women and 7.97 for men, respectively, with substantial variation between regions (Table 1). The incidence rate also varied by ethnic group, with higher rates observed in the Jewish compared with the Arab population. Among the Jewish population, those born in Israel had lower crude rates than those born abroad (data not shown), but after adjusting for age, Israel-born Jews actually had a higher incidence rate (Table 1).

Table 1. Descriptive characteristics of hairy cell leukemia in Israel 1991–2001

	No. cases (%)	Age-adjusted annual incidence rate (per million)	95% confidence interval
Sex			
Men	147 (81)	7.97	6.7–9.3
Women	34 (19)	1.62	1.1–2.2
Age at diagnosis (years)			
30–44	43 (24)	–	–
45–64	81 (45)	–	–
65–74	29 (16)	–	–
75+	28 (15)	–	–
Ethnic origin*			
Jewish	169 (94)	4.88	4.1–5.6
Israeli-born	54 (30)	6.43	3.7–9.1
North Africa	16 (9)	4.86	2.7–7.0
Asia	22 (12)	4.24	1.6–6.9
Europe/America	77 (43)	4.91	3.7–6.1
Arabs	10 (6)	2.36	0.9–3.9
Region*			
North	47 (26)	4.22	3.0–5.4
Center	89 (50)	4.75	3.8–5.7
Jerusalem	17 (10)	4.22	2.2–6.2
South	26 (14)	5.61	3.4–7.8

*Two unknown.

In 88.1% of cases, reporting to the ICR was based on a pathological report, in 4.6% the basis was a hematology report (e.g. bone marrow aspiration), in 1.9% the basis for reporting was another clinical study and in 5.5% the basis of reporting was not recorded.

The mean age at diagnosis for the entire population was 57.4 yr (SD 15). The mean age for women was 62.3 yr, and for men was 56.3 yr ($P = 0.033$). For Jews, the mean age at diagnosis was 57.8 yr while for Arabs it was 49.4 yr ($P = 0.089$).

The overall median survival from diagnosis was 146.5 months and the overall mean was 115 months. Mean survival varied by ethnicity, ranging from 77.6 months for non-Jews (mainly Arabs) to 116.6 months for Jews ($P = 0.20$) (Fig. 1). There were significant differences in the mean survival for ethnic subgroups (Israeli-born Jews 137.7 months, Asia-born Jews 124.6 months, North-African-born Jews 110.6 months and European/American-born Jews 97.6 months, $P = 0.001$). Crude survival varied minimally by geographical region (data not shown, $P = 0.09$) as well

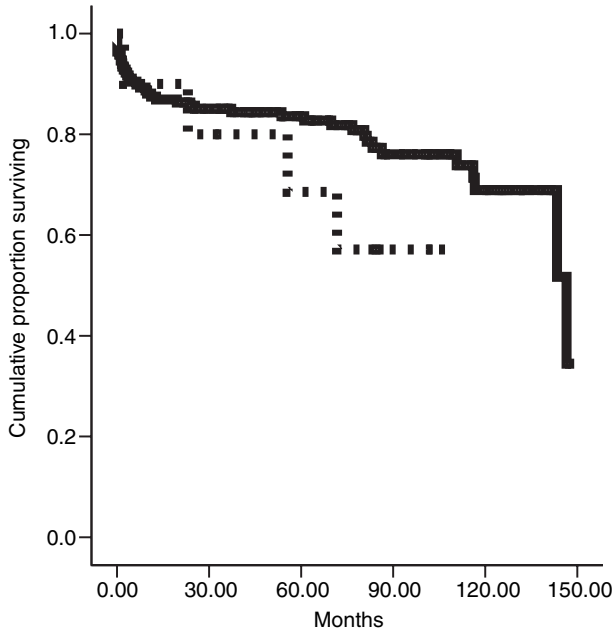

Fig. 1. Overall survival from diagnosis of hairy cell leukemia by ethnic group: solid line – Jews, broken line – non-Jews.

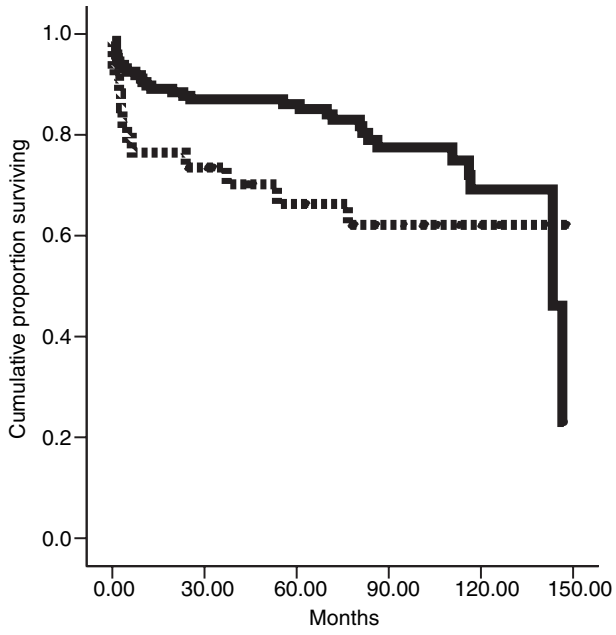

Fig. 2. Overall survival from diagnosis of hairy cell leukemia by gender: solid line – men, broken line – women.

as by gender, with a mean survival of 118 months for men and 100 months for women ($P = 0.09$) (Fig. 2).

In a multivariate model (Table 2), we found that age and ethnicity were independent predictors for survival. After adjusting for age we found that Arabs with HCL had a poorer prognosis compared with Jews [hazards ratio (HR) 4.28, $P = 0.008$].

Table 2. Multivariate analysis of survival in hairy cell leukemia

Variable	*n*	Hazard ratio	95% confidence interval	*P*-value
Age (per year)		1.09	1.06–1.12	<0.001
Sex				
Male (ref)	144	1		
Female	34	1.28	0.64–2.55	0.48
Ethnic origin				
Jewish (ref)	168	1		
Arab	10	4.28	1.47–12.4	0.008

The survival of women with the disease was modestly poorer than for men (HR 1.3), but the findings were not statistically significant. Geographical region had no effect on survival after controlling for age at diagnosis (data not shown).

Table 3 shows the additional primary neoplasms reported in this population. Twenty-two second primary malignancies occurred in 20 (11%) individuals. Of these, 11 occurred prior to the diagnosis of HCL and 10 occurred following this diagnosis (one was simultaneous). Two male patients had three primary malignancies; in both cases, one of the additional tumors was a renal cell carcinoma which developed at age 73. In patient no. 8 this tumor presented 2.5 yr before the diagnosis of HCL and in patient no. 13, 8 months following the diagnosis of HCL. The striking finding in this population is the large proportion of tumors of the male urogenital tract including renal cell carcinoma, transitional cell carcinoma of the bladder and prostate cancers.

Table 3. Additional primary malignancies in Israeli hairy cell leukemia (HCL) patients

Patient no.	Sex	Age at HCL diagnosis	Second primary site	Interval between HCL and additional primary (yrs)
1	M	64	Papillary thyroid	−15
2	F	83	Breast	−8
3	M	48	Renal cell	11
4	M	73	Bladder	8
5	M	53	Prostate	10
6	M	48	Melanoma	8
7	M	56	Acoustic neuroma	7
8	M	76	Prostate/renal cell	−3.5, −2.5
9	M	54	Prostate	0
10	M	53	Bladder	−5
11	M	55	Prostate	<0.5
12	M	77	Prostate	−5
13	M	73	Prostate/renal	−4, 0.3
14	M	64	Mesothelioma	7
15	M	54	Melanoma	−5.5
16	F	78	Breast	−1
17	M	69	Prostate	5
18	M	65	Prostate	5
19	M	68	Spindle cell tumor	4.5
20	M	70	Colon	−.5

Table 4. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) for second primary malignancies occurring after the diagnosis of hairy cell leukemia

Tumor site	Cases observed	Cases expected	SIR	95% CI
All sites	12	9.2	1.31	0.68–2.28
Prostate	5	1.37	3.64	1.18–8.51
Renal	2	0.36	5.62	0.67–20.3
Bladder	1	0.75	1.33	0.04–7.43
All genito-urinary	8	2.48	3.23	1.39–6.36
Breast	0	0.5	0	0–7.14
Melanoma	1	0.3	3.07	0.09–17.11

In a population of this size, age and sex composition, about nine tumors would be expected to occur after the diagnosis of HCL, rather than the 12 observed (SIR = 1.3, 95% confidence interval 0.68–2.28). SIRs for genito-urinary tumors were markedly increased (SIR 3.23, 95% confidence interval 1.39–6.36, $P = 0.008$) (Table 4).

Discussion

In this population-based study conducted in the 'nucleoside analog' era we found variations in the incidence and prognosis of HCL, according to gender and ethnicity. Furthermore, although second primary cancers did not appear markedly increased in this population, there appeared to be a propensity for genito-urinary tumors.

This study has the advantage of using registry-based data, which is unaffected by biases operating in hospital-based case series. Furthermore, cases were ascertained over an 11-yr period with a minimum follow-up of 21 months and median follow-up of 80 months for survivors. On the other hand, registry-based data are limited by the quality and quantity of clinical data available, as well as completeness of reporting from pathology departments and hematology laboratories. Hematopoietic malignancies are known to be under-reported in cancer registries (7). Moreover, in this study, pathologic confirmation of all cases was not obtained. We were hindered by not having data on treatment regimens or on relapse dates, and thus were not able to calculate disease-free survival. Notwithstanding these limitations, registry data can provide useful information on rare disorders.

The descriptive epidemiology of HCL has been documented in relatively few studies. Lishner *et al.* (8) summarized 44 cases of HCL in Israel based on reports from hematology departments between 1972 and 1983. There were 33 males (75%) and 11 females (25%), a slightly higher proportion of the latter than in our current series. The mean age at diagnosis was 52 yr (as opposed to 57 yr in our series). Our series, during an interval of 11 yr, included more than four times as many patients, reflecting population growth, aging of the population and possibly heightened awareness of this rare disease. In the earlier series, the median survival was not reached in those who underwent splenectomy but was <60 months in those who received chemotherapy. Interestingly, 12 patients in that series received no treatment whatsoever (8).

In our population, the incidence of HCL was found to differ among the sexes and among ethnic groups. A series from Los Angeles published in 1990 (9) showed an age-adjusted incidence rate of 2.9 per million for men and 0.6 per million for women. The rate for Jewish men was about three times higher than for Protestants. Staines and Cartwright (10) in a population-based study in the UK, found a similar population-based incidence rate, once again with a male preponderance. HCL has been found to be very rare in Mexican adults, but with a geographic predilection for farming regions (11). Other countries with low incidence rates include Hong Kong (0.35 per million/yr)(12), whereas in Iceland the reported population incidence was 4.7 per million (13).

While details of treatment in our series were not available we can surmise that during the 1990s most patients with HCL were treated with cladribine. Pentostatin was not available in Israel for most of the study period. The 5 yr survival for the entire population was 82% and 10 yr survival was 68%. This is compared with 97% overall survival rate at 108 months at a referral center in the USA (2), and 95% 5 yr survival from a UK referral center (3) for patients treated with cladribine or pentostatin. In an Italian series, overall survival was 87.5% at 5 yr (14) for patients treated mainly with α-interferon.

We did not find solid evidence to support a differential effect of treatment between the genders. In our series, women with HCL were on average 6 yr older at diagnosis than men, and in fact survival according to gender was not significantly different on multivariate analysis after controlling for age.

Although based on a small number of cases among the non-Jewish population, the survival in our series did, however, vary by ethnicity. These findings should be interpreted cautiously but possibly reflect delayed diagnosis, more advanced disease or possibly decreased access or compliance with modern treatments in the Arab population. This despite universal access to health services under the National Health Insurance Law in Israel. Similar findings have been observed in a hospital-based series on acute myeloid leukemia (15). Even in the USA among insured cancer patients, survival has been found to vary by ethnic group (16). As we measured overall survival and not disease-specific

survival, competing risks may also have played a role in the differential mortality by ethnic group.

There has been concern that patients suffering from HCL are at greater risk of second malignancies than the general population. This may be due to advanced age, or immunosuppression resulting from the disease itself or its treatment. A previous malignancy was even found by Nordstrom *et al.* (17) to be a risk factor for HCL. In the Israeli population, 11% of patients had another primary malignancy besides HCL and two (1.1%) had three primary tumors. Of these tumors, about 11 occurred prior to the diagnosis of HCL and 10 following this diagnosis. In a 1994 large Italian series (18), 3.7% of the patients were diagnosed with a second malignancy following the diagnosis of HCL. Further follow-up of the 102 Italian patients showed 54 (5.4%) with second primaries, and a cumulative risk of second cancer of 10% at 10 yr.

Although some series have shown an increase in lymphoproliferative disorders following a diagnosis of HCL (18, 19), in our population, tumors of the male urogenital tract were most prominent (specifically eight prostate, two bladder and three renal cell carcinomas), comprising 65% of the tumors among the males. In comparison, in Israel in 1995, approximately 19% of cancers diagnosed in the male population were at these three sites (20). The incidence rate of these tumors diagnosed after the onset of HCL was significantly increased compared with expected population rates. The SIRs calculated probably underestimate the risk of genito-urinary tumors in this population as they do not take into account tumors detected before the diagnosis of HCL. In a Danish case series of 50 patients with HCL, three also had renal cell carcinomas (21). Over a 20-yr period in British Columbia, 117 patients with HCL had an additional malignancy including eight prostate cancers (22). The high rate of genito-urinary malignancies occurring both prior to and following the diagnosis of HCL suggests possible common etiologic factors.

A variety of occupational and lifestyle exposures have been postulated as contributing to the etiology of HCL. These include positive associations with exposure to petrol or diesel (23) and agricultural exposures especially cattle breeding (17), pesticides (17, 23, 24), and negative associations with smoking (25, 26). Although we had no data on personal exposure history, the variable incidence rates observed among different regions in Israel, as well as those between the sexes, may reflect variations in occupational exposures.

Hairy cell leukemia is a rare malignancy with high survival rates. Differences in incidence and survival rates among population subgroups may provide clues to etiology and differential access or responsiveness to therapies.

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Conflict of interest

None.

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