Incidence, risk of infection and survival of hairy cell leukaemia in Denmark

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ABSTRACT

INTRODUCTION: Few population-based studies exist on incidence, risk of infection and mortality in hairy cell leukaemia (HCL).

MATERIAL AND METHODS: We used population-based medical databases to identify 209 patients who were diagnosed with HCL in the period from January 1997 to August 2007 in Denmark. An age- and sex-matched comparison cohort of 2,090 persons was selected from the general population. We computed the incidence of HCL using demographic data. Hospitalizations with pneumonia and bacteraemia were determined from the Danish National Patient Registry. Cox regression analysis was used to estimate the relative risk (RR) of infection and mortality ratios (MRR) adjusting for age, sex and comorbidity.

RESULTS: The HCL incidence rates were 1.97 (95% confidence interval (CI) 1.51-2.53) and 5.37 (4.57-6.28) per million person-years for women and men, respectively. During a median follow-up of 4.5 years, 48 HCL patients were hospitalized with pneumonia or bacteraemia. The adjusted RR of infection was 8.04 (4.99-12.95) the first year after diagnosis and 1.17 (0.71-1.94) for the remaining follow-up period. The adjusted MRRs were 4.26 (2.61-6.96) and 1.12 (0.75-1.65) the first year after diagnosis and the remaining follow-up period, respectively.

CONCLUSION: In the second and subsequent years after HCL diagnosis, the risk of infection and mortality was similar to that of the general population.

Hairy cell leukaemia (HCL) is a rare, indolent chronic B-cell lymphoproliferative disease, initially described by Bouroncle in 1958. It is characterized by splenomegaly and pancytopenia. With an estimated incidence of 0.2-0.8 per 100,000 person years [1-5], HCL accounts for approximately 2% of all cases of leukaemia [6-7]. However, only few of the currently published incidence studies have been population-based [1-5].

The introduction of purine analogues in the 1990's substantially improved the prognosis of HCL which resulted in complete remission rates above 80% and overall response rates near 100% [8-12]. On the other hand, purine analogues are also known to cause profound immunosuppression, especially in the form of a prolonged decrease in T-cell-mediated immunity [13], which may increase the risk of infections. Only few studies have explored the risk of infection in HCL in the purine analogue era [14-16] and these studies have lacked control groups. Consequently, it is unknown whether the infection risk is increased compared with the general population's risk.

We conducted a population-based cohort study in Denmark to estimate the incidence of HCL and to examine the risk of infections as well as survival in HCL patients. The study population was compared with an age- and sex-matched population cohort.

MATERIAL AND METHODS

Study population

The study was conducted in Denmark which has approximately 5.5 million inhabitants. Danish patients with haematological malignancies are only treated in public hospitals. Every resident in Denmark is assigned a unique 10-digit personal ID number which encodes sex and age and enables accurate linkage between different registries [17].

Identification of patients with hairy cell leukaemia

We used the Danish Pathology Registry (DPR) to identify HCL patients. This national registry was established in 1997 and all pathological specimens are categorized according to the Systematized Nomenclature of Medicine (SNOMED). The SNOMED code used for HCL was M961B3 in the period 01.01.1997 to 31.12.02 and M99403 thereafter.

The National Patient Registry (NPR) was established in 1977 and contains data on > 99% of all hospital discharges in Denmark. Outpatient visits at hospitals have been included since 1995. The NPR includes the ID number, date of admission and discharge, surgical procedures performed and discharge diagnoses [18]. The NPR coded the diagnosis according to the International Classification of Diseases, eighth revision (ICD-8) until 1994 and according to the tenth revision (ICD-10) thereafter. We also used the NPR to eliminate patients registered with HCL in the NPR before 1997.

General population comparison cohort

From the Danish Central Population Registry we ran-

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domly chose ten age- and sex-matched members of the general population who did not have an HCL diagnosis at the date their matched patient was diagnosed with HCL.

Data on serious infections

Data on HCL patients and general population members were linked to the NPR to identify all hospital contacts involving serious infections defined as pneumonia or bacteraemia. We used the following ICD-codes to identify pneumonia (ICD-10: J12x – J18x) and bacteraemia (ICD-10:A00-A09, A30-A49).

Mortality data

We obtained information on vital status, date of death and residence of all study members from the Civil Registration System, which is updated daily.

Comorbidity

Comorbidity was classified according to the Charlson Comorbidity Index [19]. We computed the index on the basis of the ICD codes for all NPR discharge diagnoses of the HCL patients and their matched controls since 1977. Weights were assigned to defined categories of comorbid diseases and the index was defined as the sum of these weights. Two levels of comorbidity were defined: 0 (''no comorbidity'') for individuals with no recorded underlying diseases included in the Charlson Index; and 1 (''comorbidity'').

Statistical analysis

We computed crude incidence rates for HCL and incidence rates stratified by age and sex. For calculations of incidence rates, the number of residents in Denmark was retrieved from Statistics Denmark using population distribution of age and sex as per 1 January for each of the years 1997-2006. We followed HCL patients and their matched controls from the date of diagnosis of HCL or from the date of inclusion in the control cohort until the first episode of pneumonia, bacteraemia, death, or end of follow-up (1 April 2008), whichever came first. To visualize the risk of infection, we constructed Kaplan-Meier curves for time-to-infection for the two cohorts. The risk of infection in HCL patients relative to that of the population comparison cohort was estimated by Cox regression analysis adjusted for age, sex and comorbidity. To estimate survival, we followed HCL patients and their matched controls until death, emigration or end of follow-up (1 April 2008), whichever came first. For both cohorts, we constructed Kaplan-Meier survival curves. In addition, we used a Cox regression analysis to estimate the mortality rate ratio (MRR) adjusted for age, sex and comorbidity.

For all statistical analyses, we used the statistical software package SAS, version 9.2 (SAS Institute Inc., Cary, NC). The study was approved by the Danish Data Protection Agency (No. 2007-41-0389).

RESULTS

In the period from January 1997 to August 2007, we identified 209 new cases of HCL (57 females and 152 males) and 2,090 general population members (570 females and 1,520 males). The female to male ratio was 1:2.7. The mean patient age at diagnosis was 63.5 years (range 32.1-89.1 years) for females and 62.7 years (range 32.2-86.6 years) for males. The HCL incidence rates were 1.97 (1.51-2.53) and 5.37 (4.57-6.28) per million person-years for females and males, respectively, as shown in **Table 1**.

Infection risk

During a median follow-up period of 4.5 years (range 0.01-10.9 years), we identified a total of 48 severe hospitalized infections (29 pneumonias and 19 bacteraemias) among the HCL patients. The median time from HCL diagnosis to infection was 3.82 years (range 0.00-10.92 years). In comparison, we identified 208 infections (137 pneumonias and 71 bacteraemias) during a median follow-up of 4.7 years among members of the general population. **Figure 1** shows the cumulative risk of infection in HCL patients and population controls. The overall adjusted relative risk (RR) of infection in HCL patients compared with the general population members was 2.59 (95% confidence interval (CI) 1.88-3.56). However, the risk depended on the time from diagnosis of HCL with an adjusted RR of 8.04 (4.99-12.95) for infections during the first year after HCL diagnosis and 1.17 (0.71-1.94) in the remaining follow-up period. This pattern of increased infection risk the first year after HCL diagnosis

TABLE 1

Incidence rates of hairy cell leukaemia (HCL) in Denmark stratified by sex and age.

Age, years	No. of HCL cases	Incidence rate per 1,000,000 person-years (95% confidence intervals)
Females		
0-60	23	1.01 (0.66-1.49)
60-70	11	4.00 (2.12-6.93)
70-80	17	8.18 (4.94-12.80)
80+	6	4.43 (1.84-9.14)
Total	57	1.97 (1.51-2.53)
Males		
0-60	67	2.85 (2.23-3.60)
60-70	34	13.23 (9.32-18.25)
70-80	43	27.16 (19.92-36.22)
80+	8	12.23 (5.77-23.08)
Total	152	5.37 (4.57-6.28)

was also found in an additional analysis stratified by sex, age and comorbidity.

Survival

A total of 51 HCL patients died during the median 4.5 years of follow-up. The one-year survival was 88.95% (83.84%-92.51%) and the five-year survival was 77.93% (70.92-83.44%) (**Figure 2**). There was no difference in survival between males and females. The crude mortality ratio for HCL patients was 1.77 (1.31-2.37). After adjustment for age, sex and comorbidity, the MRR was 1.67 (1.24-2.26). The adjusted MRRs were 4.26 (2.61-6.96) in the first year after HCL diagnosis and 1.12 (0.75-1.65) in the following period. Although the statistical precision was low, we found a similar pattern of increased mortality confined to the first year after diagnosis; a mortality that was independent of sex, gender and comorbidity (data not shown).

FIGURE 1

The cumulative risk of infection in hairy cell leukaemia patients and population controls.

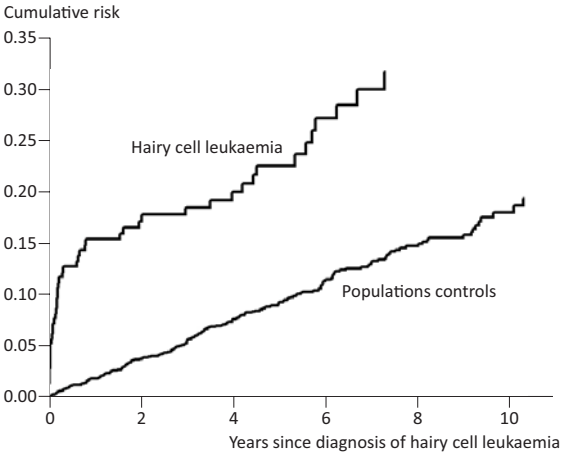
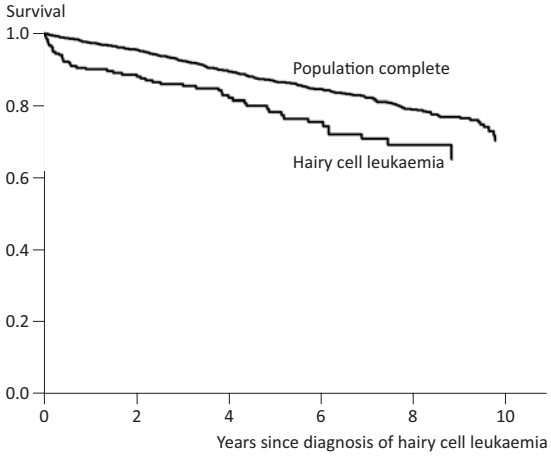


FIGURE 2

The survival rates in hairy cell leukaemia patients and the complete population.



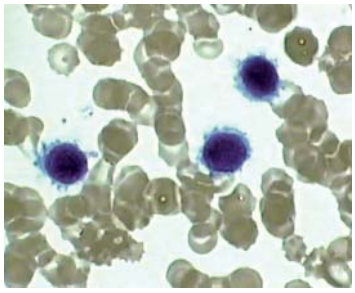
DISCUSSION

In this population-based study among incident cases of HCL during a ten-year period in Denmark, HCL was associated with a 2.5-fold increased risk of serious infections compared with the risk among members of the general population. This increased risk was, however, most pronounced in the first year after HCL diagnosis. In contrast, in the second and following years after diagnosis, the risk of infection was not substantially increased. Similarly, we found a four-fold increased mortality during the first year after HCL diagnosis. In the second and following years, the mortality was similar to that of the general population.

The Danish incidence rates for HCL have not previously been reported. The mean age at diagnosis of HCL in our study was 63.5 years, which is slightly higher than the age reported in most other studies [1, 3, 4, 16]. The reason for this may lie in the population-based nature of our study which included all verified cases in an entire country. Our incidence rates are in accordance with most other studies and confirm the increase in incidence with age and the male preponderance [1-5]. However, it is remarkable that we found a lower female to male ratio than the four-fold increase reported in most other studies [1, 4].

Previous studies have identified infection as the predominant complication in HCL, most frequently in the form of bacteraemia or pneumonia [20]. At diagnosis of HCL, leucopenia occur in 60% and severe neutropenia in 37%, which may contribute to the innate susceptibility to bacterial infections in HCL [15]. However, neutropenia is not a prerequisite for serious infections in HCL, and a recent study identified a low absolute lymphocyte count as a risk factor for infection in HCL and observed no association between neutrophil or monocyte counts and the risk of infection [16]. Multiple other immune defects have been detected in HCL, including T- and NK-cell abnormalities, profound monocytopenia and decreased production of certain cytokines.

Treatment with cladribine also causes myelosuppression, but in a follow-up on HCL patients treated with cladribine, the risk of bacterial infection was limited and confined to a period of two weeks after the end of treatment [10]. However, patients who have received purine analogues have reduced cellular-based immunity for a minimum of nine to 12 months after completion of therapy [13], and infections remain a major cause of comorbidity in HCL patients treated with the purine analogues. In a follow-up on 358 HCL patients treated with cladrib-



Hairy cells (by courtesy of Dr. Preben Johansen, Aalborg Hospital).

ine, 149 (42%) developed neutropenic fever while only 45 (13%) had documented infection during a median 58 months of follow-up [8]. Similarly, a German study demonstrated fever in 36% of HCL patients and culture-proven infections in 9% of the patients [10]. In a recent French study on 73 patients, the 10-year incidence of serious infection was 26% [16]. However, the patients included in this study had received various types of first-course treatments, including splenectomy and interferon.

Our finding that the increased risk of serious infections was confined to the first year after HCL diagnosis corroborates the observation that infection risk is not increased in long-time survivors in HCL, even though a fraction of our patients are likely to have undergone repeated treatment due to relapse during follow-up. We lacked data on type of treatment in our cohort, but since the early nineties, cladribine has been the treatment of choice for Danish patients with HCL, and pentostatin was only available in Denmark in the very last part of the study period.

The HCL patients in our study had a reduced survival compared with the control cohort during the first year after diagnosis, and their subsequent survival was similar to that of the comparison cohort. In accordance with this, a recently published large European study on 233 HCL patients treated with purine analogues found an overall survival at 15 years of 78% and a survival of 96% when non-HCL-related deaths were censored [9]. In this European study, the number of deaths was equivalent to the number expected in the general population when matched by age and sex. The median age of the patients in this centre-based European study was 49 years, which is considerably lower than the age of the patients in our study. The survival of HCL patients treated with purine analogues has been addressed in several uncontrolled studies, but the reported measures of survival vary between studies and render impossible a proper comparison of survival with our study [3, 8, 10-12]. We found a one-year survival of 89% in the Danish HCL patients which appears to be lower than the survival rate reported in most other studies. The explanation is likely to be the population-based nature of our study, which results in a higher age and possibly higher comorbidity of the HCL patients as opposed to studies based on HCL patients from single centres. The register-based design of our study did not allow for an evaluation of causes of death in the HCL cohort. Nor could we assess if the increased risk of serious infections the first year after diagnosis of HCL contributed to mortality. A study from the pre-purine analogue era found an association between infection and reduced survival in HCL [14]. However, studies on patients treated with cladribine have only listed infection as the cause of dead in few cases [8, 10, 16].

The main strengths of our study are the use of national registry-based data and a matched population comparison cohort. Data from the Danish Pathology Registry and the National Patient Registry ensure a complete countrywide registration of HCL and infection, which eliminates the risk of selection bias otherwise seen in hospital-based case series. Furthermore, the data enabled an adjustment for comorbidity. A study limitation is the risk of coding errors of infection leading to misclassification. This risk is not likely to differ between the HCL patients and the controls, and will hardly affect the relative estimates of infection. On the other hand, it is well-known that HCL has an innate infection potential. It is possible that this knowledge may have led to an increased diagnostic effort and thus to a higher likelihood of detecting serious infection in HCL patients. Such surveillance bias would tend to overestimate the risk of infection in HCL. We also lacked data on clinical factors that may explain an increased risk of infection and mortality, e.g. HCL treatment, biochemical and haematological values, response to treatment and relapse.

In conclusion, the risk of serious infection and the mortality was increased in HCL compared with the general population, but an elevation of the infection risk and the mortality was confined to the first year following HCL diagnosis. Our results emphasize the need to follow HCL patients closely during the first year after diagnosis.

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CONFLICTS OF INTEREST: None

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Exhibit 1
Stratified analysis of Danish hairy cell leukaemia patients

Age				
	Age	Variable	Hazard ratio	95% confidence interval
Infection risk	0-60	HCL vs. controls – first year	48.816	10.726-222.178
Infection risk	60-70	HCL vs. controls – first year	18.504	5.406-63.337
Infection risk	70-80	HCL vs. controls – first year	3.612	1.671-7.807
Infection risk	> 80	HCL vs. controls – first year	5.535	1.658-18.478
Infection risk	0-60	HCL vs. controls – remaining follow-up period	2.085	0.905-4.802
Infection risk	60-70	HCL vs. controls – remaining follow-up period	0.773	0.183-3.262
Infection risk	70-80	HCL vs. controls – remaining follow-up period	1.322	0.572-3.055
Infection risk	> 80	HCL vs. Controls – remaining follow-up period	0.549	0.128-2.350
Mortality	0-60	HCL vs. controls – first year	1.317	0.153-11.355
Mortality	60-70	HCL vs. controls – first year	7.166	2.272-22.598
Mortality	70-80	HCL vs. controls – first year	4.051	1.988-8.252
Mortality	> 80	HCL vs. controls – first year	4.628	1.800-11.900
Mortality	0-60	HCL vs. controls – remaining follow-up period	0.495	0.151-1.624
Mortality	60-70	HCL vs. controls – remaining follow-up period	1.064	0.378-2.994
Mortality	70-80	HCL vs. controls – remaining follow-up period	1.537	0.924-2.554
Mortality	> 80	HCL vs. controls – remaining follow-up period	0.818	0.291-2.300

Sex				
	Sex	Variable	Hazard ratio	95% confidence interval
Infection risk	Females	HCL vs. controls – first year	9.764	4.323-22.051
Infection risk	Males	HCL vs. controls – first year	7.417	4.096-13.432
Infection risk	Females	HCL vs. controls – remaining follow-up period	1.555	0.607-3.981
Infection risk	Males	HCL vs. controls – remaining follow-up period	1.070	0.588-1.946
Mortality	Females	HCL vs. controls – first year	7.041	2.597-19.085
Mortality	Males	HCL vs. controls – first year	3.666	2.066-6.505
Mortality	Females	HCL vs. controls – remaining follow-up period	1.081	0.462-2.529
Mortality	Males	HCL vs. controls – remaining follow-up period	1.137	0.729-1.771

Comorbidity				
	Comorbidity	Variable	Hazard ratio	95% confidence interval
Infection risk	0	HCL vs. controls – first year	32.542	14.468-73.193
Infection risk	1	HCL vs. controls – first year	3.693	1.948-7.003
Infection risk	0	HCL vs. controls – remaining follow-up period	2.477	1.277-4.804
Infection risk	1	HCL vs. controls – remaining follow-up period	0.630	0.291-1.364
Mortality	0	HCL vs. controls – first year	10.895	4.214-28.170
Mortality	1	HCL vs. controls – first year	2.864	1.608-5.102
Mortality	0	HCL vs. controls – remaining follow-up period	1.548	0.834-2.874
Mortality	1	HCL vs. controls – remaining follow-up period	0.962	0.579-1.599