Non-Lymphoma Hematological Malignancies in Systemic Lupus Erythematosus

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Key Words

Systemic lupus erythematosus · Malignancy · Cancer

Abstract

Objective: To describe non-lymphoma hematological malignancies in systemic lupus erythematosus (SLE). **Methods:** A large SLE cohort was linked to cancer registries. We examined the types of non-lymphoma hematological cancers. **Results:**

In 16,409 patients, 115 hematological cancers [including myelodysplastic syndrome (MDS)] occurred. Among these, 33 were non-lymphoma. Of the 33 non-lymphoma cases, 13 were of lymphoid lineage: multiple myeloma (n = 5), plasmacytoma (n = 3), B cell chronic lymphocytic leukemia (B-CLL; n = 3), precursor cell lymphoblastic leukemia (n = 1) and unspecified lymphoid leukemia (n = 1). The remaining 20 cases were of myeloid lineage: MDS (n = 7), acute myeloid leukemia (AML; n = 7), chronic myeloid leukemia (CML; n = 2) and 4

unspecified leukemias. Most of these malignancies occurred in female Caucasians, except for plasma cell neoplasms (4/5 multiple myeloma and 1/3 plasmacytoma cases occurred in blacks). **Conclusions:** In this large SLE cohort, the most common non-lymphoma hematological malignancies were myeloid types (MDS and AML). This is in contrast to the general population, where lymphoid types are 1.7 times more common than myeloid non-lymphoma hematological malignancies. Most (80%) multiple myeloma cases occurred in blacks; this requires further investigation.

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Introduction

Cancer risk in systemic lupus erythematosus (SLE) is a topic of increasing interest, but to date, much of the focus has been directed at lymphoma especially non-Hodgkin's lymphoma. Our purpose was to describe demographic factors and types of non-lymphoma hematological malignancies in a very large international, multisite SLE cohort.

Methods

Our assessment was based on a very large international, multisite cohort drawn from 30 centers, each linked to regional tumor registries to ascertain malignancies. We published recently on the overall cancer experience in this cohort [1]. In this paper, we describe the types of non-lymphoma hematological cancers occurring after SLE diagnosis and examine the distribution of demographic characteristics, including sex, race/ethnicity, age and SLE duration at the time of cancer diagnosis. The centers from which these non-lymphoma hematological cancers in SLE occurred included Canada (Montreal, Toronto and Winnipeg), the USA (Chicago, Baltimore, Pittsburgh, Brooklyn, San Francisco, Los Angeles, Chapel Hill and Birmingham), Korea (Seoul), Denmark (Copenhagen) and Sweden (Lund).

The cohort was followed from the date of cohort entry (date first seen in the clinic with confirmed SLE) up to the earliest of: date last seen in the clinic, death or end of cancer registry information. Cancer registries generally require a period of at least 1 year to have elapsed before they can confirm that their cancer data are adequately complete and accurate, so the end of the observation interval for the SLE cohort of each center was based on the earliest of that date, or the last date the patient was seen in the clinic (or the date of death, if relevant).

Regional general population cancer rates were obtained and used to generate the expected number of hematological malignancies. The total of cancers observed in our cohort, divided by this expected number, provides the standardized incidence ratio (SIR), representing the relative risk of hematologic malignancy in SLE compared to an age and sex-matched general population.

Results

Sixteen thousand four hundred and nine patients were observed for an average of 7.4 person-years. Of these, 90% were female and the majority was Caucasian [1]. In these patients, 115 hematological cancers occurred and, based on age-matched general population cancer rates, the standardized incidence ratio (SIR) for all hematological cancers after SLE onset was 2.9 in females [95% confidence interval (CI) 2.3–3.6] and 3.6 in males (95% CI 2.2–5.5). The SIR for hematological cancers for SLE patients of <40 years was 4.1 (95% CI 2.5–6.3) in comparison with SLE patients >60 years where the point estimate was SIR 2.3 (95% CI 1.7–3.1) [1].

We assessed that a total of 33 non-lymphoma hematological malignancies [including myelodysplastic syndrome (MDS)] had occurred in these patients. To provide some context, figure 1 gives an outline of the cells from which hematological malignancies arise.

For these 33 non-lymphoma hematological cancers, the mean age at cancer diagnosis was 54.3 years [standard deviation (SD) 15.2, median 55] and the mean SLE duration at the time of cancer diagnosis was 14 years (SD 8.2, median 14). Most, i.e. 30/33 patients were female (90.91%), reflecting the female predominance of the SLE cohort. With respect to race/ethnicity, 18 were Caucasian (54.6%), 12 were black (of African or Caribbean descent, 36.4%), 2 were Asian (6%) and 1 was First Nations (Canadian native).

Of these 33 non-lymphoma cases, 13 were of lymphoid lineage. This included multiple myeloma ($n = 5$), plasmacytomas ($n = 3$), B cell chronic lymphocytic leukemia (B-CLL; $n = 3$), precursor cell lymphoblastic leukemia ($n = 1$) and lymphoid leukemia not otherwise specified ($n = 1$). The remaining 20 cases were of myeloid lineage. These included MDS ($n = 7$), acute myeloid leukemia (AML; $n = 7$), chronic myeloid leukemia (CML; $n = 2$) and 4 leukemias not otherwise specified.

All of the non-lymphoma lymphoid hematological malignancies in SLE occurred in female Caucasians, except in the plasma cell neoplasms, where 4/5 multiple myeloma cases and 2/3 plasmacytoma cases were black (the others being Asian and Caucasian, respectively) (table 1). Regarding age, in B-CLL, the median age of SLE subjects at the time of onset was 65 (range 58–83) years. The median age at onset for this cancer in the female general population is 74 years [2]. At the time of multiple myeloma diagnosis in SLE, median age was 49 (range 45–57) years, while for the 3 plasmacytoma SLE cases, median age was 35 (range 25–62) years. In the female

Fig. 1. Hematological malignancies by cell lineage. ALL = Acute lymphocytic leukemia; CLL = chronic lymphocytic leukemia.

Table 1. Demographics of the SLE patients who developed non-lymphoma hematologic malignancies of the lymphoid line

Description (ICD-O-3 code)	n	Whites, n	Median age at cancer diagnosis, years ^a	Median SLE duration at cancer diagnosis, years ^a
Mature B cell neoplasms				
B-CLL (n = 9,823)	3	3 (100%)	65 (58–83)	11 (8–23)
Plasma cell neoplasms				
Multiple myeloma (n = 9,732)	5	1 (20%)	49 (45–57)	17 (8–25)
Plasmacytoma n.o.s. (n = 9,731)	3	1 (33.3%)	35 (25–62)	14 (11–25)
Other lymphoid malignancies				
Precursor cell lymphoblastic leukemia, n.o.s. (n = 9,835)	1	0	22	0
Lymphoid leukemia, n.o.s. (n = 9,820)	1	1 (100%)	84	29

All SLE patients who developed lymphoid malignancies were female. Lymphoblastic leukemias in the general population tend to occur in children, while lymphocytic leukemias tend to occur in older adults. n.o.s. = Not otherwise specified.

^a Range is shown in parentheses.

general population, the median age at time of diagnosis for multiple myeloma is 70 years [2], and 55 years for plasmacytomas [3].

Of 20 myeloid malignancies, 3 (15%) occurred in males, and 7 (35%) occurred in blacks (table 2). In female AML cases, the median age at AML diagnosis was 48

(range 34–72) years versus 66 years in the female general population. The 7 MDS cases (6 females) occurred at a median age of 48 (range 36 – 59) years versus 76 years in the general population [2]. The age at time of diagnosis for the 2 CML cases (1 female) were similar to the general population median (65 years).

Table 2. Demographic characteristics of the SLE patients who developed myeloid malignancies

Description (ICD-O-3 code)	Cases n	Whites n (%)	Females n (%)	Median age ^a years (range)	Median SLE duration ^a years (range)
AML	7	5 (71.4)	6 (85.7)	48 (34–72)	16 (5–23)
AML n.o.s. (9,861)	4	3 (75)	3 (75)	54 (41–72)	17.5 (16–21)
Acute monocytic leukemia (9,891)	1	0	1 (100)	48	23
Acute myelomonocytic leukemia (9,867)	1	1 (100)	1 (100)	34	5
Multilineage dysplasia (9,895)	1	1 (100)	1 (100)	66	10
Myeloproliferative neoplasms					
CML n.o.s. (9,863)	2	2 (100)	1 (50)	64.5 (62–67)	14.5 (3–26)
Myelodysplastic syndrome					
MDS n.o.s. (9,989)	7	2 (28.6)	6 (85.7)	48 (36–59)	8 (1–28)
Unknown myeloid neoplasm					
Leukemia n.o.s. (9,800)	2	1 (50)	2 (100)	57.5 (44–71)	13 (9–17)
Acute leukemia n.o.s. (9,801)	1	1 (100)	1 (100)	72	5
Myeloid leukemia n.o.s. (9,860)	1	1 (100)	1 (100)	71	12

n.o.s. = Not otherwise specified.

^a At time of cancer diagnosis.

Discussion

Most of the hematological malignancies that developed in our SLE cohort were female, which reflected the fact that 90% of SLE patient are female. In the general population, the risk of hematological cancers is significantly greater in males than females; for example, males have almost twice the risk for B-CLL. Our international cohort study included over 16,000 individuals and 10% of them were male. Given this, only 2–3 lymphoid malignancies would have been expected in our male SLE subjects. Thus while it may seem unusual that none of the non-lymphoma lymphoid malignancies were male, this may have just been a chance finding due to the low number of males with SLE, and the relative rarity of these cancers in general. Though our SIR point estimate for hematological cancers in males with SLE (SIR 3.6) was slightly higher than that for females (SIR 2.9), the CIs did overlap.

Five cases of multiple myeloma occurred in our SLE cohort. Although previous studies were unable to demonstrate that SLE patients have any increased risk for multiple myeloma [4, 5], 1 large study did demonstrate that patients with a family history of SLE do indeed have an increased risk of developing multiple myeloma [4]. Furthermore, there is also an increased occurrence of SLE in first-degree relatives of people with multiple myeloma [6]. We were somewhat surprised that most (80%) of these 5 multiple myeloma cases in our SLE cohort occurred in blacks. In the general population, black populations do

have a 2-fold greater multiple myeloma prevalence when compared to Caucasian populations [2]. However, blacks were a minority in our cohort. In our recent review of case reports and case series in the literature, out of 20 SLE patients that developed multiple myeloma [7–24], only 1 patient was black [22]. We are unable to explain the high proportion of multiple myeloma cases in blacks in our cohort.

A striking finding in our study was the young age at diagnosis for the majority of the neoplasms. Of course, given the relatively few number of cases, the results should be interpreted with caution. Still, with the exception of CML, median onset age for patients in this cohort was 10–20 years earlier than the general population median. While this, in part, reflects the young age of our cohort, it further emphasizes the increased risk of hematological malignancies in this population. The SIR for hematological cancers according to age suggests that it is indeed the youngest SLE patients who have the highest relative risk when comparing to age- and sex-matched general population rates.

The most common non-lymphoma hematological malignancies observed in our SLE cohort were myeloid types (MDS and AML). This is in contrast to the general population, where lymphoid types are 1.7 times more common than myeloid types, when lymphomas are excluded [2]. Our observation is similar to previous studies on myeloid malignancies and autoimmune conditions in the literature. A population-based case-control study of

hematopoietic malignancies, using SEER-Medicare data of 13,486 myeloid malignancy patients and 160,086 population-based controls, found that SLE patients had an increased risk of both AML [odds ratio (OR) 1.92] and MDS (OR 1.82) [25]. Another article on a nested case-control study, using Swedish registers as well as published case reports of SLE and AML, concluded that not only do SLE patients have an increased risk of developing myeloid leukemia, but that this risk is actually restricted to a subset of patients with hematological aberrations such as prolonged leukopenia (OR 14) and to a lesser extent, thrombocytopenia (OR 3.3) [26]. Furthermore, this study demonstrated that 30.4% of their AML cases were preceded by MDS – a rate comparable to the general population [27].

A limitation of our study is that most of our participating centers did not provide information on clinical features, such as disease activity or drugs. We were therefore unable to look at these variables in the cases. Moreover, with only 9 myeloid leukemia cases (7 AML and 2 CML), we would have difficulty confirming any previously reported association of this malignancy with cytopenias.

Conclusion

In summary, we described the demographics of those who developed hematological malignancies in our international cohort of 16,409 SLE patients. Myeloid malig-

nancies such as MDS and AML were the most common; a finding which has been reported before but has not, to date, received much attention. Most of our non-lymphoma hematological malignancy cases were younger than the general population median age-of-onset, although this could simply reflect our cohort demographics. We were surprised by the very high predominance of black race/ethnicity among the SLE patients who developed multiple myeloma. This requires further investigation.

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