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Malignancy in Pediatric-onset Systemic Lupus Erythematosus

Sasha Bernatsky¹, Ann E. Clarke², Omid Zahedi Niaki¹, Jeremy Labrecque¹, Laura E. Schanberg³, Earl D. Silverman⁴, Kristen Hayward⁵, Lisa Imundo⁶, Hermine I. Brunner⁷, Kathleen A. Haines⁸, Randy Q. Cron⁹, Kiem Oen¹⁰, Linda Wagner-Weiner¹¹, Alan M. Rosenberg¹², Kathleen M. O'Neil¹³, Ciarán M. Duffy¹⁴, Emily von Scheven¹⁵, Lawrence Joseph¹, Jennifer L. Lee¹, and Rosalind Ramsey-Goldman¹⁶

¹Research Institute of the McGill University Health Centre, Montreal, QC

²University of Calgary, Calgary, AB

³Duke University Medical Center, Durham, NC

⁴The Hospital for Sick Children, Hospital for Sick Children Research Institute, University of Toronto, Toronto, ON

⁵Seattle Children's Hospital, Seattle, WA

⁶Columbia University Medical Center, New York, NY

⁷Cincinnati Children's Hospital Medical Center, Cincinnati, OH

⁸Hackensack University Medical Center, Hackensack, NJ

⁹University of Alabama at Birmingham, Birmingham, AL

¹⁰University of Manitoba, Winnipeg, MB

¹¹University of Chicago, Chicago, IL

¹²University of Saskatchewan, Saskatoon, SK

¹³Riley Hospital for Children, Indianapolis, IN

¹⁴Children's Hospital of Eastern Ontario, Ottawa, ON

¹⁵University of California, San Francisco, San Francisco, CA

¹⁶Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

Objective—To determine cancer incidence in a large pediatric-onset systemic lupus erythematosus (SLE) population.

Methods—Data was examined from 12 pediatric SLE registries in North America. Patients were linked to their regional cancer registries to detect cancers observed after cohort entry, defined as date first seen in the clinic. The expected number of malignancies was obtained by multiplying the

Authors' contributions

All authors contributed to the study design and/or data collection and/or data analysis, and interpretation and preparation of results. In addition, all authors revised the manuscript and approved the final version.

person-years in the cohort (defined from cohort entry to end of follow-up) by the geographically matched age, sex, and calendar year-specific cancer rates. The standardized incidence ratio (SIR; ratio of cancers observed to expected) was generated, with 95% confidence intervals (CI).

Results—A total of 1,168 patients were identified from the registries. The mean age at cohort entry was 13 (standard deviation 3.3) years, and 83.7% of the subjects were female. The mean duration of follow-up was 7.6 years resulting in a total observation period of 8,839 years spanning the calendar period 1974–2009. During follow-up, fourteen invasive cancers occurred (1.6 cancers per 1,000 person-years, SIR 4.13, 95% CI 2.26, 6.93). Three of these were hematologic (all lymphomas), resulting in an SIR for hematologic cancers of 4.68 (95% CI 0.96, 13.67). SIRs were increased for both male and female patients, and across age groups.

Conclusion—Although cancer remains a relatively rare outcome in pediatric-onset SLE, our data do suggest an increase in cancer for patients followed an average of 7.6 years. Approximately one-fifth of the cancers were hematologic. Longer follow-up, and study of drug effects and disease activity, is warranted.

Introduction

Several reports have been published over the past decade examining malignancy risk in rheumatic disease populations. To date, the only cohort study published specifically on pediatric-onset systemic lupus erythematosus (SLE) was the preliminary report of our multi-centre cohort(1). The objective of this current report is to present the final updated analyses on cancer incidence in an expanded multi-centered clinical population of pediatric-onset SLE, including previously analyzed data as well as data from three additional centres.

Materials and Methods

Our analyses included four pediatric rheumatology clinics in Canada and eight in the United States (Table 1). Patients were linked to their regional cancer registries to detect observed cancers occurring after cohort entry, defined as date first seen in the SLE clinic. The end of follow-up was defined as the date of cancer registry linkage, thus allowing the inclusion of subjects who reached adulthood. The expected number of malignancies was obtained by multiplying the person-years in the cohort (defined from cohort entry to end of follow-up) by the geographically matched age-, sex-, and calendar year-specific cancer rates, and summing overall person-years of observation.

The standardized incidence ratio (SIR; ratio of cancers observed to expected) was generated for overall malignancies and for hematologic malignancies, along with 95% confidence intervals (CIs), based on the assumption of cancer occurrence as a Poisson-distributed variable. Results were also stratified by sex and age group of person-time (categorized into 0–19 and ≥ 20 years of age).

The study was approved by the ethics boards of all participating institutions including the McGill University Health Centre ethics review board (# GEN-06-031).

Results

Across the 12 cohorts, there were a total of 1,168 patients. The mean age at cohort entry was 13 (standard deviation, SD 3.3) years, and 83.7% of the subjects were female. The mean duration of follow-up was 7.6 years (SD 6.4, interquartile range 3.4 to 10.0 years) resulting in a total observation period of 8,839 years during the calendar period of 1974 to 2009. During the follow-up period, 14 invasive cancers occurred, compared to 3.39 expected (4.13, 95% CI 2.26–6.93). Three were hematologic malignancies (all non-Hodgkin's lymphoma, NHL), and the other cancers included two head and neck squamous cell carcinomas (tongue and nasopharynx) and one each of glioblastoma, thyroid cancer (papillary adenoma), breast cancer (infiltrating duct carcinoma), adenocarcinoma not otherwise specified (NOS), and three cancers whose morphology and histology codes were indeterminate. We did not detect multiple malignancies in the same subjects.

The SIR for NHL was increased at 18.6 (95% CI 3.84, 54.4). One of the malignancies occurred in the first year of follow-up. Nevertheless, excluding all events and person-time in the first year of follow-up, the SIR for cancer remained elevated at 4.35 (95% CI 2.31, 7.44).

Stratifying by sex, the SIR for all cancers was 6.26 (95% CI 1.29, 18.28) in males and 3.78 (95% CI 1.89, 6.76) in females. For cancer overall, stratifying results according to person-time contributed within age groups, the SIR was 3.29 (95% CI 0.68, 9.62) for events and person-time occurring up to age 20, which was similar to the SIR for events and person-time occurring after the age of 20 (SIR 4.44, 95% CI 2.22, 7.94).

Discussion

This present study contributes novel and compelling data on increased malignancy risk in pediatric-onset SLE. Comparing the cancer rates in 1,168 patients from 12 centres, the data suggest a higher cancer risk in pediatric-onset SLE versus the general population, which confirms our earlier preliminary report(1). The increase in cancer in pediatric-onset SLE appears in part to be driven by hematologic malignancies, which is similar to what is known in adults with SLE(2). Of course, in absolute terms, this still translates into relatively few events (1.6 cancers per 1,000 person-years), which is somewhat reassuring.

A limitation of this study is that patients may have developed cancer after relocating to another state or province, thus under-representing the true cancer incidence in this cohort. If that under-representation was present to a significant degree, it would likely bias the results towards the null. Thus, this potential limitation does not likely explain the results.

Unfortunately, we are unable to comment on the relative importance of SLE disease activity itself, versus the effect of therapeutic drugs. In adults with SLE, we have found mainly an association between lymphoma and cyclophosphamide, and possibly cumulative steroid use, though not specifically with disease activity(3). We are also unable to evaluate the effects of race/ethnicity, or of SLE clinical factors such as type of organ involvement and cumulative disease activity, as those data were not available from all the centres participating in our study.

The few published case reports of malignancy in pediatric-onset SLE(4–6) have documented Hodgkin lymphoma, NHL, and acute lymphoblastic leukemia (ALL). The three lymphoma cases in the literature occurred in teenagers after several years of SLE duration, while the fourth case, ALL, occurred in a very young SLE patient, a 6-year-old within one year of SLE diagnosis. Two additional case reports described the simultaneous presentation of pediatric-onset SLE (fulfilling ACR criteria) and ALL, at ages 3 and 7.(7, 8) As we noted in our earlier manuscript, this suggests there may be a bimodal age-related pattern of hematological malignancies in pediatric-onset SLE. Alternatively, the first peak might actually represent, at least in part, paraneoplastic presentations masquerading as pediatric-onset SLE. As noted, when we excluded the malignancies (and person-time) that occurred in the first year after the SLE diagnosis, the SIR remained elevated.

In terms of a comparison with what is known in adults, an increased hematologic cancer risk has also been demonstrated in adults with SLE (especially NHL, with an SIR 4.39, 95% CI 3.46, 5.49 in adults(2). Interestingly, in those analyses adult SLE patients with the highest cancer risk relative to the general population were in the youngest age group (below age 40 years), perhaps supporting the risk of cancer associated with the cumulative burden of SLE and its treatment. These data may also suggest moderating effects for age (of SLE onset) on cancer risk, with greater cancer risk in a developing child versus an adult.

In our pediatric-onset SLE population, the point estimate for the NHL SIR was higher than current estimates for NHL relative risk in adult-onset SLE. However, the 95% CI for our NHL SIR estimate was very wide, and so it is not possible to definitively conclude that the relative risk of NHL in pediatric-onset SLE is higher than in adult-onset SLE. Unlike many cancers in adults, childhood cancers are often not strongly linked to lifestyle or environmental risk factors, but instead, may be more likely the result of genetic factors(9). Though it is unlikely that a single genetic factor explains the link between NHL and SLE, we are beginning to understand some of the potential genetic links between malignancy and adult SLE.(10)

There is also current interest in malignancy risk for other pediatric-onset rheumatic diseases, including juvenile idiopathic arthritis (JIA). Using similar methods as the current study, we found rather different results in JIA, with nine cancers observed in 5,294 patients over 36,063 person-years, and an overall SIR that was not elevated(11). Still, in those juvenile arthritis analyses, three of the nine cancers were hematologic, potentially representing a signal for an increased risk of hematological cancer in juvenile arthritis, although it is not as striking as what we saw in our current analyses of pediatric-onset SLE.

Conclusion

In this analysis of the largest ever sample of patients with pediatric-onset SLE followed at 12 centres in North America, using tumor registry linkage, cancer was a relatively infrequent outcome. However, the analyses are consistent with an increased risk of cancer compared to the general population, which appears to be driven at least in part by hematologic risk. Longer follow-up of this population is necessary to accurately capture cancer risk in the later adult years. Additional efforts to evaluate the effects of race/ethnicity, or of clinical factors

(such as type of organ involvement, disease activity and drug exposures) on malignancy risk may help to better guide the care of patients with pediatric-onset SLE.

Acknowledgments

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Table 1

List of participating centers:

Centers	N
CANADA	
Hospital for Sick Children, Toronto, Ontario	365
Montreal Children's Hospital, Montreal, Quebec	21
University of Manitoba, Winnipeg, Manitoba	45
University of Saskatchewan, Saskatoon, Saskatchewan	34
United States	
Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio	95
Columbia University Medical Center, New York, New York	133
Duke University Medical Center, Durham, North Carolina	76
Hackensack University Medical Center, Hackensack, New Jersey	111
Seattle Children's Hospital, Seattle, Washington	169
University of Alabama at Birmingham, Birmingham, Alabama	55
University of Chicago, Chicago, Illinois	34
University of Oklahoma Health Science Centre, Oklahoma City, Oklahoma	30
TOTAL	1,168