Systemic Lupus Erythematosus and Malignancies: A Review Article

Basile Tessier-Cloutier, MD[a], Ann E. Clarke, MD, MSc[b], Rosalind Ramsey-Goldman, MD, DrPh[c], Caroline Gordon, MD[d], James E. Hansen, MD[e], Sasha Bernatsky, MD, PhD[a,*]

KEYWORDS

• Systemic lupus erythematosus • Cancer • Malignancy • Epidemiology

KEY POINTS

- Systemic lupus erythematosus (SLE) is associated with a small overall increased incidence of malignancy, including a prominent (3-fold) increased risk of non-Hodgkin lymphoma (NHL), but a marked decreased risk of other malignancies (such as breast cancer).
- Although NHL is increased 3-fold in SLE, it is still a rare event (about 1 event in 2000 person-years of follow-up, or <1% of patients followed long term).
- Inadequate viral clearance in SLE could promote the development of certain malignancies such as cervical cancer.
- To date, the evidence does not clearly point toward inherent SLE activity as a risk factor for cancer, although more research is needed. Regarding drugs and cancer risk, there are trends in the data suggesting that cyclophosphamide may be a risk factor for later hematological cancers in SLE, but even this drug exposure does not explain most of the altered cancer risk profile in SLE.
- Cancer preventive methods such as smoking cessation and regular cancer screening (eg, for cervical and breast malignancies) are important in the SLE population.

Disclosure: None.

[a] Division of Clinical Epidemiology, McGill University Health Centre, 687 Pine Avenue, V Building, Montreal, Quebec H3A 1A1, Canada; [b] Division of Rheumatology, University of Calgary, 3330 Hospital Drive Northwest, Calgary, Alberta T2N 4N1, Canada; [c] Division of Rheumatology, Northwestern University Feinberg School of Medicine, McGaw Pavilion, 240 East Huron Street, Suite M-300, Chicago, IL 60611, USA; [d] Division of Rheumatology, College of Medical and Dental Sciences, University of Birmingham, Edgbaston B15 2TT, UK; [e] Department of Therapeutic Radiology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06520, USA
* Corresponding author. Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, 687 Pine Avenue West, V Building, Room V2.09, Montreal, Quebec H3A 1A1, Canada.
E-mail address: sasha.bernatsky@mcgill.ca

Rheum Dis Clin N Am 40 (2014) 497–506
http://dx.doi.org/10.1016/j.rdc.2014.04.005 **rheumatic.theclinics.com**
0889-857X/14/$ – see front matter

INTRODUCTION

Systemic lupus erythematosus (SLE), an autoimmune disorder with complex environmental and genetic interactions, affects approximately 1 in 1000 women in North America.[1] In the last 5 decades, advances in management have improved 5-year survival to more than 90%.[2] The longer survival translates, in some cases, to considerable long-term morbidity, including distinct cancer risk profiles.

For more than a decade, autoimmune disorders such as SLE have been associated with an increased cancer risk, particularly for certain cancer types.[3] However, the underlying pathophysiologic mechanisms are still not fully understood. In SLE, the proposed pathways currently include a possible link with medications, inherent immune system abnormalities,[4] an overlap with clinical syndromes such as Sjögren,[5] viral infections, as well as traditional lifestyle cancer risk factors.[6] The most recent evidence shows a slight (standard incidence ratio [SIR], 1.14; 95% confidence interval [CI], 1.05–1.23) increase in cancer risk overall.[7] However, considerable variation between specific cancer subtypes occurs within these data. The risk of hematologic cancers, especially non-Hodgkin lymphoma (NHL), is increased about 3-fold,[7–10] although breast, endometrial, and possibly prostate and ovarian cancers seem to be associated with a decreased risk in the SLE population.[7,11,12]

HEMATOLOGIC CANCERS

An increased incidence of hematologic malignancies in the SLE population was initially suggested more than 3 decades ago[13] and has now been supported by many studies.[8–10,14] Based on incidence and mortality data generated from the large, multicentre, international SLE cohort contributed by Systemic Lupus International Collaborating Clinics (SLICC) and other investigators, it was observed that NHL incidence (SIR, 3.02; 95% CI, 2.48–3.63) and mortality (standardized mortality ratio [SMR], 2.8; 95% CI, 1.2–5.6) risks were particularly increased in patients with SLE, compared with expected general population cancer rates.[7,15] Further studies identified an increased risk for Hodgkin lymphomas (HL)[16,17] and leukemia[7–9] in patients with SLE. One study[18] suggests that the risk of developing multiple myeloma might also be increased in patients with SLE, but additional studies are required to confirm this association.

Genetic changes, such as the t(14:18) translocation (which results in overexpression of BCL2 caused by juxtaposition of the BCL2 gene next to an immunoglobulin gene) have been linked to lymphoma development.[19] In addition, a polymorphism involving the interleukin (IL)-1 receptor antagonist has been noted to be significantly overexpressed in a group of patients with secondary acute myeloid leukemia.[20]

SLE activity has been invoked as a potential factor to explain the increased lymphoma risk in SLE. Although increased disease activity has been associated with higher cancer risk in certain autoimmune disorders (for example, in rheumatoid arthritis [RA], higher disease activity was shown to be a marker of lymphoma risk, in one study),[21] the immune system is also responsible for targeting abnormal cells.[22,23] Thus, the effects of disease activity in one rheumatic disease, such as RA, may be different in another, such as SLE. Case-cohort analyses of lymphoma cases in the large international multicentre SLE cohort revealed no clear relationship between disease activity and lymphoma risk (hazard ratio [HR], 0.68; 95% CI, 0.36–1.29).[24,25]

Diffuse large B-cell lymphoma (DLBCL) is the most increased subtype of lymphoma in SLE.[16] DLBCL lesions arise from activated lymphocytes, the cell line responsible for most of the inflammation in autoimmune disorders such as SLE, which suggests that the chronic inflammatory state seen in patients with SLE contributes to the cancer risk