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Malignancy Risk in Patients with Inflammatory Eye Disease Treated with Systemic Immunosuppressive Therapy

A Tertiary Referral Cohort Study

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Objective: To ascertain whether patients on long-term systemic immunosuppressive therapy for inflammatory eye disease (IED) are at increased risk of malignancy.

Design: A single-center, retrospective cohort study.

Participants: We included 190 adults with IED treated with corticosteroids only (n = 58) or systemic immunosuppression (n = 132) for ≥6 months between 1985 and 2007. Immunosuppressed patients were treated with antimetabolites, T-cell inhibitors, and/or alkylating agents.

Methods: Incident malignancies were ascertained by self-report and confirmed by medical record review. Multiple malignancies in a single patient were counted, except for nonmelanoma skin cancer (NMSC), where only the first was counted. Standardized incidence ratios (SIRs) were calculated by malignancy type. Cox regression models were used to compare malignancy incidence by treatment type.

Main Outcome Measures: Risk of malignancy relative to the general population and within the cohort.

Results: During a median 7.34 years of follow-up, 25 malignancies were observed in 17 patients, namely, 2.10 per 100 person-years and 0.43 per 100 person-years in the immunosuppressed and corticosteroid only groups, respectively. In the immunosuppressed group, the most common malignancies were NMSC (n = 11) and non-Hodgkin's lymphoma (NHL; n = 4) and malignancy risk was significantly increased compared with the general population for any malignancy (SIR, 4.39; 95% CI, 2.78–6.59) and for any malignancy excluding NMSC (SIR, 4.16; 95% CI, 1.67–8.57). Significantly elevated SIRs were observed for NMSC and NHL in those treated with immunosuppressive agents. Compared with the corticosteroid treatment–only group, the immunosuppressed group was at an increased risk of any malignancy (adjusted hazard ratio, 4.36; 95% CI, 1.02–18.7), but not first malignancy (n = 17; adjusted hazard ratio, 2.56; 95% CI, 0.57–11.5). No cancer-related deaths were observed.

Conclusions: Our findings suggest that patients with IED treated with systemic immunosuppressive therapy are at increased risk of malignancy; however, the increase in absolute risk was modest. The types of malignancies observed at excess risk are similar to those observed in solid organ transplant recipients and patients with autoimmune diseases treated with systemic immunosuppression. Immunosuppressive therapy remains an important treatment modality in IED; however, patients may benefit from targeted malignancy-prevention strategies and long-term clinical follow-up. These findings require validation by a prospective, long-term, population-based cohort study. *Ophthalmology 2015;122:265-273 © 2015 by the American Academy of Ophthalmology.*

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Inflammatory eye disease (IED), including uveitis, scleritis, and mucous membrane pemphigoid, is responsible for 10% of blindness in the United States.[1] Therapy for IED aims to control the disease, maintain vision, and ensure quality of life. The long-term use of systemic corticosteroids has proved a double-edged sword, effective at reducing the inflammation, but associated with significant ocular and systemic side effects.[2] Immunosuppressive drugs are used as corticosteroid-sparing agents and when the ocular inflammation is severe, refractory, or a manifestation of a specific disease, such as Behçet's disease.[3]

The observation that systemic immunosuppression may predispose to malignancy has been a major concern since the early findings of increased malignancy risk in immunosuppressed solid organ transplant recipients.[4–6] It is estimated that 10% to 15% of patients who receive a kidney allograft will develop a malignancy within 10 years of initiating immunosuppressive therapy.[6–8] The overall risk of developing a malignancy in the solid organ transplant population is 3- to 4-fold greater than the general population, with nonmelanocytic skin cancer (NMSC) and non-Hodgkin's lymphoma (NHL) being the most commonly

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observed malignancies.[9,10] Particularly relevant in Australia, NMSC is associated with high levels of ambient solar radiation and correspondingly high rates of NMSC.[11] In addition, NHL is the most common malignancy in patients with rheumatoid disease who require long-term immunosuppressive therapy.[12] Similarly, the risk of NHL development in patients with systemic lupus erythematous was estimated to be 7-fold greater than the general population.[13] In contrast with solid organ transplant recipients and patients treated for rheumatoid arthritis, patients with IED will not necessarily be on lifelong immunosuppression therapy.[3,14] Furthermore, although the typical dosages of immunosuppressive agents are one half to one third lower in patients with IED compared with transplant recipients, depending on the therapeutic agent, they are similar to those with autoimmune disease.[3]

The potential mechanisms of carcinogenesis owing to immunosuppression have been discussed previously. Immunosuppressive agents may increase susceptibility to infection by oncogenic viruses, impair immune surveillance, and have a direct deleterious effect on DNA (e.g., alkylating agents).[15]

Malignancy risk in patients with IED treated with systemic immunosuppressive therapy has been assessed; however, outcomes varied significantly between studies.[16–18] A retrospective cohort study based in the United States of 2340 patients with IED treated with immunosuppressive therapy found no excess risk of death or death from malignancy.[16] However, this study was unable to quantify the risk of nonfatal malignancies and relied on the attribution of underlying cause of death to assess malignancy risk.[16] The single prior study to ascertain incident malignancies reported no difference in incidence between IED patients prescribed corticosteroids (n = 207) and those on ≥1 immunosuppressive agents (n = 330).[17] This study followed patients for a median of 1.34 years, which may be insufficient, with studies suggesting ≥5 years of follow-up is necessary.[19–21] It is possible that these studies did not adequately address the risk of neoplasia and we hypothesized that patients with IED who receive long-term systemic immunosuppressive therapy have an increased risk of malignancy. To address this risk, we performed a retrospective cohort study examining the incidence of de novo invasive malignancy in patients with IED managed with and without systemic immunosuppression at a single tertiary hospital. We computed malignancy risk relative to the general population (adjusted for age and sex), and malignancy risk in those treated with immunosuppressive agents compared with those treated with corticosteroids alone.

Methods

Study Design and Population

We performed a single-center, retrospective, cohort study at St Vincent's Clinic, Sydney, New South Wales, Australia. Patients with IED diagnosed and treated with systemic corticosteroids and/or immunosuppressive agents at the clinic between 1985 and 2007 were identified. All patients were assessed by an ophthalmologist and physician at presentation and during follow-up. Patients >15 years of age at diagnosis and treated for ≥6 months were eligible for this study. Patients reviewed only for a second opinion and those treated by a specialist outside the Clinic were ineligible. Patients with rheumatoid arthritis, Sjögren's syndrome, psoriasis, systemic lupus erythematosus, or hepatitis B/C infection were excluded, because these diseases are associated with an increased risk of malignancy. Patients with a history of malignancy before therapy (n = 4) were not excluded, but they did not contribute person-years at risk for that malignancy type.

Patients consented to participate in the study and to the retrieval of additional medical records if required. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Human Research Ethics Committee approval was obtained from St Vincent's Hospital.

Data Collection

Medical records were reviewed and information regarding IED diagnosis, type, and duration of treatments were obtained. The date of diagnosis, nature, and anatomic location of the IED and any underlying autoimmune or syndrome features were recorded. The date that corticosteroid and immunosuppressive drugs were started and stopped, the type of drug, and their dosage were collected.

A questionnaire was given to all patients at the clinic or mailed to their home address. For patients whose eyesight was poor, they could opt to answer the questions by telephone. Telephone contact was attempted if the patient did not return the questionnaire. An average of 5 phone calls was made and if there was no forwarding number the referring doctor was contacted to ensure current contact information. Patients were classified as "lost to follow-up" if they could not be contacted to complete the questionnaire. Information obtained from the questionnaire included personal history of malignancy, history of malignancy in any first-degree relatives, smoking history, and skin complexion.

Self-reported malignancy diagnoses were confirmed by medical record review and clinical examination. All relevant histopathology and immunohistochemistry reports were obtained from the treating doctor. The date of diagnosis, site, and type of each malignancy were recorded. Solid (nonhematopoietic) malignancies were classified according to the International Classification of Disease (ICD), 10th revision, and hematopoietic malignancies were classified according to the ICD for Oncology, 3rd edition. Where applicable, the date of death was recorded.

Malignancy incidence rates for the New South Wales population were obtained from the New South Wales Central Cancer Registry by 5-year age group, calendar year, and sex for 1985 to 2007; incidence rates for 2007 were applied to the 2008 through 2012 follow-up years. The Cancer Registry is population based and all cases of primary invasive malignancies, except NMSC, must be reported by statute. Because NMSCs are not notifiable malignancies in New South Wales, a large NMSC incidence survey (57 215 participants) conducted in 2002 was used to estimate the incidence of cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in the general population by sex and age group (<40, 40–49, 50–59, 60–69, ≥70 years).[11] These rates were applied to all calendar years of follow-up.

Statistical Analyses

Treatment regimen was classified as corticosteroids only or corticosteroids and immunosuppression; IED was classified as idiopathic or associated with an underlying systemic disease or IED syndrome.