Risk of malignancy in patients with rheumatic disorders

1 Introduction

Patient with rheumatic diseases are at increased risk of malignancies. The most widely known malignancies associated with rheumatic diseases other than inflammatory myositis include lymphoproliferative disorders and skin cancer. Treatment options of rheumatic diseases such as disease-modifying anti-rheumatic drugs (DMARDs) and biologics may also increase the risks of different malignancies. It is important to be aware of the association of malignancy with rheumatic diseases and anti-rheumatic agents, in order to guide our decision of treatment in these conditions.

The risk of malignancies in patients with common rheumatic diseases is reviewed here. The inflammatory myopathies, which are well-recognized paraneoplastic conditions, will not be included in this review.

2 Malignancy in individual rheumatic disease

2.1 Malignancy and RA

The risk of malignancy has been more extensively studied in patients with rheumatoid arthritis (RA) than in other rheumatic diseases. In a large study in California linking RA to Cancer Registry data for 1991–2002, including patients observed for a total of over 400,000 person years, an increased risk of developing lymphoproliferative cancers was found among both women and men with RA [1]. In a cohort of Swedish population studying the relative risk of malignancy in patients with RA comparing to the general population published in 2005, it was found that there was an increased risk of lymphoma, lung cancer and non-melanoma skin cancer in patients with RA, with the relative risks of 1.90 (1.70–2.10), 1.48 (1.33–1.65), and 1.66 (1.50–1.84), respectively [2]. From the meta-analysis in 21 publications from 1990 to 2007 on risk of malignancy in patients with RA, it was found that the risk of lymphoma was increased around twofolds standardized incidence ratio (SIR) (2.08, 95% CI 1.8, 2.39), with a greater risk of both Hodgkin’s and non-Hodgkin’s lymphoma [3]. Risk of lung cancer was also increased. Overall SIR for malignancy was slightly increased at 1.05. The overall increased risk was largely due to lymphoproliferative cancers.

Incidence of lymphoma was found to be associated with the severity of RA. Retrospective case-controlled studies were performed to assess the correlation of incidence of lymphoma with severity of RA. Around 400 lymphoma cases were matched with controls in Sweden...
from 1964 to 1999. Disease activity was assessed with a score combining erythrocyte sedimentation rate (ESR), swollen/tender joints, and physician global assessment. Results showed that higher disease activity over time and worsening physical function disproportionately affects risk of lymphoma in patients with RA. Most common type of lymphoma was diffuse large B-cell type (48%) [4].

Mortality rates of cancer were not well studied because of methodological difficulties. A cohort study of 789 randomly selected patients with RA from 1999 to 2005 in Spain comparing the incidence and mortality of cancer showed that cancer mortality in RA did not differ from that expected in general population, with the standardized mortality ratio being 1.0 (95% CI: 0.5–1.7). By cancer site, observed mortality was higher than expected for lung cancer in men and for kidney cancer in both gender. [5]

2.2 Malignancy and SLE

Several studies suggested an increased risk of malignancy in patients with systemic lupus erythematosus (SLE), with particular increased rates of both Hodgkin’s and non-Hodgkin’s lymphoma. A large multicenter international cohort of 9,574 patients with an average follow-up of 8 years confirmed an increased overall risk of cancer (SIR 1.15) in patients with SLE, with risk increase mainly driven by increased risk of lymphoproliferative cancer (SIR 2.75) [6]. Data also suggested a significant increased risk of lung cancer (SIR 1.37) and hepatobiliary cancer (SIR 2.60). Reduced risk of hormone-sensitive cancers including breast cancer, ovarian cancer, and endometrial cancers was observed. Other studies also reported possible increased risk of malignancy including thyroid cancer, breast cancer, and squamous cell skin cancer, as well as cervical dysplasia/cancer.

Increased risks of the development of malignancy in SLE may be related to greater disease severity, longer disease duration, overexpression of Bcl-2-oncogenes, and viral infection, especially Epstein-Barr Virus. [7] Leucopenia has also been shown to be a risk factor for the development of leukemia in patients with SLE. This may have an implication for bone marrow examination in patients with SLE with long-standing leucopenia and anemia.

2.3 Malignancy and Sjogren’s syndrome

Lymphoproliferative disease is the main cancer that is associated with primary Sjogren’s syndrome (SS). Lifetime risk of non-Hodgkin’s lymphoma in patients with primary SS has been reported to be 5–10% [8]. The majority of lymphomas seen in these patients are mucosa-associated lymphoid tissue (MALT) lymphomas and large B-cell lymphomas.

2.4 Malignancy and systemic sclerosis

Risk of malignancy in patients with diffused systemic sclerosis appears to be increased, but with conflicting results. Most significantly increased risks include lung cancer and non-Hodgkin’s lymphoma [9]. Risk of oropharyngeal and esophageal cancer has also been reported to be increased.

2.5 Malignancy and vasculitis

Vasculitis may be a manifestation of a paraneoplastic rheumatological syndrome. There is no major evidence to support an association between primary systemic vasculitis and cancer in overall. One study in Denmark suggested an increased risk of non-melanoma skin cancer within 2 years of diagnosis of vasculitis in granulomatosis with polyangiitis [10].

2.6 Malignancy and spondyloarthropathies

There is no major association with cancer in overall for patients with psoriatic arthropathy or ankylosing spondylitis (AS). Patients with AS do not appear to be at increased risk of malignant lymphoma.

3 Malignancy related to pharmacological treatment in rheumatic diseases

3.1 NSAIDs and steroids

Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids do not appear to be associated with increased risk of malignancy in patients with RA or other rheumatic diseases [11]. In a cohort study of patients with RA in Sweden, a total duration of oral steroid treatment less than 2 years was not associated with lymphoma risk, while treatment over 2 years was associated with a lower lymphoma risk [12], which may be accountable by a lower disease activity.
3.2 DMARDS

DMARDS including sulfasalazine, hydroxychloroquine, gold, and penicillamine do not appear to be associated with increased risk of cancer. Azathioprine may be associated with an increased risk of lymphoproliferative disorders in patients with RA and SLE. Methotrexate does not appear to increase overall malignancy risk in rheumatic diseases, though some reports suggest that risk of lymphoproliferative diseases may be increased.

Cyclophosphamide is well known to have an increased risk of cancer, with significantly elevated risks of lymphoma, leukemia, and bladder cancers [12]. Risk of bladder cancer is related to metabolites of cyclophosphamide, especially acrolein. It was recommended that the use of cyclophosphamide to be restricted to less than 6 months and only in life- or organ-threatening diseases. Risk of bladder cancer may be less with use of pulse intravenous doses than with the use of daily oral administration, as it is believed that the increased risk of bladder cancer is dose dependent. Concurrent use of intravenous mesna is advocated, which inactivates acrolein in urine and hence may reduce the risk of bladder cancer.

Cyclosporin is associated with increased risk of lymphoproliferative diseases in solid organ transplantation. The association with cancer in rheumatic diseases is not well studied. For leflunomide and Mycophenolate mofetil, no increased risk of malignancy was identified. It was noted that combination of immunosuppressants may further increase the risk of malignancy [13].

3.3 Biologics

Anti-TNF (tumor necrosis factor) agents are associated with increased risk of malignancies. Meta-analysis of adalimumab and infliximab trials in RA done in 2006 revealed a threefold increased risk of malignancies. Lymphomas and non-melanoma skin cancers take up the majority of types of cancers in the meta-analysis [14]. A recent larger meta-analysis from 74 randomized controlled trials (RCTs) of TNF inhibitors including adalimumab, etanercept, and infliximab in 2011 revealed twofold increased risk for non-melanoma skin cancers only, but not increased for other cancers [15]. Combination of methotrexate and anti-TNF may give rise to the highest risk of non-melanoma skin cancer among patients with RA, compared to that of methotrexate monotherapy, steroid monotherapy, and anti-TNF monotherapy [16].

For non-anti-TNF agents, rituximab was found to have no increase in incidence of malignancy excluding non-melanoma skin cancer in a pooled analysis of safety data from patients with RA in RCTs with more than 5,000 patient-years of exposure. Rituximab has, therefore, been suggested as a preferred biologic for patients with RA who have had a history of cancer other than non-melanoma skin cancer. There is less experience with long-term treatment with abatacept and tocilizumab. So far no evidence for increased malignancies is noted for these agents.

3.4 Current guidelines on choice of biologics in prior malignancy

According to the 2015 ACR guidelines on choice of biologics in prior malignancy, it was suggested that for previously treated or untreated skin cancer, DMARDs should be used over biologics and tofacitinib in melanoma or non-melanoma skin cancer.

For previously treated lymphoproliferative disorders, use of rituximab, combination of DMARDs, abatacept, or tocilizumab was suggested over use of anti-TNF agents. For previously treated solid organ malignancy, recommendation was the same as in patients without this condition.

References