

Malignancies Associated with Treatment of Rheumatic Diseases - to be or not to be

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Abstract

Malignancies associated with rheumatic diseases are more common than healthy individuals. What is actually the cause of increased malignancies in rheumatic diseases: autoimmunity, inflammation, immune regulation deficits? There was no a clear answer, but malignancies associated with rheumatic diseases is a certainty. Medication is also involved in the development of malignancies. Therefore we decided to address the involvement of rheumatic diseases medication in malignancies development.

Keywords: Rheumatic Diseases; Medication; Malignancy

Introduction

The immune system is a barrier against neoplasms. Treatment of rheumatic diseases is done with modulators of the immune system. Thus immunosuppressive therapy may favor malignant cell growth. Cumulative dose of immunomodulatory agents and long treatment increase the risk of cancer development [1,2].

It is known that inflammation is a component in cancer initiation and progression and therefore the reduction of systemic inflammation may reduce cancer risk [3].

The association between several systemic autoimmune diseases and lymphoproliferative malignancies is compatible with the concept of chronic activation of B cells and T cells as a driving force for the development of cancer comorbidity [4].

Methotrexate

Methotrexate is an antimetabolite. By inhibiting dihydrofolate reductase it reduces the production of purine nucleotides that are essential in DNA synthesis and cell division [5].

There are no clear data to suggest a direct role of methotrexate in developing malignancies. There are some reports that suggest an increased risk of lymphomas. Risk factors are represented by intense immunosuppression and severe disease, and increased frequency of latent infection with Epstein-Barr virus [6].

Cyclophosphamide

Cyclophosphamide is an alkylating agent from the oxazophosphorine group. It is metabolised via the cytochrome P450 enzyme system. Its mechanism in the treatment of autoimmune diseases is not well known. In patients with rheumatoid arthritis, Cyclophosphamide acts by suppressing T-helper cell function with prolonged reduction of B cells [1].

Cyclophosphamide increases the risk of developing some kinds of cancers such as bladder cancer, lymphoma and leukemia. Bladder cancer which is the most common malignancy associated with Cyclophosphamide may occur many years after this medication. The risk of development of malignancies is related to long duration of treatment and higher total dose administered [7,8].

Azathioprine

Azathioprine, a purine analogue, interferes with DNA synthesis which is necessary for growth and cell division [9].

Risk of malignancy associated with Azathioprine therapy is significant and depends on cumulative dose and duration of treatment. Oncologic side effects have included an increased risk of lymphoproliferative disorders, particularly malignant lymphoma. Concomitant use of Azathioprine with other immunosuppressive agents enhances the risk of developing neoplasia [8,10].

Cyclosporine

Cyclosporine inhibits T cell activation and the generation of T cell lymphokine production [1,3].

There are no clear evidence to support the relationship between therapy with cyclosporine and developing malignancies in patients with rheumatic diseases. It is known that patients with organ transplantation may develop lymphoproliferative disorders [10].

Leflunomide

Leflunomide is a selective inhibitor of de novo pyrimidine synthesis. The active metabolite of leflunomide, A771726, is an immunosuppressive compound that has been shown to be an antiproliferative agent for mononuclear and T-cells [11].

Leflunomide therapy does not increase the risk of malignancy in patients with rheumatic diseases [6].

Tumor necrosis factor inhibitors

Biologic response modifiers are treatments that target cytokines or the regulation of T or B cells. TNF inhibitors are potent modulators of

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inflammation, apoptosis and other processes. It is important that they can either inhibit or to promote cancer development [12].

Observational studies did not show an increased risk of malignancy associated with anti-TNF therapy for rheumatoid arthritis. However, there are meta-analyses and randomized studies which show a link between treatment with anti-TNF agents such as Etanercept, Infliximab and Adalimumab, and increased risk of cancer development. The most common form of cancer is lymphoma. Only a few studies have found an increased risk of nonmelanoma skin cancer [13-15].

Association between the immunomodulatory agents and cancer development must take into account the following: severity of disease, increased risk of malignancy in patients with rheumatoid arthritis, and these patients also received immunomodulatory agents before starting therapy with anti-TNF agents [12].

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