Journal of BUON **16:** 112-115, 2011

ORIGINAL ARTICLE

Malignancies after rituximab treatment: just coincidence or more?

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Summary

Purpose: *Rituximab has been successfully used in the treatment of B-cell non-Hodgkin's lymphoma (NHL) and some autoimmune diseases nearly for a decade. Several other malignancies and CD20-negative lymphomas have been reported in the literature after rituximab treatment. We aimed to investigate whether there is an association between rituximab treatment and the development of second malignancies.*

Methods: *A detailed search in English language literature on reports about rituximab treatment and secondary malignancies was made through Medline. The papers were reviewed and the cases were summarized according to secondary tumor types, intervals between rituximab treatment and second malignancy occurrence, indications for rituximab treatment and cytotoxic chemotherapy administration.*

Results: *There were 26 previously reported cases of CD20-negative lymphoma and solid tumors after rituximab treatment. The median age of these cases was 62 years (range 34-80). The median time period from the initiation of rituximab treatment to diagnosis of second malignancies was 5 months (range 1-40). The most frequently reported solid tumors were skin tumors (squamous cell carcinoma and Merkel cell carcinoma) (n=7; 27%), CD20-negative lymphomas (n=5; 20%), Kaposi sarcoma (n=4; 15%), and others (n=10; 38%).*

Conclusion: *Association between rituximab and subsequent development of second malignancies might be a coincidence. However, we suggest close monitoring for second malignancies, particularly skin tumors, in patients treated with rituximab. This issue should be evaluated in further studies.*

Key words: non-Hodgkin's lymphoma, rituximab, second malignancy, secondary tumors

Introduction

Rituximab is a human/mouse chimeric monoclonal antibody (IgG1) which targets CD20 antigen expressed in more than 95% of normal and malignant B-cells, inducing complement-mediated and antibody-dependent cellular cytotoxicity. In patients with relapsed, low-grade NHL, peripheral blood B-cell depletion occurs within 24-48 h after the first infusion of rituximab. Recovery of B-cells begins 6-9 months after the completion of therapy, and normal levels are achieved after 9-12 months [1]. The prolonged period of rituximab-induced B-cell depletion might compromise the immune system. We know that immunosuppressive state may provoke the development and progression of some malignancies [2].

Secondary tumors in the course of lymphoproliferative diseases are a well-known issue and this association is primarily related to immune dysfunction in these patients [3,4]. This immune dysfunction primarily consists of T-cell impairment, as in the case of fludarabine-associated T-cell dysfunction and subsequent skin tumors. The large body of information on rituximab used to treat lymphoma (with over 1 million treated patients) does not indicate any excess risk of solid cancers [5]. Nevertheless, there are some studies that report progression or recurrence of some malignancies after rituximab treatment.

This study analyzed the main characteristics of the patients who developed new cancers or experienced progression of existing cancers after rituximab-containing regimens reported in the literature.

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Received 27-08-2010; Accepted 10-10-2010

Methods

We reviewed the relevant English language literature searching through Medline. We used the generic name rituximab and the key words tumor, second malignancy, carcinoma, cancer, sarcoma. The references from the identified articles were reviewed for additional sources. Although we identified more than 100 patients who developed malignancies after rituximab treatment, we selected those cases which described malignancies in detail. We summarized 26 reported second malignancies after rituximab treatment. The basic characteristics of these cases were described.

Results

There were 26 reported cases (10 male, 10 female, and 6 gender not reported) with the diagnosis of CD20-negative lymphoma or solid tumors after rituximab treatment. The median age of the cases was 62 years (range 34-80). The median time period from the start of rituximab treatment to progression or diagnosis of malignancies was 5 months (range 1-40). The most frequently reported solid tumors were skin tumors (squamous cell carcinoma and Merkel cell carcinoma; n=7; 27%), CD20-negative lymphomas (n=5; 20%), Kaposi sarcoma (n=4; 15%), and others (n=10; 38%).

The frequencies of the malignancies after rituximab treatment are shown in Table 1. Among the patients, 18 (69%) received rituximab treatment for CD20-positive lymphomas, 6 (23%) for rheumatologic diseases, and 2 (8%) for autoimmune diseases. Rituximab was used as monotherapy in 7 of the 26 patients and the remaining 19 patients received rituximab plus chemotherapy. Six patients had a history of treatment with purine analogues (fludarabine or cladribine), a known risk factor for second malignancies, at any stage of their treatment.

Seven of the 26 patients had existing malignancies at the time of rituximab therapy and these tumors progressed after rituximab treatment, and the remaining patients developed new cancers. Data on the clinical course and outcome of these patients was lacking but those with existing malignancies had an aggressive course.

Table 1. Malignancies after rituximab treatment

Malignancies	*Frequency n (%)*	*[Ref. no.]*
Carcinomas		
Squamous cell carcinoma of skin	4 (15)	[6,7]
Merkel cell carcinoma of skin	3 (11.5)	[8-10]
Breast carcinoma	3 (11.5)	[11]
Ovarian carcinoma	1 (3.8)	[11]
Transitional cell carcinoma	1 (3.8)	[11]
Renal cell carcinoma	1 (3.8)	[11]
Small cell lung carcinoma	1 (3.8)	[12]
Lymphomas		
PTCL	2 (8)	[13,14]
Hodgkin's lymphoma	1 (3.8)	[15]
CD20-negative lymphoma	5 (20)	[16-18]
Sarcomas		
Kaposi sarcoma	4 (15)	[19-21]
Total	26 (100)	

PTCL: peripheral T cell lymphoma

Discussion

Whether rituximab treatment increases the risk for malignancy or not is currently unknown. But, a number of hypotheses are proposed on how rituximab / B-cell depletion may cause tumor growth. The most acceptable one is viral infection-related carcinogenesis. Rituximab-induced exacerbation of viral infections has been previously reported [22-26]. Rituximab is used to treat some lymphoproliferative diseases that are directly or indirectly induced by viruses (e.g., lymphoma associated with HIV infection, Castleman's disease associated with HHV8 infection, and lymphoproliferation with cryoglobulinemia associated with hepatitis C virus [HCV] infection) [27]. In our study, all the patients with Kaposi sarcoma experienced a flare/ progression of disease after rituximab administration, possibly related the HHV8 activation. Based on the current understanding of the immunological effects of rituximab, one could postulate that T-cell activation is significantly decreased following B-cell depletion because of decreased antigen presentation by B cells. This could then allow increased viral activity. In our opinion, altered immune status in these patients induced primarily by rituximab was aggravated by concomitant fludarabine-induced T-lymphocyte depletion, which therefore facilitated the growth and aggressive behavior of malignancies.

Another hypothesis is that increased risk of cancer might be due to the primary disease of the patients. Various autoimmune diseases characterized by B-cell overactivity are associated with malignancies, which include not only lymphomas, but also solid cancers, as in the case of excess risk of lung cancer in patients with rheumatoid arthritis. Another explanation may be that, following treatment, a new set of antibodies are formed under nonphysiologic conditions. Autoantibodies against T-cells could occur during this time [2].

In a similar way, with no data declaring excess risk for solid cancers with rituximab treatment of lymphomas, pharmacovigilance data from patients with rheumatoid arthritis - albeit limited - show no unexpected

increase in the number of solid cancers. In the 1053 patients with rheumatoid arthritis treated during clinical trials and monitored on an open-label basis, for a total of 2438 patient/years, including patients given up to 7 rituximab cycles, only 36 malignancies (in 32 patients) have been reported. The most common malignancies were skin cancers without metastases. The incidence of cancer in rituximab-treated patients was 1.5/100 patient/years, which was similar to the incidence in the same-age, same-sex general population [28].

In long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab with two different schedules as short-course (n=78) and long-course (consolidation, n=73) in SAKK 35/98 study, there were 21 cases of second malignancies. Second malignancies were not more abundant in the prolonged arm. Eleven of these 21 patients were in the short-course arm and the remaining 10 in the consolidation arm. So, one could conclude that there was no increase in second malignancies in the prolonged rituximab administration [29].

Rituximab-induced B-cell dysfunction resulted in hypogammaglobulinemia and this condition lasted several years in some patients, especially in those who had rituximab maintenance therapy. This rituximab-induced immunodeficiency (hypogammaglobulinemia) simulates the mild form of Bruton agammaglobulinemia. Bruton agammaglobulinemia (X-linked agammaglobulinemia) is a primary immunodeficiency condition caused by mutations in the gene for Bruton tyrosine kinase that result in deficient proliferation and differentiation of B lymphocytes. Patients with Bruton agammaglobulinemia have hypogammaglobulinemia, markedly reduced levels of serum antibodies, and markedly reduced levels of B-cells. As a result, they have an increased susceptibility to a variety of encapsulated bacteria and enteroviruses, microorganisms for which antibodies play an especially critical role in host defense [30,31]. Although malignancies are not a significant cause of mortality, the incidence of malignancies is increased. In one study, 4 of 201 patients diagnosed with Bruton agammaglobulinemia developed malignancies; one each with osteosarcoma, lymphoma, reticulum cell sarcoma, and adenocarcinoma of the colon [32].

In conclusion, this article summarized the previously reported new primary tumors or progression of existing malignancies after rituximab treatment. Physicians using rituximab should be aware of this information. Studies to elucidate a possible link between rituximab and carcinogenesis are needed. Given the relatively higher incidence of skin cancers, careful skin examination should be considered as a part of routine physical examination. To what extent screening for other malignancies should be performed is currently unclear.

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