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Review

Clinical and microbiological characteristics of the infections in patients treated with rituximab for autoimmune and/or malignant hematological disorders

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ABSTRACT

Introduction: Rituximab is commonly used for the treatment of hematological malignancies and autoimmune diseases. Despite a reputation for good tolerance, case-series and registries reported rituximab-related infections of variable severity including opportunistic infections. We aimed at describing the natural history of infectious events (IE) after treatment by rituximab providing clinical and microbiological features and outcome.
Patients and methods: We retrospectively analyzed the medical records of patients treated with rituximab in an internal medicine department of a tertiary hospital between 2007 and 2015, and identified all IE after this therapy. Events' severity was assessed using the Common Terminological Criteria of Adverse Events (version 4.3) definitions.
Results: Among 101 patients treated with rituximab, we identified 228 IE in 74 (73.3%) of these patients (median follow-up 30.4 months). Indication for rituximab was either autoimmune disease (AID) (52.5% of patients), or monoclonal hematological disease (MHD) (47.5%). Patients received an overall median number of 5 rituximab infusions [interquartile range: 4–8], representing a cumulative dose of 4340 mg [2620–6160]. After last rituximab infusion, IE occurred after 3.1 months [0.7–9.4]. Respectively, IE were severe in 28.1% of cases in patients treated for AID vs 58.0% in patients treated for MHD ($p < 0.001$), due to opportunistic pathogens in 7.8% vs 11.0% ($p = 0.49$) and fatal in 4.7% vs 13.0% ($p = 0.044$). Factor associated with mortality were polymicrobial infection ($p < 0.001$), monoclonal hematological disease ($p = 0.035$), use of steroids over 10 mg/d within the last two weeks ($p = 0.003$), and rituximab cumulative dose ($p < 0.001$). We identified a group of 10 patients (9.9%) showing life-threatening, polymicrobial, and opportunistic infections constituting a 'catastrophic infectious syndrome', which was lethal in 7 cases.
Conclusion: IE after treatment by rituximab can be extremely severe, especially in patients immunocompromised by several other drugs. Further studies should focus on the group with life-threatening polymicrobial infections.

Contents

Abbreviations: AID, AutoImune Disease; CMV, Cytomegalovirus; CTCAE, Common Terminological Criteria of Adverse Events; ICU, Intensive Care Unit; IE, Infectious Event; MHD, Monoclonal Hematological Disorder; PML, Progressive Multifocal Leukoencephalopathy; SIE, Severe Infectious Event.

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1. Introduction

Rituximab is a chimeric monoclonal antibody, which targets the B-cell-specific marker CD20. Rituximab has been given since the late 1990's for the treatment of non-Hodgkin's B-cell lymphomas, and is considered as a safe, efficient drug in addition to polychemotherapy [1,2]. In the last 15 years, rituximab also demonstrated efficiency in autoimmune diseases [3], especially in the most aggressive and refractory cases. Nowadays, it plays an important role both as first-line treatment (e.g. rheumatoid arthritis, ANCA-associated vasculitides) and as therapeutic agent for refractory diseases [4]. The efficacy of rituximab is based on several effects that include B-cell apoptosis [5] leading to a deep and early B-cell depletion [6], and modulation of T-cell cytokine responses [7].

The safety profile of rituximab is considered satisfactory with notably few related-infections [8]. However, the occurrence of infectious events (IE) has been observed after rituximab therapy for hematological disorders (in association with polychemotherapy) as well as for autoimmune diseases. Registries by disease taught us incidence rates of IE following rituximab infusion [9,10]. In addition, case series have highlighted rare and/or life-threatening infections especially opportunistic diseases like progressive multifocal leukoencephalopathy [11] and *Pneumocystis jirovecii* pneumonia [12]. However, the natural history of infectious complications after rituximab therapy in the short-, middle- and long-term has been poorly investigated and remains not precisely described. In the present study, we aimed at studying the natural history of IE following rituximab infusion, and focused on a cohort of patients from a tertiary department of internal medicine.

2. Patients and methods

2.1. Design of the study

This retrospective monocentric study was conducted in the department of Internal Medicine and Multi-Organic Diseases of Saint Eloi University Hospital, which is the local referral center for autoimmune diseases in the area of Montpellier, which represents 2,751,592 inhabitants (Institut National de la Statistique et des Etudes Economiques, Paris, France, 2014).

2.2. Population

All consecutive patients who received at least 1 rituximab infusion between January 1st, 2007 and February 28th, 2015, in our department were enrolled in the study. The patients were identified using the electronic pharmaceutical file of the Oncological Clinical Pharmacy Unit (Montpellier University Hospital, Montpellier, France). No exclusion criterion was defined.

2.3. Ethical considerations

This study was approved by the ethics committee "Comité de Protection des Personnes – Sud Méditerranée IV" of Montpellier (no Q-2017-04-05), and given its observational nature, informed consent was waived. Electronic file has been declared to the "Commission Nationale Informatique et Libertés", regarding to French legislation.

2.4. Data collection

Data were retrospectively collected from the patients' electronic medical records (DxCare software, Medasys S.A, Clamart, France), which enables retrospective collection of prospectively recorded data. Demographic data, main comorbidities, immune suppression condition, treatments before and along with rituximab, indication for rituximab therapy, number and doses of rituximab infusion, non-infectious and infectious adverse events, follow-up time, and cause of death were collected. IE were retrospectively confirmed by two physicians reviewing the medical charts. Several parameters related to IE were also collected including: time that elapsed from first and last rituximab infusions, cumulative rituximab dose, former or ongoing immunosuppressive agents, anti-infective prophylaxis, diagnosis, microbiological identification, severity and treatment of infection, hospital and intensive care unit (ICU) admission. Short and long term outcome were also recorded. All collected items are detailed in Supplementary Table 1.

The severity of each IE was defined according to the 4th revision of Common Terminological Criteria of Adverse Events (CTCAE 4.3. National Cancer Institute, NIH, DHHS. June 14, 2010). IE were graded as follows: 1 for asymptomatic or mild symptoms, with no intervention needed; 2 for