Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution


Abstract: We assessed the feasibility of a rapid infusion of rituximab with or without steroid-containing chemotherapy. Inclusion criteria: previous infusion of rituximab without grade 3 or 4 toxicity, lymphoid cells < 5 x 10^9/L and rituximab dose of 375 mg/m^2. Seventy patients were treated with a total of 319 rapid rituximab infusions [126 (40%) with and 193 (60%) without steroids]. Overall, rapid infusion of rituximab was well tolerated – there were no grade 3 or 4 adverse events. Only, three patients developed symptoms, all grade 1. In conclusion, rituximab administration in a 90-min infusion schedule is well tolerated and safe, both in patients who are administered steroids and in patients who are not.

The chimeric monoclonal anti-CD20 antibody rituximab is now an integral component of therapy for non-Hodgkin’s lymphoma (1). Moreover, rituximab is being increasingly used for other non-malignant conditions, such as immune cytopenias, autoimmune diseases, etc (2). Administration of rituximab can be associated with substantial infusion-related toxicity, including hypersensitivity reactions causing fever, rash, cardiovascular and respiratory compromise and rarely a fatal cytokine release syndrome. It is interesting to note that the incidence of infusion-related reactions decreases with the second and subsequent doses of rituximab (3).

Some recommendations have been made in order to reduce the risk of these infusion-related reactions. These include the administration of rituximab over a prolonged period, usually 5–6 h for the first infusion and 3–4 h for subsequent infusions (4). These extended infusions cause long stays in day units, which are inconvenient for patients and have significant resource implications. Recently, Sehn et al. (5) have suggested that a rapid rituximab infusion schedule in combination with steroid-containing chemotherapy is safe. The aims of this study were to assess the safety of a rapid infusion of rituximab with or without steroid-containing chemotherapy schedules and to evaluate the feasibility of this schedule in terms of shortening stays in hospital.

Patients and methods

The study was carried out at the Department of Clinical Haematology in the Hospital del Mar, a University Hospital in Barcelona, Spain. The recruitment period was from February 2005 to February 2006. Informed consent was obtained in all patients. Patients were included in the study if they had been diagnosed with a CD20+ lymphoproliferative disorder or another disease susceptible of treatment with rituximab. All patients had received previous treatment with a first infusion of rituximab according to prescribing information in the Roche Summary of Product Characteristics (4). Patients were excluded if they had lymphocytosis (> 5 x 10^9/L), experienced toxicity grade ≥3 during the previous infusion of rituximab or had to...
receive a dose $>375 \text{ mg/m}^2$ in their planned treatment schedule.

Patients were treated with rituximab administered over a total time of 90 min in a total volume of 250 mL. During the 90-min infusion, 20% of the dose was given in the first 30 min and the remaining 80% was infused over 60 min. Patients who were treated with steroid-containing chemotherapy received acetaminophen, diphenhydramine and methylprednisolone. The dose of methylprednisolone changed according to the planned immunotherapy schedule. The equivalent dose of intravenous methylprednisolone was used instead of oral prednisone. This was based on availability issues of our Hospital Pharmacy. Those patients who did not receive steroid-containing chemotherapy were only administered acetaminophen and diphenhydramine, and did not receive steroids, either as premedication or to reduce vomiting. Most of the infusions were given on an outpatient basis. Vital signs were measured every 15 min during the first hour or until stable, then hourly until the end of the infusion. Secondary adverse effects were prospectively monitored.

**Results**

A total of 70 patients were enrolled into the study. Patient characteristics are listed in Table 1. Patients received a cumulative total of 319 rapid rituximab infusions. Each patient received a median number of 4 (range: 1–12) rapid infusions. The number of rapid rituximab infusions according to the chemotherapy regimen is shown in Table 2. A total of 126 (40%) rituximab infusions were administered with steroids and 193 (60%) were given without steroids. The median time from the previous rituximab infusion to the first rapid infusion was 28 d (range: 7–272). In 16 of 70 patients (23%), the first rapid infusion was administered with an interval $>90$ d from the previous standard infusion. These cases corresponded to patients who received retreatment with rituximab because of progressive disease or those who were under rituximab maintenance.

This rapid rituximab administration schedule was very well tolerated. No grade 3 or 4 adverse events were observed. In 3 (0.9%) rapid infusions, grade 1 symptoms were recorded, two of these events beginning within the first 30 min. One patient had a sore throat that required a reduction in the infusion speed and a second patient reported abdominal discomfort that disappeared spontaneously. A third patient complained of fever 24 h after rituximab infusion. This case was finally considered an adverse event because no symptoms suggestive of infection were found and cultures from blood and urine were negative. All these reactions occurred in patients who did not receive steroid-containing chemotherapy. The first case was taken off the protocol and despite the fact that successive rituximab infusions were administered according to standard practice in this patient, she complained of mild sore throat in almost all of the successive infusions. Of note, the other two patients received rapid rituximab in the subsequent infusions without any noteworthy events.

**Discussion**

Over the past decade, there has been a considerable increase in the use of cytotoxic chemotherapy to treat cancer, a fact that has had a significant impact on the capacity of outpatient chemotherapy clinics. In the last years, the recommendations for the use of rituximab have increased, and many patients with CD20 lymphoproliferative disorders or autoimmune diseases are now candidates for rituximab infusion. Long infusion times for rituximab administration mean that oncology patients spent many hours in day units for treatment, and may increase patients’ waiting times for chemotherapy. Shortening the infusion time of rituximab by 1.5–2.5 h was preferred by patients as their visits to the hospital
were reduced to 2–3 h compared with the 4–5 h schedule needed in case of long infusions. Moreover, the new infusion schedule has also helped us to treat our patients more quickly and to improve our targets for oncology waiting times.

Although the recommended infusion rate for subsequent infusions is up to double that of the first infusion, several groups have investigated faster infusion rates of rituximab to allow a reduction in the total administration time (5–7). Other groups are making modifications to premedication schedules, such as omitting premedication, to test their feasibility. No significant increase in adverse events has been reported with rapid infusion when rituximab is combined with chemotherapy that contains steroids (5). We decided to investigate the feasibility of a rapid infusion of rituximab not only in patients treated with steroid containing chemotherapy but also in patients who were not receiving steroids in their chemotherapy courses. We also explored the group of patients under rituximab maintenance because the number of patients in this condition is increasing. Therefore, we tested the tolerance of this rapid infusion of rituximab in two clinical situations in which no data have yet been reported.

In our experience, rituximab administration in a 90-min infusion schedule is safe in all patients who met our inclusion criteria regardless of whether they were receiving steroid-containing chemotherapy or not. This fact is important because many lymphoma patients receive rituximab as monotherapy or as maintenance, and some patients with non-malignant conditions can attain beneficial results from rituximab treatment. No significant adverse effects were seen even in patients who had received rapid rituximab infusions with an interval > 90 d from the previous standard infusion, an observation which could be of interest in candidates for maintenance strategies with rituximab.

To summarize, rituximab administration in a 90-min infusion schedule in second or subsequent infusions is safe and well tolerated by all patients regardless of whether they were receiving steroid-containing chemotherapy or not. Moreover, additional benefits include greater patient satisfaction and the optimization of nurse time, particularly in the outpatient setting.

References