Rapid Rituximab Infusion: Local Center Experience

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Abstract

Rituximab, a chimeric monoclonal antibody (MoAb) targeting CD20 has been widely used in the management of B-cell lympho-proliferative disorders. The usual recommended schedule of regular administration over 3 to 4 hours requires considerable healthcare resources and oftentimes inconvenient for patients. Literature shows the availability of published reports proving the safety and feasibility of rapid infusion of rituximab. This study explored the safety and tolerability of rituximab infusion over a shorter total infusion time.

A total of 24 patients diagnosed with CD20+ Non-Hodgkin’s lymphoma and planned to receive rituximab at a dose of 375mg/m2 in combination with standard chemotherapy regimens were included in the study from January 2009 to December 2009. The administration of first rituximab dose was unaltered and given as per standard practice of 3-4 hours infusion. The second and subsequent doses were delivered over a total infusion time of only 90 minutes (20% of dose in the first 30 minutes, remaining 80% over the next 60 minutes).

These patients, aged between 15 and 79 years, received a total of 152 rituximab infusions with an average of 6.33 (+/-2.37) infusions per patient. Grade 1 infusion related toxicity was reported in 5 infusions (3.2%), and there were no acute reactions or G3/4 toxicity in any infusion episode.

A rapid infusion of rituximab is well tolerated, feasible and safe when administered as second and subsequent infusions in the course of therapy for those who tolerate the first dose without significant infusion related toxicity. This shortened infusion method results in a substantial reduction in resource utilization. Our institution has now adopted this as a routine practice.

Keywords

Rituximab, Short infusion, Oman

Introduction

Rituximab, a chimeric monoclonal antibody (MoAb) targeting CD20, has been widely used in the management of B-cell lympho-proliferative disorders. Rituximab was introduced in 1995 and approved by the U.S. FDA in 1997 as a monotherapy for relapsed follicular or low-grade non-Hodgkin lymphoma (NHL). It’s labeled and off-label indications have continued to expand. Rituximab is now routinely used in combination with chemotherapy for the treatment of NHL and the treatment of non-malignant conditions and autoimmune diseases like SLE, ITP, RA, Psoriasis, etc.

Rituximab administration is associated with a risk of infusion-related toxicity including hypersensitivity reactions causing fever, rash, angioedema, pulmonary infiltrates, MI, cardiovascular (VF) or respiratory compromise (ARDS), and rarely a fatal cytokine release syndrome. The exact mechanism of these reactions is not known. The risk of reaction is greatest with the first infusion (77%) and is significantly diminished with all subsequent infusions (grade 3 or 4 toxicity; 7% with first, 2% with fourth, and 0% with eighth infusion) The incidence and the severity of infusion-related side effects consistently decrease in the successive administrations. Indeed after the second rituximab infusion, almost no B cells are left in the blood for at least 2 to 3 months. Reconstitution begins usually after 6 months and is completed after a median of 12 months.

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The risk is more pronounced with high tumor burden and usually seen within 30-120 minutes after the start of infusion \(^{(1,2,21)}\). As a consequence, the recommended infusion durations are prolonged (average 5-6 hours for first infusion and 3-4 hours for second and subsequent infusions).

The increase in labeled and off-label usage of rituximab and prolonged infusion time has placed a huge strain on medical resources of many cancer centers which are already over stretched \(^{(1,5)}\). The usual recommended prolong infusion in a high output center is often demanding and requires expansion of infusion and day care services. The prolonged treatment waiting times on the other hand may negatively affect patient outcomes and compliance \(^{(6)}\).

There are substantial clinical evidences from published reports, unpublished data and personal correspondences that the abbreviated infusions are feasible and safe \(^{(5,22)}\). We were thus logically prompted in 2009 to study the use of 90-minute rapid infusion method for rituximab at the Medical Oncology Department of the National Oncology Center in Royal Hospital, Sultanate of Oman.

**Patients and Methods**

This prospective study was carried out from January 2009 to December 2009. A total of 24 patients diagnosed with CD20+ Non-Hodgkin’s lymphoma were enrolled. The patients were consented and the study was conducted under the institutional ethical guidelines. The eligibility criteria were: age less than 80 years; no past history of allergy or hypersensitivity in general and to biological products in particular; normal laboratory parameters (hepatic, renal, hematologic); and an Ejection Fraction of > 50% on echocardiography. The exclusion criteria were: enrolment in a concomitant clinical trial, cardiovascular disease, congestive cardiac failure (CCF), unstable angina, arrhythmia, MI in the preceding year, active hepatitis B or C, pregnancy or lactation, and poor performance status or expected survival of less than 6 months.

A rapid infusion method for rituximab was used in all patients with CD20+ NHL planned to receive rituximab at a dose of 375mg/m\(^2\) in combination with standard chemotherapy regimens. Patients who experienced grade 3 (or more) infusion-related reactions were excluded from the study and were crossed-over to prolonged method while those who tolerated it well were continued with short abbreviated infusion.

The schedule of administration of rituximab at the first cycle was unaltered and delivered according to the product monograph. In this first infusion the initial infusion rate was 50mg/hour, and after 30 minutes increased by increments of 50mg every 30 minutes up to a maximum of 400mg/hour. Patients who tolerated the first prolonged rituximab infusion without a significant infusion-related reaction were included in this study. These patients had second and subsequent rituximab infusions administered over a total infusion time of 90 min (20% of the dose administered in the first 30 minutes, remaining 80% administered over next 60 minutes, and the total dose was delivered in 500ml normal saline). All patients were premedicated with 1000 mg of oral Paracetamol and 8mg of intravenous Dexamethasone. Most of the infusions were given on an outpatient basis in chemotherapy day care unit and under close clinical observation.

Clinical evaluation was done before each cycle. Vital signs (temperature, blood pressure, heart rate) and symptoms were assessed every 15 min during infusion. A laboratory exam with complete blood cell count and chemistry were repeated before each cycle. Circulating B cells (CD19) though desirable, could not be evaluated as done in other studies. ECG monitoring was done before, during and after infusion. Cardiac enzyme profile was assessed wherever indicated.

In patients who were receiving chemo-immunotherapy, rituximab infusion always preceded the scheduled chemotherapy. The toxicity was graded as per NCI criteria of toxicity grading. The demographic data and toxicity observed were recorded.
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Results

Patients’ demographic characteristics, disease related features, and treatment related parameters are summarized in Table 1. The age range was 15-79 years (Median 52 years). 8 patients (33%) have B symptoms. The clinical staging was done by clinical examination, radiology evaluation (CT scan, MRI, PET-CT) and bone marrow examination. The clinical stage distribution was CS II 8 patients (33%), CS I and III 6 patients (25%) each, and CS IV 4 patients (17%). The majority of 62% received CHOP-R, while 17% received CVP-R. Twenty-four patients (11 male and 13 female) received a total of 152 rapid rituximab infusions episodes with an average of 6.33 (+/-2.37) infusions per patient (range 3-13).

Rapid infusion rituximab was well tolerated and no grade 2, 3 or 4 infusion-related reactions were observed. Grade 1 symptoms were reported in 5 (3.2%) infusions, two patients complained of redness of the face, two complained of headache and one patient complained of itching. All the five patients were administered start dose of 100mg Hydrocortisone intravenously with subsequent rapid resolution of all symptoms and infusions were continued. There were no ECG changes of significance observed in any of these patients in any infusion episode. All subsequent infusions for these patients were uneventful and well-tolerated.

Discussion

The availability of rituximab has revolutionized treatment practices for NHL and many other diseases leading to a marked improvement in treatment outcomes (1,5-10). The associated risk of infusion-related toxicity, with consequent recommendations for prolonged infusion time has created substantial logistical challenges (6). These include prolonged stay in the chemotherapy day-care unit for treatment, additional work load for chemotherapy nurses, long waiting time for patients, and more utilization of medical resources. It was thus an interesting logistical priority to investigate the safety and tolerability of short rituximab infusion and its impact on health care service in the local setting.

A rapid rituximab infusion over 90 minutes is well tolerated and safe when administered as the second and subsequent infusions in the course of therapy for patients who have tolerated the first dose of rituximab without significant infusion-related toxicity (5,15-16, 22). Shorter infusion times would yield substantial time savings for patients and benefit outpatient day-care infusion facilities by increasing both the number of infusion chairs available during clinic hours and nursing efficiency. This shortened infusion schedule has resulted in a substantial reduction in resource utilization (22). Our institution has now adopted this as routine practice after the promising conclusion of this study.

There were 5 studies published in the literature from 2001 to 2009 (total of 176 cases) where G1/2 toxicities were seen in only 15 (8.52%) cases with an ultra-rapid 60-minute rituximab infusions, and no G3/4 toxicities were seen (4,17-18, 21, 23). There were 7 published studies on a 90-minute rituximab infusion from 2006 to 2009 totaling 398 cases (5, 14-15, 19-20, 22, 24). The grade 1/2 toxicities were 2.3% and G3/4 toxicities reported were 0.3% in this published data. No significant acute infusion related reactions were reported.

Several large studies(12) are underway to

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evaluate the safety of the 90-minute infusion protocol. In an open-label phase IIIIB trial, the MAXIMA (Maintenance Rituximab in Follicular Lymphoma) study, 549 patients with follicular lymphoma will receive maintenance rituximab every 8 weeks for a maximum of 2 years at either the standard or 90-minute infusion rates. To date, interim early data has shown that adverse events occurred in 0.9% of rapid infusions (12 of 1,367 infusion episodes) compared with 0.8% of standard infusions (32 of 3,980 infusion episodes), and no serious adverse events were reported within 24 hours of completion of rapid infusion. The median infusion time was 3.26 hours for the standard administration arm and 1.63 hours for the rapid infusion arm. Another phase III, open-label trial—the RATE (Rituximab Alternative Dosing Rate in Patients With Previously Untreated Diffuse Large B-Cell or Follicular Non-Hodgkin’s Lymphoma) study (NCT 00719472 Genentech) which is still recruiting and open, is specifically designed to investigate the safety of the 90-minute infusion protocol and will enroll 385 patients with previously untreated diffuse large B-cell or follicular non-Hodgkin’s lymphoma. The primary end point for this study is to evaluate the frequency of grade 3 or 4 infusion-related toxicity.

Patients with high numbers of circulating malignant cells, pre-existing cardiac or pulmonary conditions, higher tumor burden, rapid cell turnover, and those who experience significant cardiopulmonary adverse events with the first infusion are at increased risk of an infusion reaction (25). The patients with cardiac or respiratory risk factors should be reassessed before a short infusion protocol, and carefully monitored during treatment. The very low number of circulating B cells from the second administration onwards as shown by blood immunophenotyping can explain the lack of infusion reactions.

Sehn et. al. (26) first reported a prospective observation of 150 patients receiving a total of 473 administrations of rituximab in 90 minutes. The safety and feasibility of this schedule was confirmed by a retrospective analysis of a further 1,200 patients treated in British Columbia (24). In this study, part of the rituximab administrations was given as maintenance. In 52 of these cases, treatment was given without steroid premedication and no grade 3-4 toxicities were observed. Similar conclusions were reached in another two Spanish studies.

The adoption of this rapid infusion rituximab schedule resulted in a positive impact on resource utilization (26). Rituximab administration times have been cut in half or less with a concomitant reduction in nursing workload. Most patients can be conveniently treated with rituximab in a shorter time interval and on the same day as their chemotherapy. As a consequence, patient satisfaction has improved and treatment waiting times for rituximab have been eliminated. Many trials are underway and yet there is limited reported experience with abbreviated rituximab which need to be verified by large-scale, randomized, multi-center studies.

References


