

ORIGINAL ARTICLE

Rapid infusion of rituximab over 60 minMark Tuthill¹, Tim Crook¹, Tim Corbet², Jenny King¹, Andrew Webb¹¹Department of Oncology, Royal Sussex County Hospital, Eastern Road, Brighton, BN2 5BE, UK; ²Department of Haematology, Royal Sussex County Hospital, Eastern Road, Brighton, BN2 5BE, UK**Abstract**

The use of rituximab is increasing and regular administration over 2 to 3 h requires considerable healthcare resources and is inconvenient for patients. There is interest in reducing rituximab administration times and although infusion of rituximab over 90 min is safe, there is limited data on the safety of 60 min infusions. We recently changed our second and subsequent rituximab infusion protocol to a 60 min constant rate infusion for patients who had no significant reaction to their first infusion and conducted a prospective safety audit. Fifty-four patients aged between 20 and 86 received 105 rapid 60-min-rituximab infusions without any significant infusion reactions. We also conducted a survey of 20 major cancer centres in the UK and asked about their local rituximab administration policy. We found that 70% are using 90 min rituximab infusion protocols and that 25% are using slower rate infusions. Only one surveyed unit (5%) was using a 60 min rituximab infusion protocol. This study shows that rapid rituximab infusions over 60 min is safe and can be considered for most patients. This finding has considerable beneficial service implications for patients and healthcare providers and shows that there is considerable scope for further reduction in rituximab administration times within the UK.

Key words rapid; rituximab; infusion**Correspondence** Dr Mark Tuthill, Department of Oncology, Royal Sussex County Hospital, Eastern Road, Brighton, BN2 5BE, UK. Tel: 0208 3831000; Fax: 01273 623312; e-mail: marktuthill@doctors.org.uk

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Rituximab (Rituxan[®], Roche, Basel, Switzerland) is a chimeric anti-CD20 monoclonal antibody used to treat non-Hodgkins lymphoma (NHL) and diseases such as rheumatoid arthritis and multicentric Castleman's disease (1–4). Since its launch in 1997, an estimated 1.5 million people across the world have received treatment with rituximab for a wide variety of haematological malignancies and an increasing number of autoimmune diseases (Roche product information). In Europe and the United States, an estimated 140 000 patients are diagnosed with NHL each year (5, 6) and the majority of these patients are likely to receive treatment with rituximab (7).

The first infusion of rituximab is usually well tolerated but around 7% patients will have a grade 3 or 4 infusion reaction (8). Symptoms include rash and bronchospasm and there may be fevers and hypotension, which result from a combination of tumour lysis and release of inflammatory cytokines. Infusion reactions

usually respond quickly to slowing or stopping of the infusion and administration of paracetamol, anti-histamines and steroids. Fatal infusion reactions are very rare and are estimated to occur in 0.04–0.07% of patients (9). Routine premedication and rate protocol rituximab administration, usually given over 6 h, reduce the rate and severity of first infusion reactions. Subsequent infusions have lower reaction rates (2–3%) and are usually given using infusion rate based protocols over around 4 h.

There is interest in reducing rituximab administration time to reduce the burden on health care resources and patient inconvenience. Although rapid infusion of rituximab over 90 min is safe and widely adopted (8, 10). There has only been one small study of rapid infusion of rituximab over 60 min. Therefore, the purpose of this study was to add additional safety data for the rapid infusion of rituximab over 60 min.

Patients and methods

On the 4 September 2006, we changed our rituximab administration practice from a 90 min rate infusion to a 60 min constant rate infusion with a prospective audit on the incidence and severity of infusion reactions. The local ethics committee did not consider that the protocol change required formal ethical approval. All patients received rituximab (375 mg/m^2 in 500 mL of 0.9% normal saline) and premedication with intravenous hydrocortisone (100 mg), paracetamol (1000 mg, oral) and chlorphenamine 10 mg IV. Patients were eligible for rapid rituximab infusion if they had no grade III or IV reactions during their first rituximab infusion. Patients were allowed to cross over from the standard 90 min rapid infusion protocol to the 60 min rapid infusion protocol.

As the current use of rapid rituximab administration in UK is unknown, we conducted a telephone survey of 20 major cancer centres across the UK and enquired about their rituximab administration policy. We contacted the drugs manufacturer Roche to enquire about the number of rituximab infusions administered to patients in the UK, Europe and across the world to assess the service and patient benefits of switching from a 90 to 60 min rituximab infusion. We also contacted the European Medicines agency to ask if they had received any reports of serious reactions attributed to rapid rituximab administration.

Results

Rapid infusion of rituximab (375 mg/m^2) over 60 min was administered to 54 patients between 4 September 2006, and 4 March 2008. The cohort included 34 patients with diffuse large B-cell lymphoma, 10 patients with follicular lymphoma, four patients with mantle cell lymphoma, one patient with maltoma and five patients with immune mediated thrombocytopenias. The median age was 60 yr (range 20–86) with patients receiving a median of two rapid rituximab infusions (range: 1–4). The first infusion of rituximab was well tolerated by all patients within the group with only four patients (7%) having grade 1 or 2 infusion reactions. Rapid rituximab infusion over 60 min was well tolerated with no patients having significant reactions to rapid rituximab infusion over 1 h.

Twenty independent NHS trusts from across the UK were contacted by telephone between 6 October 2008, and 7 October 2008 and all kindly provided information about their rituximab administration policy. All units were following the manufacturer's recommended rituximab administration protocol or using a similar rate controlled first rituximab infusion protocol. The majority of

units, 70% (14/20), were administering second and subsequent rituximab infusions over 90 min if patients had no significant reactions to the first rituximab infusion. Only one (5%) unit was administering rituximab over 1 h. Five units were administering second rituximab infusion infusions using a rate related protocols with patients receiving treatment over 2–3 h.

Roche medicines information kindly provided estimates that around 1.5 million rituximab infusions have been administered since the drug was launched. Unfortunately detailed statistics for the use of rituximab according to country were not available. The European Medicines Agency kindly performed a search of their database of postmarketing reports of adverse drug reactions which did not reveal any reports of severe reactions from rapid rituximab administration in Europe.

Discussion

This study has demonstrated that second and subsequent rituximab infusions can be safely administered over 60 min without risk of significant infusion reaction. The patient characteristics and low incidence of significant infusion reactions are very similar to other studies of rapid rituximab infusion over 60 and 90 min (9–11). Therefore, the results of this study are widely applicable to patients receiving rituximab in normal clinical practice.

We have also shown that the majority of chemotherapy units surveyed in the UK (70%) are using rapid 90 min infusions for second and subsequent cycles of rituximab. However 25% are still using slower rate of rituximab infusion for second and subsequent cycles. Reasons for not using the rapid rituximab infusions varied from concerns about using drugs 'off licence' and the potential for serious drug reactions. Only one unit surveyed (5%) was using 60 min rituximab infusion for second and subsequent infusions of rituximab. None of the units contacted, reported any serious concerns about the use of 90 or 60 min rituximab infusion protocols.

Roche Pharmaceuticals drug information estimates that around 1.5 million patients have been treated with rituximab since its launch. We estimate that each patient with NHL will spend around 690 min receiving a first and then five rapid 90 min infusions of rituximab over a course of six cycles of treatment. A reduction in the infusion time to 60 min will save around 150 min of patient time and chemotherapy unit resources over a course of six cycles of treatment. Globally, assuming 80% of patients diagnosed with NHL each year will receive rituximab, switching infusion protocols from rates from 90 to 60 min would save around 280 000 h of patient and chemotherapy unit time each year.

Table 1 Summary of published studies of rapid rituximab administration

Study	Exclusion criteria	Number of patients	Infusion time (min)	Number of infusions given	Rituximab schedule	Grade 1 or 2 reaction rate per infusion	Grade 3 or 4 reaction rate
Tuthill <i>et al.</i> 2009 (12)	Grade 3 or 4 first infusion reaction	54	60	105	60 min constant rate infusion	0	0
Provencio <i>et al.</i> (11)	Not listed	40	60	223	60 min constant rate infusion	0.02%	0
Sehn <i>et al.</i> (8)	Not listed	156	90	473	20% of dose in the first 30 min and the remaining 80% infused over 60 min	0	0
Salar <i>et al.</i> (10)	Grade 3 or 4 first infusion reaction, lymphocytosis $>5 \times 10^9/L$ or $>375 \text{ mg/m}^2$ rituximab	70	90	319	20% of dose in the first 30 min and the remaining 80% infused over 60 min	0.90%	0

There is now a published data on 320 patients who have received a total of 1120 rapid infusions of rituximab over a 60 to 90 min period (Table 1). We have also shown that many centres in the UK are now using 90 min rituximab administration protocols for the second and subsequent cycles of rituximab and that the European Medicines agency has received no significant reports of drug reactions to rapid rituximab administration. These data provide reassurance that rapid rituximab infusions are safe and should be considered for most patients.

The absence of significant reactions to 60 min infusions of rituximab suggests that faster administrations are likely to be safe and well tolerated. Rituximab (375 mg/m^2) is usually administered in 500 mL of 0.9% normal saline via 24 grey cannula, which have a maximum flow rate of around 20–25 mL/min. Reducing rituximab infusion times to 30 min is feasible using 24 grey cannula, however faster rituximab administration would require larger cannula or a reduction in the volume of administration. Prospective trials investigating 30–15 min infusion times are needed and if successful, would have practice changing implications.

This study shows that there is considerable scope to further reduce rituximab administration times in the UK from 90 to 60 min infusions. This will have significant beneficial service and patient implications and provides scope for evaluation of further reductions in rituximab infusion times. The publication of internationally agreed guidelines or amending the European licence for rituximab administration would allow many chemotherapy units across Europe to consider the use of rapid rituximab administration for most patients. If implemented worldwide, this would save a significant amount of patient time and healthcare resources.

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