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Rapid rituximab infusion is safe in paediatric and young adult patients with non-malignant indications

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Rituximab, a chimeric monoclonal anti CD20-antibody, is used to treat indications, such as Epstein–Barr virus (EBV) viraemia, autoimmune cytopenias and graft-*versus*-host disease (GVHD), in haematopoietic stem cell transplant recipients (Cutler *et al*, 2006; Au *et al*, 2007; Rao *et al*, 2008; Khellaf *et al*, 2014). It is recommended to administer rituximab using a drug titration protocol due to a high risk of infusion reactions. The first infusion is usually takes 4–6 h and subsequent infusions are given over 2–4 h if tolerated.

Adult studies reported that rapid rituximab infusions (RRI) given over 60–90 min are safe with a low infusion-associated reaction rate of 0·9–2·6%, but there are no safety data of RRI in children (Sehn *et al*, 2007; Tuthill *et al*, 2009; Lang *et al*, 2011; Swan *et al*, 2014). Based on our experience in adults, we implemented uniform clinical practice using RRI for second and subsequent doses in children and young adults who received rituximab for non-malignant indications and were not at risk for tumour lysis syndrome from 1 June 2013 (Al Zahrani *et al*, 2009).

Patients who previously received at least one rituximab infusion (375 mg/m^2 per dose) using a standard drug titration protocol without any adverse reactions received subsequent infusions given over 1 h using the RRI protocol. Patients were observed for infusion-related reactions during and 30 min after RRI. Any new clinical symptoms, administration of steroids, diphenhydramine or acetaminophen were recorded for 24 h before and after each infusion. After 6 months of prospective safety monitoring of each infusion, the Pharmacy and Therapeutics committee at our centre approved RRI as acceptable clinical practice. Our

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Conflict of interest disclosures

None of the other authors have any competing financial interests to report.

Authorship contributions

GW, KM, AT, SMD and SJ designed the study, performed research and wrote the paper.

study goal was to report RRI safety in children and young adults after Institutional Review Board approval of this retrospective review.

Over the study period of 18 months, 22 patients received 80 doses of rituximab using RRI. Study cohort characteristics are summarized in Table I. Indications for rituximab were autoimmune cytopenias (50%), EBV viraemia (36%) and GVHD (14%).

Eighty per cent of all infusions (64/80) were given to children (<18 years) and 20% to young adults (16/80). The median number of RRI administered was 4 (range 1–10). Overall, 78/80 (97·5%) infusions were tolerated without any adverse events. There were no adverse events reported in young adults. Out of 64 RRI given to children, one infusion resulted in transient rash that resolved in 24 h without interventions. At the time of infusion the patient was receiving 1 mg/kg/d of methylprednisolone for GVHD and was not treated with any additional premedications. This patient subsequently received four additional RRI without incident. Another child developed nausea with the fourth RRI that resolved with ondansetron and pausing infusion. He was given 1 mg/kg per dose of hydrocortisone as premedication prior to re-starting rituximab as he was not on any steroids. Infusion was resumed after 15 min using the manufacturers recommended titration protocol, but the patient developed shortness of breath. Infusion was discontinued. Symptoms resolved with administration of 1 mg/kg per dose of hydrocortisone and he was discharged home. This patient was listed as having rituximab allergy and did not receive any further doses.

At the time of RRI, 10 of 22 patients (45·5%) were receiving steroid therapy at a median dose of 1 mg/kg/d methylprednisolone equivalent (range 0·14–2 mg/kg/d). Eight of 12 (66·7%) patients were not on steroids and were administered 1 mg/kg per dose hydrocortisone as premedication for each RRI without any events, with the exception of the one patient listed above. Premedication with hydrocortisone was given based on primary treating physician preference. Four patients did not receive any steroids and had no adverse events. Each outpatient stay for RRI was about 2 h. All patients receiving RRI in the outpatient setting were discharged after observation for 30 min. There were no re-admissions to the hospital within 24 h after infusions. A total of 160 clinical care hours were saved using RRI.

Rapid rituximab infusions given over 1 h was safe and well tolerated in children and young adults when administered as the second and subsequent doses. Only 1 of all 80 (1·25%) infusions resulted in an adverse event warranting discontinuation of the therapy. Out of 64 infusions given to children, 2 (3%) resulted in adverse events that resolved without long-term sequelae. There were no severe life-threatening events. Overall, infusion-associated reaction rate was low and similar to that reported in adults receiving RRI (Lang *et al*, 2011). The need to use hydrocortisone premedication for patients not receiving steroids should be further studied.

We conclude that RRI is a safe option in children and young adults with non-malignant indications, such as EBV viremia, GVHD or autoimmune cytopenias. This regimen should not be considered for subjects with active B-cell malignancies or post-transplant lymphoproliferative disorder due to the risk of tumour lysis syndrome. RRI will probably

have a positive impact on patient satisfaction and resource utilization for busy paediatric practices where these medications are commonly used.

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Table I

Study cohort characteristics.

Study subjects (*n* = 22)	**Number of subjects (%)**
Age (median, years) (total *n* = 22)	11·5 (0·25–31·5)
Paediatric patients (<18 years) (*n* = 17)	10·2 (0·25–14)
Young adults (≥18 years) (*n* = 5)	28 (20–31·5)
Male	14/22 (63%)
Allogeneic transplant recipients	19/22 (86·4%)
Pre-transplant patients	3/22 (13·6%)
Diagnosis group	
Malignancy	6/22 (27·3%)
Immunodeficiency	8/22 (36·4%)
Bone marrow failure	5/22 (22·7%)
Other (haematological/genetic)	3/22 (13·6%)
Donor type	
Unrelated	19/20 (95%)
Related	1/20 (5%)
Human leucocyte antigen match	
Fully matched	14/19 (73·7%)
Mismatched	5/19 (26·3%)
Indication for rituximab use	
Epstein-Barr viraemia	8/22 (36·4%)
Autoimmune cytopenias	11/22 (50%)
Graft-*versus*-host disease (GVHD)	3/22 (13·6%)
Total number of rituximab doses given using rapid infusion protocol	80
Paediatric patients (<18 years old) (*n* = 17)	64 (80%)
Young adult (≥18 years old) (*n* = 5)	16 (20%)
Median rituximab doses given using fast infusion protocol (*n* = 22)	3·6 (range 1–10)
Paediatric patients (<18 years) (*n* = 17)	3 (1–10)
Young adult (≥18 years) (*n* = 5)	4 (1–5)
Steroid use during rituximab infusion	
On chronic steroid therapy	10/22 (45·5%)
Premedication for rituximab infusion	8/22 (36·4%)
No steroids received	4/22 (18·1%)
Adverse events associated with rapid rituximab infusion (*n* = 80)	
Total	2/80 (2·5%)
Self-limited without interventions	1/80 (1·25%)
Resolved with medical interventions	1/80 (1·25%)
Life threatening	0/80 (0%)