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Adoption of Rapid Obinutuzumab Infusions: Real World Experience

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BACKGROUND

Obinutuzumab is a type II monoclonal anti-CD20 antibody, now used in clinical practice for the treatment of Chronic Lymphocytic Leukaemia (CLL) and Follicular Lymphoma (FL) [1,2]. Infusion-related reactions (IRRs) were recorded during trials, at higher rates than with rituximab treatment [1,2].

The obinutuzumab monograph states that the first administration requires slow rate incrementation, with a minimum infusion time of 255 minutes for 1g [3]. In the absence of significant IRR, subsequent doses can be given with a faster rate incrementation, though the minimum infusion duration is 195 minutes. These infusions require over three hours per visit and three rate changes, imposing lengthy attendances on patients and incurring significant chemotherapy chair time and nursing activity.

Recent publications from the GATS and GATHER studies demonstrate safe administration of 1g obinutuzumab in 90-minute infusions from cycle 2 onwards in selected patient groups, with no severe IRR events reported [4,5]. Based on this evidence, our department has implemented a rapid infusion protocol. We report here our initial real-world experience.

METHODS

The Norfolk and Norwich University Hospital (NNUH) haematology unit adopted a 90-minute fixed-rate infusion protocol from 9th October 2018.

Eligible patients treated with obinutuzumab for FL and CLL received rapid infusions from cycle 2 onwards (Figure 1, below). Patients who experienced a grade 3 or 4 IRR during cycle 1, and patients with CLL who had a lymphocyte count >5x10^9/L at the commencement of cycle 2 were deemed ineligible for rapid infusion. Corticosteroid, anti-pyretic and anti-histaminic premedication was given prior to each obinutuzumab infusion.

Data was retrospectively collated from patients treated between initial protocol change and 17th January 2020. Demographic details, prescription charts and medical/nursing notes were reviewed. IRR events were graded as per Common Terminology Criteria for Adverse Events (Ver 5.0) [6].

FIGURE 1: TREATMENT PROTOCOL

	STANDARD INFUSION PROTOCOL	RAPID INFUSION PROTOCOL
CYCLE 1 – DAY 1	Commence at 50mg/hr, incrementing by 50mg/hr every 30 minutes (max 400mg/hr) (CLL – day 1 comprises 100mg at 25mg/hour)	Commence at 50mg/hr, incrementing by 50mg/hr every 30 minutes (max 400mg/hr) (CLL – day 1 comprises 100mg at 25mg/hour)
CYCLE 1 – DAY 8	Commence at 100mg/hr, incrementing by 100mg/hr every 30 minutes (max 400mg/hr)	Commence at 100mg/hr, incrementing by 100mg/hr every 30 minutes (max 400mg/hr)
CYCLE 1 – DAY 15	Commence at 100mg/hr, incrementing by 100mg/hr every 30 minutes (max 400mg/hr)	Commence at 100mg/hr, incrementing by 100mg/hr every 30 minutes (max 400mg/hr)
	If no grade 3/4 IRR. (CLL, if lymphocyte count <5x10^9/L)	
CYCLE 2 – DAY 1 (ONWARDS)	Commence at 100mg/hr, incrementing by 100mg/hr every 30 minutes (max 400mg/hr)	Fixed rate 90 minute infusion (666mg/hr)

RESULTS

21 patients received obinutuzumab-based treatment between 9th October 2018 and 17th January 2020. 15 patients were suitable for rapid obinutuzumab infusion. 6 patients did not receive rapid infusions (3 excluded due to grade 3 IRRs during cycle 1, 2 ceased therapy before cycle 2, and 1 was treated within trial).

Pre-infusion characteristics

Patients received rapid infusions for both FL and CLL, with a younger age range seen in patients treated for FL (Table 1). 7 patients (46%) experienced grade 1 or 2 reactions during initial cycle 1 standard rate infusions.

Rapid infusion administration

12 patients (80%) commenced rapid infusions from cycle 2. 3 patients started in later cycles due to initial incorrect utilisation of standard rate infusions. 52 rapid obinutuzumab infusions were administered.

	FL	CLL	TOTAL
Number of patients	6	9	15
Median age (years)	63 (38-81)	78 (69-91)	74 (38-91)
Female (patients)	2	6	8
Regimens used (patients)	3 x O-Benda 2 x O-CVP 1 x O-CHOP	9x O-Chlor	9x O-Chlor 3 x O-Benda 2 x O-CVP 1 x O-CHOP
Median lymphocyte count prior to rapid infusion (x10^9/L)	-	0.69 (0.24-1.33)	-
Median no. of rapid infusions at time of data collection	3 (1-8)	3 (1-5)	3 (1-8)
IRRs during cycle 1 (patients), by grade of reaction	1 x grade 2	1 x grade 1, 5 x grade 2	1 x grade 1, 6 x grade 2
IRRs during rapid 90-minute infusions (patients)	0	0	0
Total number of rapid 90-minute infusions completed	27	25	52
Culmulative infusion time saved (hours)	47.25	43.75	91

Table 1: Characteristics and outcomes for patients receiving rapid infusions. O, Obinutuzumab; Benda, Bendamustine; CVP, Cyclophosphasmide-Vincristine-Prednisolone; CHOP, Cyclophosphamide-Vincristine-Doxorubicin-Prednisolone; Chlor, Chlorambucil.

Patient outcomes

No patients experienced infusion related reactions of any grade during rapid 90-minute infusions. 3 patients ceased obinutuzumab-based treatment early due to other intolerance (1 patient passed away due to infection, and 2 patients experienced recurrent infections). 5 patients continue on therapy (3 continue on induction and 2 on maintenance infusions). At the time of data evaluation (median follow up duration of 4 months, range 0-12 months), 7 patients remained on watch and wait follow-up and 2 patients experienced disease progression (1 patient started second line therapy and one patient received palliative care).

Resource outcomes

Infusion duration was shortened by approximately 105 minutes. In this cohort, an estimated minimum of 91 hours of treatment time was saved.

DISCUSSION

The NNUH experience suggests that fixed-rate 90 minute obinutuzumab infusions are well tolerated from cycle two onwards in selected patient groups. No IRR events were observed during rapid infusions, even though almost half of patients had experienced grade 1 or 2 IRR events during the first cycle of treatment. We estimate that this intervention has saved over 91 hours of patient and chemotherapy chair time to date and has reduced nursing acuity by eliminating the need for repeated rate incrementation. This study is limited by small patient numbers and by the retrospective nature of data collation. However, this data adds valuable real-world experience to previously reported trial data. Authors of the GATS study reported 31 patients who successfully received 90-minute fixed-rate obinutuzumab infusions from cycle 2 onwards, with only 3 grade 1 IRR events noted [4]. The GATHER study included 70 patients who received rapidly-incremented 90 minute infusions, with only 2 patients experiencing mild (grade 1/2) IRR events [5].

It is incumbent upon haemato-oncology units to maximise resource utilisation and minimise the burden of anti-cancer therapy upon our patients. Novel techniques of administering anti-cancer therapies are becoming ever-more important; subcutaneous daratumumab administration and home bortezomib administration are other clear examples of recent innovative change in the provision of systemic anti-cancer therapy in haematology clinical practice [7,8].

We will continue to audit outcomes from our rapid obinutuzuamb infusion protocol. We also await completion of the GAZELLE study which will provide further trial data on the tolerance of rapid obinutuzumab administration [9]. We advocate further discussion at a national level regarding the safe introduction of rapid obinutuzumab infusion protocols, similar to the widespread adoption of rapid rituximab infusion protocols several years ago.

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