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Real-world safety and tolerability of rapid infusion obinutuzumab in chronic lymphocytic leukemia, small lymphocytic lymphoma and non-Hodgkin lymphoma: a provincial review

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Obinutuzumab, a glycoengineered anti-CD20 monoclonal antibody is used for the treatment of Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), and for the treatment of rituximab-refractory indolent non-Hodgkin Lymphoma (NHL). Although infusion-related reactions (IRRs) remain a concern, especially during the first cycle, shortened infusion times have been explored to enhance healthcare efficiency and patient experience starting at cycle 2 in non-Hodgkin Lymphoma.[1,2] In response to treatment room constraints during the COVID-19 pandemic, we implemented rapid obinutuzumab infusion in all obinutuzumab protocols used in the treatment of CLL, SLL and relapsed/refractory NHL in our province. We evaluated the safety, tolerability, and feasibility of this approach in Manitoba, administering 667 rapid infusions over a 4.5-year period. Our findings support using rapid infusion obinutuzumab starting with cycle 2, and it should be considered in all future clinical trials.

Obinutuzumab is associated with infusion-related reactions (IRR), ranging from minor headaches to more serious cytokine release-like symptoms[3]. It can require long infusion times which limit resources and cost. The phase II GATHER trial investigated the safety and efficacy of cyclophosphamide, doxorubicin, vincristine, and prednisone in combination with obinutuzumab (O-CHOP) in patients with previously untreated advanced diffuse large B-cell lymphoma. This study introduced two shorter duration infusions of obinutuzumab (120-minute infusion and 93-minute infusion) in patients who received three or more doses at the standard infusion rate without experiencing any grade 3 or greater IRRs, and had an absolute lymphocyte count less than 5×10^9/L prior to administration of the shorter duration infusion. There were no grade 3 or 4 IRRs in either group, but one IRR of grade 2 or less in the 120-minute infusion group and three in the 93-minute infusion group.[1]

Similarly, the phase II GATS trial determined the safety, tolerability, and pharmacokinetics of shorter duration obinutuzumab infusions in patients diagnosed with untreated B-cell NHL. Patients received obinutuzumab in combination with CHOP chemotherapy through standard infusion rates for cycle 1. There was no grade 3 or 4 infusion-related obinutuzumab reactions in patients who received rapid infusion.[2]

CancerCare Manitoba (CCMB) is a centralized tertiary care center for the Province of Manitoba, Canada. All cancer patients are initially assessed at CCMB and thereafter treatment is initiated either at the tertiary cancer center or community oncology sites dispersed across the province. Since September 29th, 2020, Manitoba adopted rapid infusion obinutuzumab protocols in treatment-naïve CLL, SLL and relapsed/refractory NHL patients for cycle 2 and onwards. Eligibility for rapid infusion included an absolute lymphocyte count of less than or equal to 5 X 10^9/L prior to obinutuzumab dose and no grade 3 or 4 IRRs during cycle 1 (in any of their previous 3 obinutuzumab infusions). We describe the real-world experience with respect to safety, practical implementation, and chair-time savings with rapid obinutuzumab infusions in our institution.

Patients who were prescribed an obinutuzumab-based regimen were identified in the electronic patient health record. Ethics approval for this retrospective review was obtained from Institutional Ethics Review Board (HS26942). All regimens using a rapid obinutuzumab infusion for CLL, SLL, and/or relapsed/refractory-NHL were captured from September 29, 2020, to March 31, 2025, inclusively. For cycles 2 to 6 of all obinutuzumab protocols and for obinutuzumab maintenance doses in NHL, obinutuzumab 1000 mg is administered intravenously on day 1. Obinutuzumab is prepared in a final volume of 250 mL normal saline. Nurses administer obinutuzumab at a rate of 25 mL/hour for 30 minutes (5% of dose) followed by 225

mL/hour for 63 minutes (95% of dose) for a total infusion time of 93 minutes. This 93-minute infusion schedule was intentionally chosen to help treatment room nurses distinguish it from the institutional rapid infusion protocol used for rituximab, which involves 20% of the dose over 30 minutes and the remaining 80% over 60 minutes.

During each infusion, complete documentation of IRRs was required in the patient electronic patient record by the treatment room nurse. If an IRR occurred, it was graded and documented if the full dose was administered after a same day rechallenge. IRRs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE).

We report outcomes from obinutuzumab-based regimens in 137 patients diagnosed with CLL, SLL, or NHL (**Table 1**) who received one or more doses of rapid infusion obinutuzumab. In total, 667 rapid obinutuzumab infusions were administered for CLL. SLL and relapsed/refractory NHL province wide (**Table 1**). Importantly, no IRRs occurred in patients who received rapid infusions. Rapid obinutuzumab infusions resulted in a cumulative chair time savings of 102 minutes per infusion [195 min (3.25 hours) compared to 93 minutes] resulting in a total of 68,034 minutes (~1134 hours) compared to standard infusion rates.

Patients were pre-medicated prior to obinutuzumab infusions to minimize IRRs (**Table 2**). In our cohort, all patients received acetaminophen 650 mg orally and an anti-histamine prior to obinutuzumab. Cetirizine is favored over diphenhydramine in our provincial protocols due to less side effects. Dexamethasone was administered in 288 infusions (43.2%) while it was not administered in 379 infusions (56.8%). For patients who received dexamethasone, the most commonly used dexamethasone dose was 12mg once in the treatment room as an anti-emetic for the chemotherapy backbone used for the treatment of their lymphoma and a dexamethasone dose of 20 mg once prior to obinutuzumab if used for CLL or SLL on day 1 of cycles 2 to 6 (patient

and physician preference dependent) (**Table 2**). Since obinutuzumab is combined with chemotherapy in NHL protocols, the use of dexamethasone was for anti-emetic purposes. The use of dexamethasone did not affect the incidence of IRRs. In our retrospective review, there were 5 rapid infusions administered to patients with a lymphocyte count higher than 5.0 x 10^9/L (range: 5.41 x 10^9/L – 11.97 x 10^9/L), but none of these patients experienced IRRs.

Manitoba's geography is vast, and patients are required to travel long distances to a tertiary care centre. Our retrospective review showed a large percentage of patients who were able to safely receive their dose of rapidly infused obinutuzumab outside of urban care centres, with 169 out of 667 infusions (25.3%) being administered at a rural/community setting (**Figure 1**).

The adoption of rapid obinutuzumab infusions markedly improves treatment room efficiency across healthcare settings in Manitoba. Our retrospective review demonstrates that rapid infusions are safe and feasible in rural settings. Between September 2020 and March 2025, 667 rapid infusions were safely administered, resulting in a total of 1134 hours of chair time saved, demonstrating resource and associated cost savings as well as improved accessibility for patients able to receive treatment closer to home.

As obinutuzumab utilization is increasing, treatment centers and clinical trials should strongly consider incorporation of rapid obinutuzumab infusions to enhance healthcare efficiency and remove geographic barriers for treatment; this would also allow for equitable and accessible care across nations. Clinical trial participation may also improve if these changes were to be adopted.

We acknowledge certain limitations of our study. As a retrospective chart review, the analysis is subject to selection bias and limited by the accuracy and completeness of charted data.

Dexamethasone was used to reduce infusion-related reactions in CLL, SLL and NHL regimens and as an anti-emetic agent in NHL regimens. Since 2024, its use as a pre-medication in all obinutuzumab protocols has no longer been recommended beyond cycle 1 in Manitoba. Therefore, clearer documentation of its administration is needed to better understand the rationale for its use at the time of infusion. However, IRRs are systematically documented using standardized templates at CancerCare Manitoba, which strengthens the reliability of our findings. The data capture was only related to symptoms that occurred during the treatment infusion and would not capture any side effects a patient would experience post-infusion at home.

Overall, our data support the safety and feasibility of administering obinutuzumab via rapid infusion protocols. Our province continues to use rapid infusion obinutuzumab with all patients who meet criteria starting at cycle 2 and could be considered to be implemented earlier in Cycle 1 (starting at cycle 1, day 8). Obinutuzumab is being explored for emerging indications in other specialties, including nephrology and rheumatology[4,5,6]. As such, the implementation of rapid infusion protocols may offer meaningful benefits across all clinical settings and improve patient experiences where obinutuzumab is chosen as the therapeutic agent.

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Table 1. Patient Demographic Data and Obinutuzumab-containing regimens

	ALL	DIAGNOSIS		
		*CLL	*SLL	*r/r-NHL
Characteristics (%)	**N = 137**	**N = 89**	**N = 17**	**N = 31**
Median age at time of treatment	64	67	73	70
Range	43 - 75	46 - 87	45 - 86	43 - 86
40 - 59	22 (16.1)	17 (19.1)	1 (5.9)	4 (12.9)
60 - 69	54 (39.4)	38 (42.7)	5 (29.4)	11 (35.5)
70 - 79	53 (38.7)	30 (33.7)	9 (52.9)	14 (45.1)
80+	8 (5.8)	4 (4.5)	2 (11.8)	2 (6.5)
Biological Sex (%)				
Male	86 (62.8)	57 (64.0)	11 (64.7)	18 (58.1)
Female	51 (37.2)	32 (36.0)	6 (35.3)	13 (41.9)
Lymphocyte count at treatment (x 10^9 /L)				
Average	57.4	82.2	2.2	1.5
Median	20.3	48.3	1.9	0.8
Range	0.2 - 397.9	5.4 - 397.9	0.83 - 4.65	0.2 -18.9
Regimen (%)				
O-Chlorambucil	6 (4.4)	4 (4.5)	2 (11.8)	0
Venetoclax -O	96 (70.4)	84 (94.4)	12 (70.6)	0
Bendamustine - O	6 (4.4)	0	0	6 (19.4)
Acalabrutinib - O	1 (0.7)	0	1 (5.9)	0
Ibrutinib - O	1 (0.7)	0	1 (5.9)	0
O-CHOP	19 (13.9)	0	0	19 (61.3)
O-GDP	6 (4.4)	0	0	6 (19.4)
Obinutuzumab Alone	2 (1.5)	1 (1.1)	1 (5.9)	0
Rapid Infusions (%)				
Number of infusions administered	667	402 (60.3)	75 (11.2)	190 (28.5)

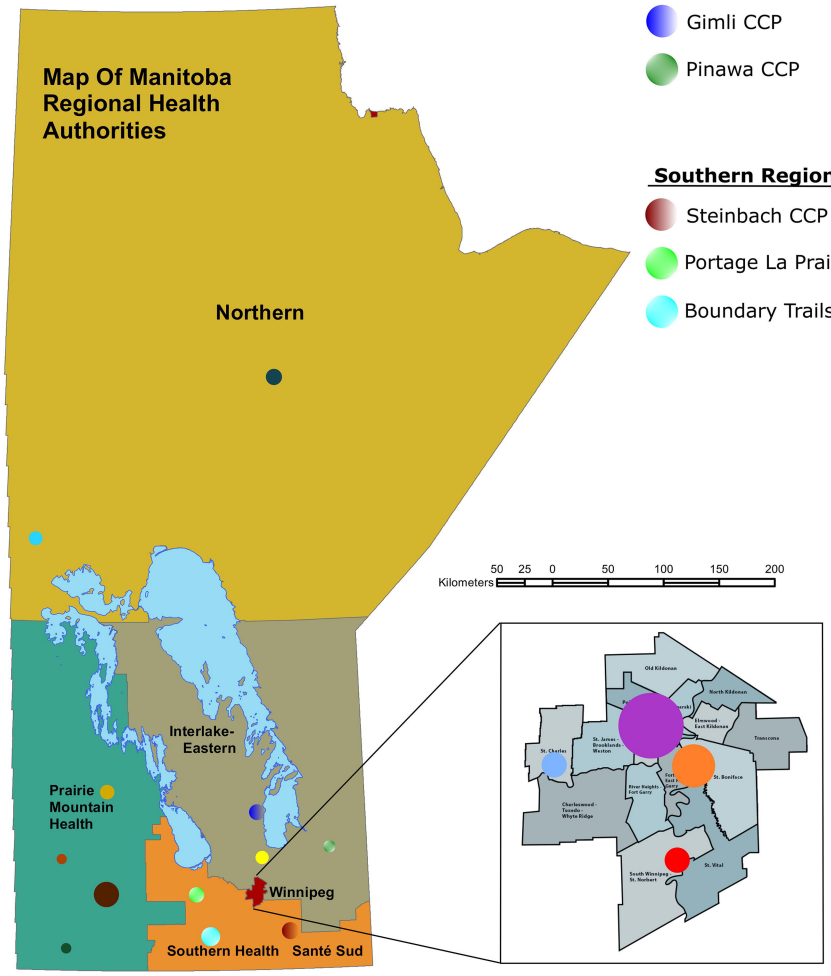
*CLL = Chronic Lymphocytic Leukemia, SLL = Small Lymphocytic Lymphoma, r/r-NHL = relapsed-refractory non-Hodgkin Lymphoma

Table 2. Pre-treatment median lymphocyte counts for all patients from cycles 2-6 and maintenance. Pre-medications used in each cycle, and infusion-related reactions

	Cycle 2 (N=136)	Cycle 3 (N=126)	Cycle 4 (N=116)	Cycle 5 (N=106)	Cycle 6 (N=100)	Maintenance (N=87)
Median Absolute Lymphocyte Count ($x10^9$/L)	0.89	0.89	0.81	0.99	1.1	0.89
Number of Patients Experiencing IRR	0	0	0	0	0	0
Grade 1-2*	0	0	0	0	0	0
Grade 3-4*	0	0	0	0	0	0
Pre-Medications, N of patients						
Acetaminophen	136	126	116	106	100	87
Cetirizine (H1 Antagonist)	116	113	103	95	95	57
Diphenhydramine (H1 Antagonist)	8	9	9	6	4	0
Dexamethasone	74	59	45	40	34	38

*IRR = Infusion-related reactions. Severity of IRR (Grade 1-2 or Grade 3-4) was graded using the Common Terminology Criteria for Adverse Events (CTCAE)

Figure 1: Doses of rapid obinutuzumab infusions administered throughout Manitoba in our cohort. The color blocks represent the various health regions, the circles represent the location of delivery, and the size of the circle represents the number of infusions



Interlake East Regional Health Authority (n=34)

- Selkirk CCP
- Gimli CCP
- Pinawa CCP

Prairie Mountain Regional Health Authority (n=71)

- Western Manitoba Cancer Centre
- Dauphin CCP
- Deloraine CCP
- Hamiota

Southern Regional Health Authority (n=46)

- Steinbach CCP
- Portage La Prairie CCP
- Boundary Trails CCP

Northern Regional Health Authority (n=18)

- The Pas CCP
- Thompson CCP

Winnipeg Regional Health Authority (n=498)

- CancerCare MacCharles
- Grace Hospital
- CancerCare St. Boniface Unit
- Victoria General Hospital