Descriptive Analysis and Review of Utilization of Rituximab in the Maintenance Treatment of Non-Hodgkin's Lymphoma in Five University Teaching Hospitals in Quebec, Canada

Nathalie Letarte, BPharm, MSc, BCOP[1], France Varin[1], Daniel Froment[1], Elaine Pelletier[2], Benoit Bailey[2], Martin Turgeon[3], Benoit Cossette[3], Paul Farand[3], Marie-Claude Michel[4], Nathalie Marcotte[4], Louise Deschenes[4], Raghu Rajan[5] and Celine Dupont[5]

[1]CHUM Notre-Dame, Montreal, QC, Canada; [2]CHU Sainte-Justine, Montreal, QC, Canada; [3]CHUS, Sherbrooke, QC, Canada; [4]CHUQ, QC, Canada; [5]MUHC,Montreal, QC, Canada.

BACKGROUND

Rituximab, a monoclonal antibody targeting CD20 receptors widely used in the treatment of non-Hodgkin's lymphoma, is now being used in various indications, on and off-label. For five University Hospitals in Quebec, Canada, rituximab represents more than 10% of their total drug expenses. More than 10 million dollars were spent in one year for rituximab in these centers. Pharmacy managers gave the Therapeutic Drug Management Program (TDMP – www.pgtm.qc.ca) the mandate to evaluate rituximab use in those centers.

OBJECTIVES

The objectives of the study were to describe rituximab use for all indications in our hospitals and to review the utilization of rituximab in maintenance therapy for follicular lymphoma according to predefined criteria[1].

Criteria for maintenance therapy

- Follicular lymphoma
- Treatment following induction therapy
- Dose of 375 mg/m^2 iv
- 3 schedules of administration allowed
- Maximum duration of treatment of 2 years

METHODS

A review of pharmacy databases was performed to identify patients who received rituximab between April 1st 2008 and March 31st 2009. Every patient file containing rituximab was reviewed. Patients' medical records were also reviewed for pathology and side effects. No sampling was performed.

RESULTS

All patients

The most frequent indications were follicular lymphoma (36%) and diffuse large B-cell lymphoma (26%) followed by chronic lymphoid leukemia (CLL) (8%). Various off label indications represented 30% of the use in our population. Thirty-eight patients (4.8%) died during the study period. The evaluation of patients' outcome for off-label indications could not be performed due to the complexity, variety and chronic courses of diseases treated.

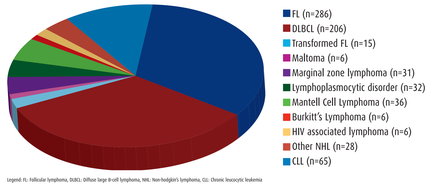
Table 1 Patient characteristics (all indications)

	N=797
Mean age	61,9 years (18-95)
Men	423 (53%)
Status at the end of data collection	
Treatment completed	335 (42%)
On treatment	360 (45,2%)
Died	38 (4,8%)
Reason for discontinuation	
Disease progression	13
Adverse events	17
Patient withdrawal	3
Other/Unknon	17

Table 2

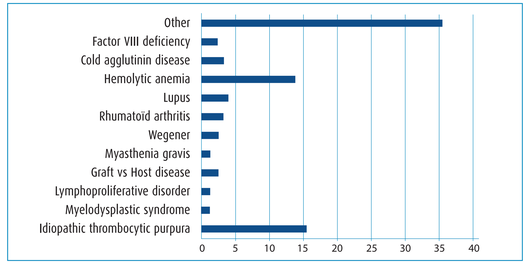
Adverse events causing discontinuation (n=17)	
Asthenia	Neutropenia, febrile neutropenia
Fever	Prolonged pancytopenia
Nausea	Pulmonary fibrosis
Kidney failure	Rash
Hypomagnesemia	Allergic reactions

Figure 1 Lymphoma indications, all population (n=697)



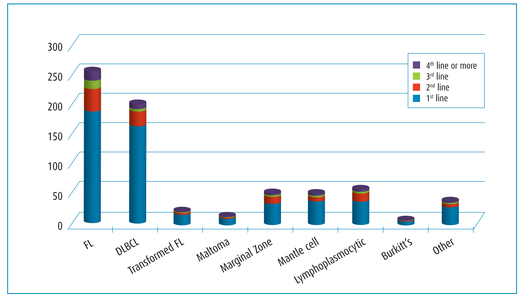
Legend: FL: Follicular lymphoma, DLBCL: Diffuse large B-cell lymphoma, NHL: Non-hodgkin's lymphoma, CLL: Chronic leucocytic leukemia

Figure 2 Other indications (off-label) (n=100)



Other indications (n=35); ALL, Hodgkin's (4), T-cell lymphoma, vasculitis (4), MM, nephropathy, liver transplant, glomerulonephritis (3), kidney graft rejection (6), Sjogren, AML, TTP, HUS, Pemphigus vulgaris, chronic neutropenia, cryoglobulinemia (2), granulomatosis.

Figure 3 Lines of therapy including rituximab for lymphoma indications



Pediatric indications

41 pediatric patients received rituximab for different indications, mostly off-label. At the end of data collection, 73% had received all planned treatments and 12% had discontinued or died. Mean number of doses received varied for each indication (3-6 doses) over a period of time extending from 12 days to 16 months. Other outcomes could not be measured due to the heterogeneity of indications and lack of documentation.

Table 3 Rituximab indications in pediatric population

PEDIATRIC INDICATIONS	(n=41)
DLBCL	10 %(n=4)
Burkitt's lymphoma	2 % (n=1)
ITP	5 % (n=2)
Graft vs Host disease	5 % (n=2)
Myasthenia gravis	5 % (n=2)
Wegener	2 % (n=1)
Rheumatoïd arthritis	2 % (n=1)
Lupus	7 % (n=3)
Hemolytic anemia	12 % (n=5)
Nephrotic syndrome	27 % (n=11)
Other	22 % (n=9)

Maintenance therapy

53% received rituximab maintenance after first-line treatment with R-CVP and 19% after R-CHOP. Only one patient receiving maintenance treatment stopped therapy because of disease progression. No death was reported while on maintenance therapy. Most patients received maintenance treatment following a response to induction therapy (88%).

Figure 4 Indications for maintenance therapy (n=232)

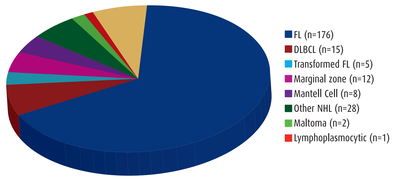


Table 4 Description of maintenance treatment

		N=232
Dosage used	375 mg/m^2 iv	100%
Frequency	1 dose every 3 months	97%
Administration of drug	50-100 mg/h increased q 30 min up to 400 mg/h	31%
	Accelerated infusion	30%

Table 5 Conformity to criteria

		Conformity
Indication	Follicular Lymphoma	72%
Dose	375 mg/m2 iv	100%
Dosage schedule	1 dose q 2 months or 1 dose q 3 months or 4 weekly doses q 6 months	99%
Duration of treatment	2 years	87%

DISCUSSION

Most of the patients receiving rituximab in our centers were treated for follicular lymphoma or DLBCL (62%). Literature is scarce concerning use of rituximab in other types of lymphoma. Although a small number of patients with rare histological subtypes were included in clinical trials, the widespread use of rituximab for other B lymphoma has been observed in our study and in many guidelines for non-Hodgkin's lymphoma. Use was similar in our 4 adult centers.

Rituximab use for off-label indications in adult and pediatric populations is not surprising. Our hospitals are quaternary, university-teaching hospitals. Our population includes patients who have exhausted the usual first-line treatments and who are referred to our centers for special expertise. Most of the off-label indications were supported by some kind of literature varying from case reports to phase II trials. Most of the patients receiving rituximab for those indications received it as a last resort. Unfortunately, since rituximab treatment in these cases were for chronic diseases and documentation of efficacy was not systematically required, it was impossible to measure outcomes for these patients.

Patients receiving rituximab maintenance treatment in our study received it after first-line induction therapy, second and even third line, following a Rituximab-containing chemotherapy regimen. We mostly use R-CVP as our first-line chemotherapy regimen. Although the Prima study is not yet published, we seem to have used rituximab before all evidenced-based data was available and we still do not know the real benefit of rituximab maintenance following first-line R-CVP.

Follicular lymphoma patients were not the only ones receiving maintenance therapy in our study. Studies published supporting maintenance treatment mostly included patients with follicular lymphoma, some SLL and mantle cell patients. Controversy about extending use of maintenance regimen of rituximab to other indolent lymphoma exists and one might argue that the biology might not be that different. Again, these histological subtypes are less frequent and will likely not be studied in clinical trials.

CONCLUSION

The widespread use or rituximab in our centers is not likely to diminish in the next few years. Indications for use need to be clarified in our centers by setting local evidence-based practice guidelines. Results of this study have been presented to our physicians for discussion. Recommendations were also made to our physicians to better document and measure the outcomes and to present the results to our P&T committees once a year. Pharmacists in our centers will also be asked to discuss with prescribers when an unusual rituximab order (indication, length of treatment) is identified. One of the objectives of the Therapeutic Drug Management Program (TDMP) is to promote the optimal use of drugs in our centers in view of efficacy, safety and costs.

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