



Rituximab (Anti-CD20 Monoclonal Antibody) in Lymphoproliferative Malignancies : Tata Memorial Experience

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Abstract

Rituximab has been used extensively in lymphoproliferative disorders. We evaluated the results of 64 consecutive patients treated between 2001 and 2004 at our institution. This included 54 males and 10 females. The median age was 54 years (range 17 to 85 years). One-fourth of patients were above 60 years. The histology was aggressive NHL in 35, indolent NHL in 22 and 7 cases were diagnosed as CLL. Among NHL, sixteen were in early stage (I/II) and the remaining forty-one were in advanced stage (III/IV) of disease. B symptoms were present in 47% of cases. A total of 33 were *de novo* cases and 31 were previously treated. Rituximab monotherapy was used in 17 cases. Rituximab was used in combination with chemotherapy in the other 47 cases. Infusional toxicity included anaphylaxis in one, hypotension in one and minor infusional reactions in four others. The patient who developed anaphylaxis required discontinuation of further Rituximab. Growth factors were used in 25 patients. Febrile neutropenia occurred in 19 patients. The overall RR (CR + PR) was 72%. One patient had stable disease and progressive disease was documented in 17 patients. A total of seven patients died, three due to progressive disease, three due to chemotherapy related toxicity and one due to an unrelated cause. We conclude that Rituximab is a valuable addition to the treatment armamentarium of lymphoproliferative disorders. ©

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) includes a heterogeneous group of biologically distinct lymphoid malignancies. At Tata Memorial Hospital we see approximately 680 cases of lymphoma every year, accounting for 4.3% of all cancer cases. 80% of these are chemo-naïve patients. In our experience, the complete response rate to Doxorubicin-based first-line chemotherapy is 58%.² The overall survival and disease free survival amongst new cases at 5 years was 62% and 50% respectively.² In previously treated patients, we have earlier obtained complete remission in 36% of patients with a 2 year overall survival and disease free survival of 35% and 20% respectively.³

Rituximab (Mabthera) was the first Monoclonal antibody (Moab) to be approved for the treatment of cancer. This chimeric antibody is directed against the CD20 antigen, which is present on the cell surface of 80-90% of B-cell lymphomas. Its mechanism of action includes antibody-dependant cell cytotoxicity (ADCC),

complement-dependant cytotoxicity as well as induction of apoptosis in vitro.⁴⁻⁶ Objective clinical responses, both as single agent and in combination with cytotoxic chemotherapy, have been demonstrated in a large number of adult patients with relapsed or newly diagnosed indolent as well as aggressive lymphomas. We present our experience with Mabthera therapy in treatment of lymphoproliferative diseases, the largest single institution experience from India so far.

PATIENTS AND METHODS

This is a retrospective evaluation of all consecutive CD20 positive lymphomas treated at our institute with Mabthera based therapy. The primary objectives were to assess the response rate and safety profile. Progression-free survival and overall survival were also evaluated.

Rituximab was given as single agent weekly or 3 weekly in combination with chemotherapy. It was administered in a dose of 375 mg/m² in 500ml normal saline after premedication (oral Paracetamol and Chlorpheniramine maleate). The infusion was started at 50 mg per hour for the first half hour. If there was no reaction, the infusion rate was increased so as to complete it over 3-4 hours. Patients who developed grade 4 febrile

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neutropenia were given granulocyte colony stimulating factor (G-CSF) in subsequent cycles.

Treatment responses were assessed after the planned number of cycles and defined as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) as per the standard criteria.⁷ Toxicity was graded as per NCI criteria.⁸

The progression free and overall survival was analyzed separately for the low-grade (including CLL) and high-grade groups by the log rank test and the survival curves were expressed as Kaplan – Meier plots.

RESULTS

There were a total of 64 patients in this study. The median age was 54 years (range 17-85 years). Approximately one-fourth (n=17, 27%) of the patients were above 60 years of age. Eighty four percent (54/64) of the patients were males. Forty seven percent (27/57) had class B symptoms (CLL excluded). Ninety two

percent of the patients had a performance status of less than or equal to 2 (8% had PS 3). IPI score were low in 13 patients (23%), low-intermediate in 22 (38.5 %), high-intermediate in 20 (35%) and high in 2 cases (3.5%). Two patients were HIV positive. Fifty two percent (33/64) were chemo-naïve (Tables 1 and 2). Of the 48% (31/64) who were treated at relapse, 65% were in first relapse, 32% in second relapse and 3% were in third relapse (Tables 3 and 4). A total of 35 patients had high-grade histology, 22 had low-grade histology and seven were cases of CLL. Treatment was discontinued in one patient due to Mabthera infusion- related anaphylaxis. This patient attained CR with COP chemotherapy thereafter.

We had 22 patients with low-grade NHL, of whom 18 were follicular lymphoma and four were marginal zone lymphomas. Of these 22, there were seven newly diagnosed cases and 15 relapsed cases. Nine patients received monotherapy with Rituximab and the rest received it in combination with chemotherapy. For the newly diagnosed patients (n=7) there was one patient

Table 1 : Newly diagnosed and monotherapy with rituximab

Sl	Initials	Accession no.	Stg	Hpr	Best res	Status lfu	Toxicity
1	BS	BS-17524	1A	MZ	SD	Alive	None
2	JP	BR-21316	2A	FL	PR	Alive	None
3	BS	BM-04302	CLL	PR	Alive	None	
4	MD	BU-08974	CLL	CR	Alive	None	

Table 2 : Newly diagnosed and combination treatment with chemotherapy

Sl	Initials	Accession no.	Stg	Hpr	Chemo t/t	Best res	Status lfu	Toxicity
1	AG	BS-19086	4B	DLBCL	R-CHOP	CR	Alive	PNS
2	SM	BS-13128	3B	DLBCL	R-CHOP	PR	Alive	PNS
3	JA	BS-15328	2A	DLBCL	R-CHOP	CR	Alive	GIT
4	AK	BS-15423	4B	DLBCL	R-CHOP	CR	Alive	Hypersen
5	SB	BT-08469	2A	DLBCL	R-CHOP	PD	LFU	None
6	PD	BT-14272	4B	DLBCL	R-CHOP	CR	Alive	FN
7	RJ	BT-15241	3B	DLBCL	R-CHOP	PD	LFU	None
8	MS	BT-18761	1A	DLBCL	R-CHOP	PR	Alive	PNS
9	MJ	BU-01949	1AE	DLBCL	R-DHAP	PR	Dead	GIT,Neph
10	YS	BT-13044	4B	DLBCL	R-CHOP	CR	Alive	PNS
11	VG	BU-01994	3A	DLBCL	R-CHOP	PD	Dead	None
12	VA	BU-03012	1A	DLBCL	R-COP..	CR	Alive	Hypersen
13	PS	BT-07472	3B	DLBCL	R-CHOP	CR	Alive	FN
14	PE	BT-17729	4B	DLBCL	R-CHOP	PR	Alive	FN,Muco
15	SM	BU-03691	2B	DLBCL	R-CMOP	CR	Alive	FN
16	MT	BT-19773	2B	DLBCL	R-CHOP	PR	Alive	None
17	BR	BU-5343	1B	DLBCL	R-CHOP	CR	Alive	None
18	SG	BU-8689	3A	DLBCL	R-CHOP	PR	Alive	FN
19	SS	BU-9320	4B	DLBCL	R-CHOP	PR	Alive	None
20	BP	BU-12903	4A	DLBCL	R-CHOP	PR	Alive	None
21	MC	BU-19002	2AE	DLBCL	R-CHOP	PR	Alive	FN, GIT
22	SS	BU-17839	2AE	DLBCL	R-CHOP	CR	Alive	None
23	NP	BU-13813	4AE	DLBCL	R-CNOP	CR	Alive	FN
24	AB	BU-03903	4B	FL	R-CHOP	PR	Alive	None
25	SD	BU-10464	4A	FL	R-CHOP	PD	Dead	FN
26	AM	BT-18559	4B	FL	R-CHOP	CR	Alive	FN,Muco
27	IB	BS-09284	3A	FL	R-CHOP	CR	Alive	None
28	HM	BU-03040	3B	FL	R-CHOP	PR	Alive	PNS
29	RH	BS-02985		CLL	R-CHOP	PD	Alive	FN,Muco

Table 3 : Relapsed / refractory and monotherapy with Rituximab

Sl	Initial	Accession no.	Stg	Hpr	Prev CT	Best res	Status lfu	Toxicity
1	GD	BL-00649	4B	FL	Fludara	PD	Dead	None
2	RD	BP-14728	4B	FL	CEOP	PD	Alive	None
3	RP	BT-07176	3A	FL	CHOP, LP	PD	Alive	None
4	SS	BS-11492	3B	FL	ATT	PD	Alive	None
5	SB	BR-02049	3A	FL	CEOP	PD	LFU	None
6	SR	BR-17035	4A	FL	COP	CR	Alive	None
7	AG	BT-07339	4A	FL	CHOP	CR	Alive	None
8	AG	BR-06603	3A	DLBCL	ASAP/ MINE	CR	Alive	None
9	SK	BM-09211	4B	DLBCL	CHOP	PR	Alive	None
10	KB	BR-09404	1B	DLBCL	CHOP	PR	Alive	None
11	AZ	BL-22897		CLL	Fludara	CR	Alive	None
12	RM	BR-04918		CLL	LP	CR	Alive	None
13	KS	BT-18535		CLL	Fludara	PD	Alive	None

Table 4 : Relapsed / refractory and combination treatment with chemotherapy

Sl	Initial	Accession no.	Stg	Hpr	Prev chemo	Chemo t/t	Best res	Status lfu	Toxicity
1	RD	BP-12962	4A	DLBCL	ATT	R-EPOCH	PD	Alive	Nf, Muco
2	SJ	BK-11372	3B	DLBCL	CHOP / MIN	R-MACOP-B	PD	Dead	None
3	PP	BL-18177	1A	DLBCL	CHOP / MIN	R-DHAP	PR	Alive	GIT, PNS
4	SJ	BS-02695	1B	DLBCL	CHOP	R-MINE/ESH	CR	Alive	GIT
5	NS	BT-09816	3B	DLBCL	CHOP / MIN	R-MINE/ESH	PR	Alive	Nf
6	VM	BU-05115	3A	DLBCL	CHOP / MIN	R-ESH	PR	Alive	Nf, Muco,
7	BP	BU-01797	4A	DLBCL	CHOP	R-MINE	PR	Alive	None
8	PD	BT-16369	3A	DLBCL	CNOP	R-MINE	PD	Dead	Nf, Muco
9	IK	BU-21698	4A	DLBCL	CHOP	R-MINE/ESH	PD	Alive	Nf, Muco
10	BB	BS-02967	4A	MZ	CHOP / MIN	R-ESH	PR	Alive	Nf
11	MN	BN-10836	1A	MZ	PEN	R-CHOP	CR	Alive	None
12	BR	BP-15792	3A	MZ	CHOP / MIN	R-DHAP	CR	Alive	None
13	SR	BS-12730	4B	FL	LP	R-CHOP	PR	Dead	None
14	RB	BK-12798	3A	FL	Fludara	R-CHOP	PR	Alive	Nf
15	RR	BM-11167	4B	FL	Fludara	R-CHOP	CR	Alive	Nf, PNS
16	BS	BS-11613	3AS	FL	RT	R-CHOP	CR	Alive	None
17	RS	BP-15906	3A	FL	ATT/EPOC	R-COP	PD	Alive	None
18	JS	BR-1650		CLL	LP	R-Fludara	PR	Alive	None

who achieved CR, 4 had PR, one showed SD and one had PD. For the relapsed cases (n=15) six achieved CR, two PR and seven had PD. The overall response rates were 71% for the chemo naive patients and 53% for the previously treated patients. There were three deaths.

Bcl-2 protein was overexpressed in 14 out of the 16 cases evaluated. Most of them were follicular lymphoma and had advanced disease (11 patients). The ORR was 79% (11/ 14) for bcl-2 positive patients.

Rituximab was tolerated well. The toxicity profile was acceptable and evaluated in 304 cycles administered to the 64 patients. Infusion related events occurred in six patients. In one case anaphylactic reaction, necessitated drug withdrawal. Nineteen patients had episodes of febrile neutropenia (all in patients who received Mabthera in combination with chemotherapy).

Growth factors were used in 39% of the patients. Dose modifications due to repeated febrile neutropenia were required in seven patients. One patient had *pneumocystis carinii* pneumonia. On follow up (upto 46 months), we encountered nine patients with Vincristine induced

peripheral neuropathy and one case each of Cisplatin induced sensorineural deafness and nephrotoxicity. There were no cases of cardiotoxicity.

TREATMENT

Forty-seven patients received Mabthera in combination with varying chemotherapy regimens in a 3 weekly schedule (Tables 2 and 4). Seventeen patients received monotherapy with Mabthera in a weekly schedule (Tables 1 and 3).

Treatment response

The median number of treatment cycles were 5 (range 1 - 8 cycles) and 86% of patients received the planned schedule. G-CSF was used in 39% of cases. The toxicity profile is detailed in the Tables 1 to 4. Best overall response after Rituximab treatment included 23 CR, 23 PR, one with SD and 17 with PD. Nine patients did not complete planned treatment with Rituximab. These included three patients who were lost to follow-up after one cycle, five early deaths and one discontinued because of anaphylaxis.

Survival

The Progression free survival (PFS) for low-grade and high-grade group is 29% and 41% respectively (Figs. 1 and 2). The overall survival (OS) for low-grade and high-grade group is 65% and 88% respectively (Figs. 1 and 2). At last follow up (median 6.2 months; range 3 days to 46 months), 22 are alive and disease free, 32 are alive with disease, three patients died due to progressive disease, one patient died of complications resulting from a head injury, three died of chemotherapy related toxicity and three patients were lost to follow up.

DISCUSSION

Since most lymphoproliferative disorders are of B cell origin, pan B cell antigens have been extensively evaluated as potential targets for antibody therapy. The CD20 antigen is a 297 amino acid phosphoprotein measuring 33-35 kilo Daltons in size. It is a B cell lineage antigen, which is expressed in more than 80-90% of B cell lymphomas, expression being particularly of high density in follicular lymphomas. It is also stable and does not get shed or secreted. Therefore it serves as an excellent target. Under the circumstances, it is not surprising that Mabthera (anti CD20 Moab) became the first commercially available Moab for cancers – which we have used in this study.

Combining Rituximab with chemotherapy is based on substantial single agent activity of Rituximab, nonoverlapping toxicities, the different mechanism of action, and the potential synergy with chemotherapeutic agents. The first study including patients treated with chemotherapy (CHOP) and Rituximab in low-grade lymphomas and was published in 1999.⁹ The 9-year follow-up of these patients ORR of 100%; 87% of patients achieved a complete response or unconfirmed CR. The median TTP and DR were 82.3 months and 83.5 months respectively.¹⁰ In our study ORR was 72%. One patient

had stable disease and progressive disease was documented in 17 patients. The OS for low-grade and high-grade group is 65% and 88% respectively at a median follow up of 6.2 months (range 3 days to 46 months).

Patients with follicular lymphomas generally have a favorable pharmacokinetics and higher response rate. In our study response was documented in 10 out of 18 cases (55.5%).

Two studies¹¹⁻¹² demonstrated that weekly Rituximab has significant activity in previously untreated chronic lymphocytic leukemia (CLL). It has been demonstrated that Rituximab monotherapy down regulates the anti-apoptotic proteins in CLL cells in vivo,¹⁴⁻¹⁵ thus offering enhanced response to fludarabine-based therapy. In our study, there were seven patients of CLL (new=3 and relapsed=4). Three attained CR, two achieved PR and two had PD. The responses in CLL are lower than seen with NHL possibly due to less CD20 expression on cell surface membranes as well as more rapid antibody clearance among non-responders. Two recent trials¹⁶⁻¹⁷ incorporating Rituximab with fludarabine alone and with cyclophosphamide have shown CR of 50% and 30-50% respectively with acceptable toxicity. This antibody is likely to make its greatest impact in combination treatment strategies. Maintenance treatment with Rituximab is one option that may prevent emergence of circulating malignant B cells, extend the duration of response and prolong the time to progression in responding patients.¹⁸

There were 35 patients with high-grade lymphomas. Of these 23 were newly diagnosed and 12 were relapsed patients. There were 13 CRs, 15 PRs and seven PD, with an overall response rate of 80%. Four patients died. There were 11 CRs, nine PRs among the newly diagnosed (ORR=87%). Clinical data suggests that Rituximab may be useful in the treatment of aggressive lymphomas.

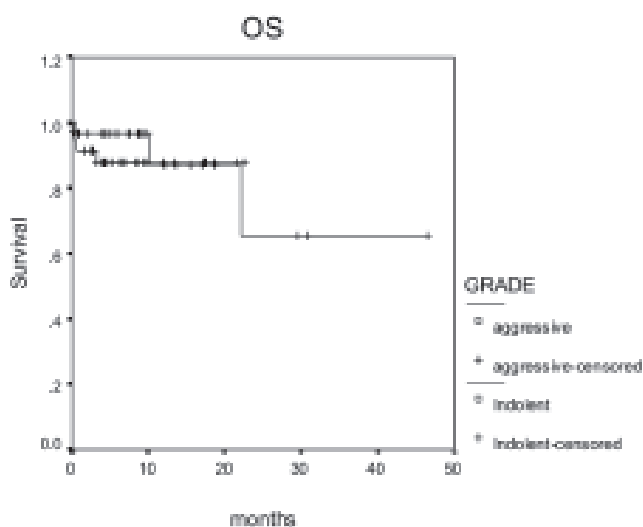


Fig. 1

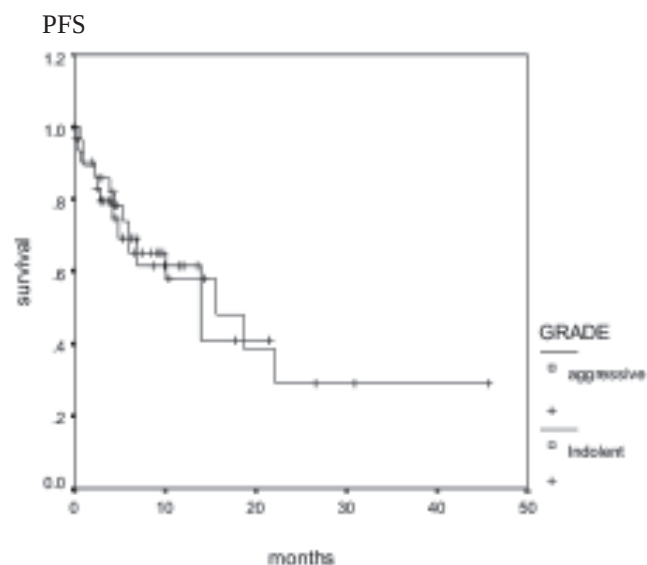


Fig. 2

Patients with high International Prognostic Indicator (IPI) score had a trend towards lower response rate but this was not statistically significant probably in view of the small number of patients.¹⁹

The GELA trial²⁰ was a randomized phase 3 study done in elderly patients with untreated DLBCL. This showed a CR of 75%, which was statistically better in the Rituximab plus CHOP arm as opposed to arm treated with CHOP alone (RR of 63%). Twenty seven percent (n=17) of patients were elderly. Ten were of high-grade histology and seven of low-grade histology (three cases of CLL). Among patients in the low grade NHL group there were four CRs, two PRs and one SDs. Among the high-grade group there were four CRs, four PRs and two progressive disease. Thus the overall complete response rate in this subgroup of our study was 47% with acceptable toxicity.

Patients were also analyzed separately, which showed bcl-2 positivity. Response rate was similar to what was observed for the whole group.

CONCLUSION

Rituximab provides a new paradigm in the treatment of lymphoproliferative malignancies. Rituximab can be safely given in our population. There was only one patient who had anaphylaxis and had to discontinue this drug. A total of 19 patients had febrile neutropenic episodes, when Rituximab was administered in combination with chemotherapy. The response rates are comparable with results in literature, when we stratify the various subsets. With this present data (and available data in literature) we confirm recommend use of Rituximab in all lymphomas with CD20+ve.

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