Rituximab (Chimeric Anti-CD20 Antibody) for Posttransplant Lymphoproliferative Disorder after Solid Organ Transplantation in Adults: Long-Term Experience from a Single Center

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Background. Occurrence of posttransplant lymphoproliferative disorder (PTLD) after transplantation is known. Drastic reduction or withdrawal of immunosuppression with anti-viral therapy for Ebstein-Barr virus (EBV) is the primary treatment for all PTLD. Many PTLD are B cell in origin have CD20 antigen on the cell surface. Rituximab is a chimeric anti CD20 antibody, which has been used to treat PTLD with variable success. This study aims to report long-term experience with rituximab for PTLD from a single center.

Methods. Seventeen patients (13 male, 4 female, mean age 51.2 years) received rituximab to treat PTLD. Five patients received rituximab with drastic reduction in immunosuppression (primary). Nine patients received rituximab after failure of primary therapy (rescue) and three patients received it after resolution of PTLD (prophylactic). Mean follow-up period was 60 months.

Results. Overall 1-, 3-, and 5-year patient survivals were 64.7%, 47.1% and 35.3%, respectively. In the primary group, three patients had complete and one had partial response; however, only two (40%) patients are currently alive. In the rescue group, none of the patients had a complete response, four patients had partial response, and only two (22%) patients are currently alive. In the prophylactic group, two patients died at 28 and 41 months due to recurrence and graft failure, respectively.

Conclusion. Sixty percent (3 of 5) of patients who received rituximab as primary therapy had complete resolution, and 44% (4 of 9) of patients who received it as rescue therapy had partial response. Overall 5-year patient survival was a disappointing 35%.

Keywords: Rituximab, Liver transplantation, Posttransplant lymphoproliferative disorder.

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Development of posttransplant lymphoproliferative disorders (PTLD) is a well-established complication after successful transplantation. This was first predicted and reported by Dr. Starzl and Penn et al. in 1968-69 (*1*, *2*). Initially, the management was controversial until, Dr. Starzl et al. in 1984 showed that it can be treated successfully by drastic reduction in immunosuppression (*3*). It has remained the accepted mode of treatment since then. However, this regimen, may lead to rejection of some allografts. Kidney or pancreas allograft can be sacrificed in some cases to control PTLD in order to save life. However, in liver transplant, holding the immunosuppression to control the PTLD can lead to irreversible, acute or chronic rejection, resulting in graft loss or even death. Although the rate of PTLD is lower in adults compared to children, the mortality rate is much higher in adults (*4*). At times, PTLD is Epstein-Barr virus (EBV) negative and can involve multiple sites. Despite conventional treatment consisting of antiviral therapy (acyclovir/ganciclovir) and withdrawal of immunosuppression (*5*), it carries significant mortality; hence, adjunct therapy becomes necessary. For adjunct therapy, immunomodulation (interferon, LAK cell (*6*)), chemotherapeutic agents and radiation, either simultaneously or sequentially, have been used (*5*, *7–11*). Antiviral and immunomodulation therapies are relatively safe but, unfortunately, offer limited success. Chemotherapy and radiotherapy carry significant amount of morbidity from their toxicity. The need for other less toxic adjunct agents is desirable.

The majority of PTLD is B-cell derived and carry CD20 proteins on their cell surfaces. Rituximab (Rituxam; Genetech Inc., San Francisco, CA and IDEL Pharmaceutical Corp., San Diego, CA) is a chimeric monoclonal (human IgG1Kappa/mouse variable region anti-CD20 IDEC-2B8) anti-CD 20 antibody, discovered in 1991. It binds with great affinity to cells expressing CD20 antigens on their surfaces. After binding, it causes complement dependent cell lysis and apoptosis. The drug was approved in November 1997 by the U.S. FDA and by European FDA in June 1998 for relapsed or refractory, low-grade follicular non-Hodgkin's lymphoma (*9*).

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Large multicenter trials have shown a response rate of up to 40 to 60% with rituximab in refractory or relapsing aggressive lymphoma following chemotherapy. The drug has been used as a primary therapy for follicular lymphoma or low-grade non-Hodgkin's lymphoma with a response rate of 72% (*12*, *13*). Since then, the drug has been used for treatment of PTLD with variable success, in the majority of cases as a primary therapy with reduction in the immunosuppression (*14–16*).

This aim of this study is to examine the role of Rituximab for PTLD in adult population after solid organ transplantation from our institution with long-term follow-up.

PATIENTS AND METHODS

Seventeen patients (13 males and 4 females with the mean age of 51.2±14.2 years) received rituximab to treat PTLD between March 1999 and July 2001. Among these 17 patients, 13 received a liver transplant alone, whereas four received a kidney transplant (KTx), of which three patients also received either a heart transplant (before KTx), liver transplant (before KTx) or pancreas transplantation (with KTx) (Table 1). Among 17 patients, 10 had PTLD at single site, 5 had PTLD at two different sites, one had PTLD at three different sites (Case 9) and another patient had PTLD at four different sites (Case 14). Thus, PTLD was encountered at 27 different sites in 17 patients. The distribution of sites of PTLD in each individual is shown in Table 2. Involvement of mesenteric lymph nodes with the gastrointestinal tract was considered as a single site. Involvement of more than one region within the same system was also considered as a single site (e.g., caecum and right sided bowel, cerebral and spinal cord or lymph nodes at different sites).

Types and Grading of PTLD

Histological findings were graded according to hematological workshop reported by Harris et al. (*17*). The status of Ebstein Barr Virus - encoded small nuclear RNA (EBER) in situ hybridization is shown in Table 2. All patients were given Rituximab 375 mg/m^2 weekly for 4 weeks. Two patients (Case 3, 9) received two courses of Rituximab. Except case 3, all patients completed the entire course of Rituximab therapy without any side effects.

Rituximab was used under 3 different settings: 1) With intial reduction or total withdrawl of immunosuppression with or without anti-viral therapy (primary therapy) or 2) after failure of initial reduction or total withdrawl of immunosuppression with or without anti-viral therapy (rescue group) or 3) after resolution of PTLD (prophylaxis).

All patients were followed till March 2005. The mean follow-up period was 59.6±11.2 months from the time of PTLD and 149.7±66.4 months from the time of transplant.

All patients received tacrolimus-based immunosuppression except three patients (Case # 2, 6, 16). The immunosuppressive protocol has been described from our institution in the past (*18*). The medical records including biochemical, radiological and pathological data was retrieved retrospectively after institutional review board approval. Their postPTLD management was also evaluated carefully.

RESULTS

Patient Survival

Overall 1-, 3-, and 5-year patient survival was 64.7%, 47.1% and 35.3% respectively. One-, 3-, and 5-year patient survival in primary group was 60%, 40% and 40%, that for rescue group was 55.6%, 33.3%, and 33.3% and for the prophylactic group was 100%, 100%, and 33.3% respectively. Although 1- to 3-year patient survival for prophylactic group was better initially, it was not different in long term.

At the last follow-up, 11 (64.7%) patients died and 6 patients (35.3%) were alive (Fig. 1A). Patient survival for different groups at last follow-up was 40% for Primary group 33.3% for Rescue group and 33.3% for Prophylaxis group (P=0.85) (Fig. 1B; Fig. 2).

Initial Response to Rituximab and Subsequent Outcome

When rituximab was used as a primary therapy, PTLD initially resolved completely in three patients (60%) (Case # 2, 4 and 5), it responded partially in one patient (20%) (Case # 3); and it did not respond in one patient (20%) (Case # 1). One patient (Case # 3) received a second course of rituximab, however, after 3 weeks it was discontinued due to bone marrow suppression. Patients with partial response and no response died at 8 and 7.5 months respectively after PTLD. Another patient (Case # 5) who had initial complete response subsequently developed recurrent PTLD and died at 17.3 months postPTLD, while other two patients (Case # 2 and 4) maintained the response at 52 and 54 months postPTLD. Therefore the long term response was only 40% for this group.

When the drug was used after failure of primary therapy (group II), none of the patients (0%) showed a complete response, four patients (44.4%) had a partial response (Case # 6, 8, 9 and 11) while remaining 5 patients (56.4%) had no response whatsoever. Out of 5 patients who had no response to rituximab, one patient (case # 9) received a second course of rituximab, three died at 4.6, 2.5 and 1.7 months after PTLD and the other two (Case # 10 and 12) are alive at 55 and 49 months after PTLD. Both these patients also received chemotherapy and one patient (Case # 10) underwent surgical excision of mesenteric mass in addition to chemotherapy, which was CD20− although the primary PTLD was CD20+ before administration of rituximab. Among patients who had a partial response, 3 died after chemotherapy and 1 survived (Case # 8) after chemotherapy 77 months postPTLD.

Three patients received rituximab as prophylaxis either following resection of the primary lesion (Case # 17) or after chemotherapy (Case # 15 and 16), when they were disease free. However, two of these patients (66.7%) (Case # 16 and 17) eventually died from recurrence of PTLD at 28 and 41 months from diagnosis.

Favorable Factors for Rituximab Response

Single Site vs. Multiple Sites

Two patients who had more than two sites involved (Case #9, 3 sites; Case # 14, 4 sites), died after 32 and 1.7 months postPTLD. Two patients (40%) out of 5, who had PTLD at two different sites, are currently alive and 4 patients (40%) out of 10, who had PTLD at single site, are currently alive.

TABLE 1. Patient characteristics

Patient no.	Age at transplant	Sex	Organ (s) transplanted	Time to PTLD from transplant (months)	Baseline immunosuppression	No. of rejections before PTLD	Treatment of rejection before PTLD
Group 1: Rituximab used as primary therapy							
1	60.9	M	Liver	107.7	Tacrolimus	NA	NA
2	53.1	M	Liver	56.4	Cyclosporine A	0	None
3	50.6	M	Kidney + heart	12.9	Tacrolimus	11	Steroid bolus, thymoglobulin
4	48.1	M	Liver	193.9	Tacrolimus	2	Steroid bolus, cyclosporine
5	72.6	M	Liver	56.7	Tacrolimus	0	None
Group 2: Rituximab used as rescue therapy after failure of primary therapy							
6	77.0	F	Liver	129.6	Cyclosporine A	0	None
7	67.0	F	Liver	25.2	Tacrolimus	NA	NA
8	53.2	M	Liver	12.3	Tacrolimus	0	None
9	24.3	M	Liver	31.4	Tacrolimus	NA	NA
10	32.0	M	Kidney + pancreas	77.6	Tacrolimus	1	Steroid bolus
11	49.3	F	Liver	106.6	Tacrolimus	2	Steroid bolus
12	51.7	M	Liver	45.7	Tacrolimus	0	None
13	65.3	M	Kidney + liver	213.0	Tacrolimus	2	Steroid bolus
14	48.8	M	Liver	2.6	Tacrolimus	2	Steroid bolus
Group 3: Rituximab used prophylactically after complete resolution of PTLD							
15	38.6	F	Liver	177.3	Tacrolimus	2	Steroid bolus
16	38.0	M	Kidney	170.5	Cyclosporine A	1	Steriod bolus
17	40.6	M	Liver	207.6	Tacrolimus	0	None

NA, not available.

TABLE 2. Sites and types of PTLD

Patient no.	Site of PTLD	No. of sites	Pathology	CD20 status	EBER status	Severity (Harry classification)
1	Sacral bone	1	Burkitt like Lymphoma	+	−	NA
2	Cervical lymph nodes	1	Large B-cell type, monomorphic, lymphomatous	+	−	3
3	Liver, lymph nodes	2	Monomorphic, diffuse large cell lymphoma	+	−	NA
4	Stomach	1	Polymomorphic	+	+	3
5	Duodenum	1	Monomorphic, diffuse large cell lymphoma	+	−	3
6	Skin on leg	1	Monomorphic, non-Hodgkin's lymphoma	+	−	3
7	Cervical, mesenteric and medistinal lymph nodes	2	Non-Hodgkin's lymphoma, small cleaved cell	+	−	NA
8	Pelvis, bone marrow, right lung, mediastinal lymph nodes	2	Monomorphic, monoclonal B and T clones	+	+	3
9	CoIon, spine, mandible, gluteal mass, kidney, testes, orbit	3	Small noncleaved cell, non-Burkitt lymphoma, monomorphic	+	+	3
10	Pancreas, small intestine, mesentric lymph nodes	1	Monomorphic, monoclonal	+ initially, − after rituximab	−	NA
11	Multiple lymph nodes, kidney	2	Disseminated non-Hodgkin's lymphoma, large cell type	+	NA	3
12	Left 3rd rib	1	Diffuse large B cell malignant lymphoma, monomorphic	−	−	3
13	Aorto-caval region mass	1	Diffuse large B cell lymphoma, monoclonal, monomorphic	+	−	4
14	Bone marrow, gastointestinal, mesentric and axillary lymph nodes, lung, CNS	4	Widespread extensive, polyclonal	+	+	NA
15	Liver, kidney, retroperitoneal lymph nodes	2	Malignant lymphoma diffuse large cell type monoclonal, monomorphic	+	NA	3
16	Lung, abdominal wall	2	Hodgkin's lymphoma		+	NA
17	Gastrointestinal	1	Monomorphic	+	−	3

NA, not available.

EBER+ vs. EBER–

Out of 17 patients, EBER status was determined in 15 patients and 5 were found to be EBER+ and 10 were EBER–. Initial survival for EBER+ at 3 years was 60% and for EBER− was 40%. However, two (40%) out of five EBER+ patients, and three (30%) out of 10 EBER− patients, are currently alive (P=0.63).

Other Treatments

Chemotherapy was used in 14 patients while radiotherapy was used in four. Sequential treatment and outcome of individual patients is shown in Table 3.

DISCUSSION

It is believed that some PTLD will respond if the host's immune system is allowed to reconstitute by stoppage of immunosuppression (by natural surveillance of immune system). However, this strategy can invariably lead to irreversible rejection of allograft. In cases where the patient has received non-life saving organs like kidney and pancreas, the transplanted organ can be sacrificed; however, it may not be acceptable in recipients where life saving organs like liver and/or heart is involved. Some sort of balance has to be reached in order to preserve the allograft function (even though compromised) so as to sustain life and, at the same time, allow PTLD to regress. In some patients, this balance is reached safely by dosage reduction or stoppage of immunosuppression. If PTLD resolves before rejection begins, re-introduction of immunosuppression at a much smaller dose will control the rejection in future and avoid recurrence of PTLD. On the other hand, if rejection occurs much before the PTLD is resolved, other treatment options are necessary. Chemotherapy and/or radiotherapy has been used successfully but not without associated toxicity, including morbidity or even mortality. Other treatment options like INF-a, INF-γ, anti-CD23 antibody and

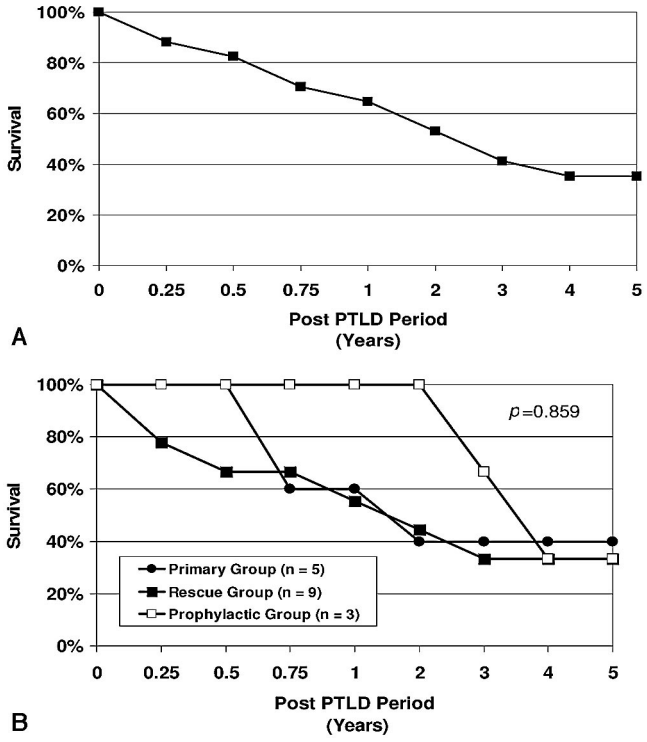

FIGURE 1. (A) Overall patient survival after PTLD. (B) Patient survival after PTLD, groupwise.

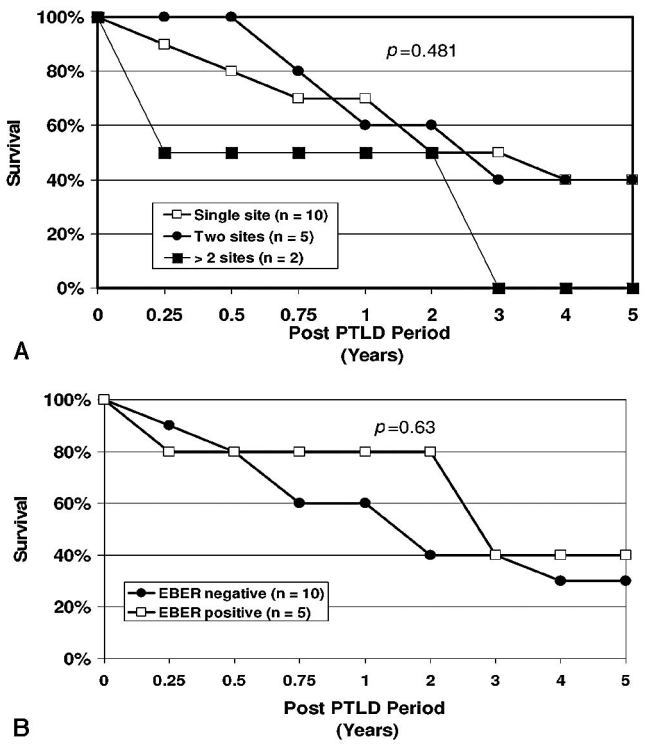

FIGURE 2. (A) Patient survival according to number of sites involved. (B) Patient survival according to EBER status.

LAK cell treatment have been tried in the past but with little benefits (*5*).

It is also recognized that PTLD in children is more often EBER+ and low grade, which responds favorably to the above strategy. Response rate of up to 72% has been observed with low grade PTLD. Unfortunately, in adult population, high grade PTLD occurs more frequently leading to higher mortality as compared to children (*4*). In this population, majority of PTLD when graded was found to be of high grade and not of a low grade (where 72% response rate is observed). Also, while partial response rate in follicular lymphoma or non-Hodgkin's lymphoma (non-immunosuppressed) patients, may be acceptable, it is not sufficient in patients with allografts, since restarting the immunosuppression will worsen the residual PTLD. In such situations, the institution of rituximab is an attractive treatment option for the population where PTLD is CD20+ve. This drug was first used in relapsed or chemotherapy refractory lymphoma and showed either partial or complete response in 48% of cases. There are several reports available to confirm its success in low-grade follicular or non-Hodgkin's lymphoma (*12*, *13*).

Some centers have reported similar success of rituximab in PTLD. The largest population of PTLD, treated with rituximab is reported by the French study which included 14 centers and incurred 32 patients (30 primary treatment and two prophylactic) in eight kidney transplants, eight liver transplants, six bone marrow transplants, four heart transplants, three lung transplants and combination of heart and lung, kidney and pancreas or liver and kidney transplants. Twenty patients had complete response while two patients had partial response (total 69%). Despite the significant success report, survival was only 73% among those who responded (*19*). This is comparable to survival observed in the large population from our center without rituximab (*4*). Ganne et al. found response in seven out of eight patients with primary therapy (*20*). Ifthikharuddin et al. reported three cases of PTLD and considered Rituximab as an effective treatment (*21*). Nonetheless, combination of chemotherapy with Rituximab has been suggested and used with partial to complete response in 95 to 100% of patients (*22*, *23*). Zompi et al. treated three patients, two patients treated prophylactically responded quickly with longer remission, but one patient with large-cell, non-Hodgkin's lymphoma did not respond (*16*). O'Dwyer has reported a single case of successful resolution of PTLD in kidney transplant with Rituximab (*14*). Oerstel treated one patient post-LTx successfully with Rituximab (*15*). Colombat et al. had suggested rituximab as a primary treatment for low tumor burden with partial or complete response rate of 73% (*12*).

Unfortunately, we did not find the kind of results others have observed, despite the fact that the drug was well tolerated in most of our patients. Our poor results, in part, may be related to the fact that majority of our patients had high tumor burden that involved multiple sites and high grade PTLD. A higher tumor burden is known to have poor response rate. Ghobrial et al. has suggested better response with low international prognostic index (*24*). The response rate was higher when the drug was used as a primary therapy. However, it is not possible to determine the efficacy of rituximab with certainty in this group of patients because these patients could have responded anyway without rituximab. Also, for rescue group, use of rituximab after failure of pri-

TABLE 3. Management and survival outcome

Use of rituximab	Patient no.	Primary therapy	Initial response to rituximab	Subsequent course and management	Rejection episodes	Dead or alive	Cause of death	Survival (months)	Current immunosuppression
Primary: rituximab used as primary therapy	1	Immunosuppression reduced by 50% rituximab	No response	Chemotherapy	NA	Dead	Unresolved PTLD	7.5	
	2	Immunosuppression reduced by 50% rituximab	Resolved	Recurrence free	2	Alive		52.4	Neoral 100 mg BID, prednisolone 5 mg QD
	3	Immunosuppression stopped rituximab	Partial response	Chemotherapy	3	Dead	Cardiac disease	8.0	
	4	Tacrolimus reduced and subsequently stopped, switched to sirolimus, rituximab	Resolved		NA	Alive		58.0	Sirolimus 3 mg QD, prednisolone 5 mg TIW
	5	Immunosuppression reduced, DHPG, rituximab	Resolved	Recurrence treated with chemotherapy	0	Dead	Recurrent PTLD	17.3	
Rescue: rituximab used after failure of primary therapy	6	Immunosuppression reduced, radiotherapy	Partial response	Chemotherapy	1	Dead	Sepsis due to colonic perforation	20.0	
	7	Immunosuppression reduced and subsequently stopped	No response	Chemotherapy	1	Dead	Unresolved PTLD	4.7	
	8	Immunosuppression stopped, DHPG	Partial response, recurrence of PTLD	Chemotherapy, surgical resection	1	Alive		77.2	Tacrolimus 1 mg QD, prednisolone 5 mg QD
	9	Immunosuppression reduced and subsequently stopped	Partial response	Chemotherapy, radiation	2	Dead	Unresolved PTLD	32.0	
	10	Immunosuppression reduced and subsequently stopped	No response	Chemotherapy	2	Alive		55.5	Tacrolimus 3 mg BID
	11	Immunosupprssion stopped	Partial response	Radiotherapy	NA	Dead	Unresolved PTLD	10.6	
	12	Immunosuppression stopped, DHPG	No response	Chemotherapy	1	Alive		49.1	Tacrolimus 1 mg BID
	13	Immunosuppression stopped, acyclovir	No response	Chemotherapy	0	Dead	Unresolved PTLD	2.5	
	14	Immunosuppression stopped, gancyclovir	No response		0	Dead	Unresolved PTLD	1.7	
Prophylactic: rituximab used after resolution of PTLD	15	Chemotherapy, immunosuppression stopped	Not applicable		0	Alive		71.8	Tacrolimus 1 mg QD, prednisolone 5 mg QOD
	16	Immunosuppression reduced and subsequently stopped, chemotherapy, surgical resection	Not applicable	Recurrence	0	Dead	Recurrent PTLD	28.5	
	17	Surgical excision, immunosuppression stopped	Not applicable	Steroid resistant rejection leading to graft failure	1	Dead	Liver and kidney failure	41.3	

NA, not available.

mary therapy and drastic reduction of immunosuppression with or without anti-viral therapy delayed the institution of chemotherapy and/or radiotherapy, which could have inadvertently affected the rate of resolution of PTLD. More prospective randomized trials are needed to determine the precise efficacy and role of rituximab in treating PTLD. Until such results are available, based on our experience, we feel that rituximab may only be used either as adjunct with conventional therapy or with chemotherapy where conventional therapy has failed or prophylactically after surgical excision of the lesion. Using rituximab as a definitive therapy after failure of conventional treatment may have a poor outcome resulting in delay in the institution of more potent regimen of proven efficacy (chemotherapy or radiotherapy), which may inadvertently affect the resolution and survival outcomes. Our observations are further supported by Orjuela et al. (*25*). He reported that the combination of chemotherapy and rituximab was well tolerated and had better response rates. Similarly Dotti et al. reported five cases of PTLD after heart or liver transplantation and observed favorable clinical outcomes where surgery or radiotherapy has produced significant debulking and in advanced clinical stage where only partial response is expected (*26*). In addition, European best practice guidelines recommends rituximab and CHOP regimen for diffuse lymphoma, which supports our argument in part (*27*).

In the adult population, PTLD, which failed to respond to conventional treatment also failed to respond to subsequent use of rituximab. Overall 5-year patient survival was 35%. Based on our findings, rituximab may be used as an adjuvant therapy in the adult population, rather than sequential therapy.

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