

Usefulness and Limitations of Rituximab in Managing Patients With Lymphoproliferative Disorder After Heart Transplantation

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Abstract

Posttransplant lymphoproliferative disorders remain an uncommon complication of heart transplant with a high mortality rate reported after conventional therapies. Four patients with posttransplant lymphoproliferative disorders, of whom 3 were CD20 positive, received intravenous dosages of rituximab, 375 mg/m², weekly, for 6 ± 2 weeks. The overall response rate was 75% with 3 complete responses (CD20 positive) and 1 case of progressive disease (CD20 negative). Rituximab should be considered as a first-line therapy for patients with CD20 positive posttransplant lymphoproliferative disorders.

Key words: Rituximab, Lymphoma, Heart transplant, CD20

Introduction

Posttransplant lymphoproliferative disorders (PTLD) remains an uncommon complication of heart transplant, occurring in 2% to 6% of cases.¹⁻³ Most patients will develop CD20 positive malignancies.⁴ The Epstein-Barr virus (EBV) has been identified as a causative agent in the pathogenesis of PTLD and is believed to be associated with as much as 90% of the cases.⁵ The highest risk of developing PTLD is during the first year after transplant.⁶ In solid-organ

transplant recipients, the median time of onset of PTLD is about 6 months. These lymphomas tend to behave more aggressively and outcomes are believed to be poorer than in the general population.³⁻⁶ Despite the use of a variety of therapies, which include a reduction in immunosuppressive therapy, chemotherapy, radiation, and sometimes surgical resection, mortality rates are high and treatment remains challenging. As a result, new therapeutic options have been studied. Immunotherapy with monoclonal antibodies, such as rituximab (Hoffman La Roche, Grenzachstrasse 124, CH-4070 Basel Switzerland) has showed interesting results in the nontransplant populations.^{2,3} Reports concerning the safety and efficacy of rituximab in heart transplant recipients with PTLD are limited. We describe 4 consecutive heart transplant recipients who received a diagnostic of pathologically proven PTLD and were treated with anti-CD20 antibody treatment between June 2003 and August 2009.

Case Reports

The first patient is a 24-year-old EBV-seronegative man who underwent a cardiac transplant in June 2003 from an EBV-positive donor. The posttransplant evolution was favorable until January 2004 when he was hospitalized with complaints of upper respiratory tract symptoms, fever, and abundant diarrhea. Lactate dehydrogenase levels were elevated at 3338 U/L.

A thoraco-abdominal computed tomography (CT) scan showed enlarged mediastinal lymph nodes and hepatosplenomegaly with multiple hypodense lesions (Figure 1) as well as mesenteric lymphadenopathies and a subcutaneous paraumbilical mass of 3.2 × 2.2 cm was biopsied. Immunohistochemical stains on paraffin-embedded tissue

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Acknowledgements: We thank Michelle Dubois RN BSc, for her technical assistance in the preparation of the manuscript.

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Experimental and Clinical Transplantation (2012) 5: 513-518

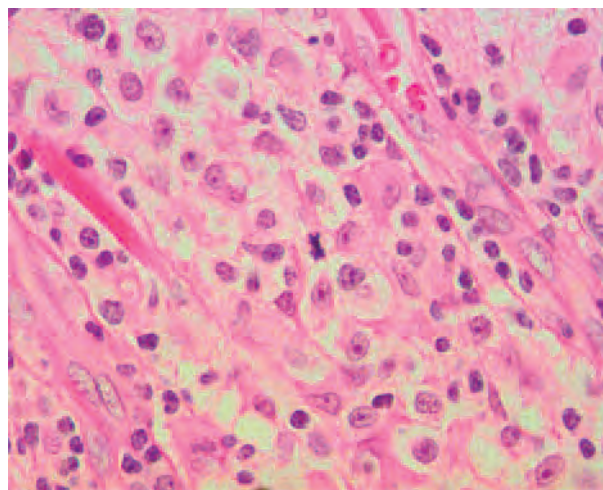
Figure 1. Abdominal CT Scan Showing Hepatosplenomegaly With Multiple Hepatic and Splenic Hypodense Lesions



sections showed strong reactivity for CD20 (Figure 2). A diagnosis of diffuse, large, B-cell lymphoma was made. The tumor was EBV-positive while blood EBV PCR remained negative. Tacrolimus was reduced and mycophenolate mofetil was discontinued (Table 1). Rituximab was the initial choice of treatment and was administered at standard dosages for 4 weeks with no adverse events. One month after discharge, a CT scan showed persistent lymphoma in the spleen and liver. Another rituximab cycle was initiated for total of 8 treatments. More than 72 months after diagnosis, there is no evidence of persistence or recurrence of the disease.

The second patient is a 62-year-old EBV-seronegative man who underwent a cardiac transplant in October 2003 from an EBV-seropositive donor. His evolution posttransplant went well until May 2004 when he presented with abdominal pain and weight loss. The initial work-up was normal except for a slightly elevated lactate dehydrogenase level (378 U/L). An abdominal CT was done demonstrating multiple adenopathies and an ileal mass compatible with PTLD. The patient was referred to surgery and a partial intestinal resection was done. Immunohistochemical stains showed a diffuse, large-cell lymphoma type B. The EBV and

Figure 2. Histology of Periumbilical Nodule Biopsy Showing a Diffuse Malignant Lymphoid Proliferation (Original Magnification $\times 1000$; Hematoxylin-Eosin Stain)



CD20 in the tumor were positive. Tacrolimus was reduced and prednisone and mycophenolate were discontinued. The patient was then started on rituximab therapy, for a total of 6 treatments without adverse reactions. Six years after the diagnosis of PTLD, he is considered to be in remission.

The third patient is a 54-year-old EBV-seropositive woman who received a heart transplant in February 2006 from an EBV-positive donor. The posttransplant period was unremarkable. A CT scan of the abdomen obtained in March 2009 because of an elevated sedimentation rate at 90, showed multiple mesenteric adenopathies, some ≥ 3 centimeters. The patient was asymptomatic and an initial work-up including lactate dehydrogenase was normal. Immunohistochemical stains of these nodes showed a diffuse, large-cell lymphoma type B. The EBV and CD20 in the tumor were positive. Mycophenolate mofetil was discontinued, tacrolimus was reduced, and this patient received a standard rituximab cycle of 4 weeks. She developed a papular rash that was deemed to be an adverse reaction to rituximab. Four years after the diagnosis of PTLD, she is considered to be in complete remission.

The fourth patient is a 58-year-old EBV-seropositive man who underwent cardiac

Table 1. Immunosuppressive Agents at the Time of Diagnosis and 3 Months After Diagnosis (mg/24 h)

Patient	Prednisone at Diagnosis	Prednisone After 3 mo	Tacrolimus at Diagnosis	Tacrolimus After 3 mo	Mycophenolate at Diagnosis	Mycophenolate After 3 mo
1	0	0	15	9	2500	0
2	5	2.5	7	3.5	1500	0
3	0	2.0	4	2	1000	0
4	0	0	3.5	2	750	0

Abbreviations: mo, months

transplant in June 2006 from a donor of unknown EBV status. He was initially evaluated at his community hospital in August 2009 for fatigue and abdominal pain. An abdominal CT scan showed ileal masses, compatible with PTLT. He underwent a partial resection of the intestine with vesical plasty. Macroscopic examination revealed multiple lesions with “fish-flesh” appearance. The immunohistochemical study showed an elevated proliferation index (90%), CD20 receptor and EBV tumor staining were negative. The final diagnosis was that of diffuse, large, B-cell PTLT. Tacrolimus was reduced and mycophenolate mofetil was discontinued. A 4-week cycle of rituximab was started in September without any adverse reactions. One month later, a positron emission topography scan demonstrated persistent activity in the ileum and new foci in the jejunum and stomach. These results prompted the initiation of another rituximab cycle. The evolution was complicated by clostridium difficile colitis after the fifth rituximab treatment. Another positron emission topography scan was done in November 2009 and showed continued progression of the PTLT. At that time, a chemotherapy regimen was initiated and the patient responded favorably. A year later, he remains asymptomatic and abdominal imaging remains negative for PTLT.

Of note, despite significant reduction in calcineurin inhibitor levels, none of these patients have experienced significant cardiac rejection (ISHLT grade 2 or 3) or decrease in ejection fraction.

Discussion

Posttransplant lymphoproliferative disorders are among the most-serious complications of chronic immunosuppression in transplant recipients. These patients have a 20- to 120-fold higher incidence of non-Hodgkin lymphoma. Historically, there have been several therapeutic approaches to PTLT. Reduction in immunosuppression is considered the first-line therapy for PTLT.⁷⁻¹⁰ In this context, proper follow-up with repeated cardiac biopsy is important; using this strategy cardiac rejection did not occur in our cohort. Surgical resection and radiotherapy have been tried and proven effective primarily in patients with limited-stage disease.^{3, 11, 12}

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed at the

CD20 receptor of normal and malignant B lymphocytes. The CD20 receptor is involved in regulating transmembrane calcium conductance and cell-cycle progression during human B-cell activation. Rituximab has 3 potential mechanisms of action including apoptosis, complement activation, and antibody-dependent cell-mediated cytotoxicity.¹³⁻¹⁷ The majority of PTLTs after solid-organ transplant is known to be CD20-positive and diffuse large B-cell lymphomas represents about 75% of all cases of PTLT in adults. Several cases of PTLT treated with rituximab have been presented using a standard regimen of 375 mg/m² once a week for 4 consecutive weeks. The majority of these reports describe the use of rituximab in early onset PTLT. In late-onset CD-20-positive PTLT (> 2 years posttransplant), Dotti and associates presented a series of 5 successfully treated cases with rituximab.¹⁸ Other reports suggest a response rate of 37% to 69% over an 8- to 32-month follow-up.^{12, 19-26} The factors explaining the differences in rate response are still unknown; clear predictors of complete remission after rituximab also are not identified. In the largest prospective trial of rituximab in PTLT, Choquet and associates showed that in patients unresponsive to reduction of immunosuppression, adjunct rituximab resulted in a response rate of 44% (including 28% remission) at 3 months. In two-thirds of these patients, the response was maintained at 1 year.⁸ In a recent series, rituximab was demonstrated effective in 11 patients with CD20-positive PTLT. In these patients, a rituximab cycle was repeated every 6 months for 2 years in responders. The median follow-up was 10 months. The overall response rate was 64%, with 6 complete response, 1 partial response, 2 cases of progressive disease, and 2 deaths.²

In our center, the rituximab antibody was administered to 4 patients with PTLT and yielded 3 complete remissions. Our patients received 4 to 8 treatments, depending on the response noted after the end of the first cycle (Table 2). Minor adverse events were observed, and the only nonresponder had a CD20-negative tumor (Table 3). This suggests that as in nontransplant patients, CD20 positivity may be important for rituximab efficacy.^{1, 8, 12} In most series, CD20 status was unknown. In a large study evaluating a low-dose chemotherapy regimen in children with CD20-positive PTLT with failed front-line therapy (immunosuppression

Table 2. Effects of Anti-CD20 Antibody Treatment on PTLD and Other Treatments

Patient	Treatment	Results	Duration (mo)	Status	Surgery	Chemotherapy
1	8 Rituximab	CR	74	Alive	No	No
2	6 Rituximab	CR	69	Alive	Yes	No
3	4 Rituximab	CR	10	Alive	No	No
4	5 Rituximab	NR	10	Alive	Yes	Yes

Abbreviations: CR, complete remission; NR, no response; PTLD, posttransplant lymphoproliferative disorder

Table 3. Patients and PTLD Characteristics

Patient	Age/Sex	Time to Diagn (mo)	Affected Sites	Stage	LDH	Histology	Phenotype / CD20	EBV Donor	EBV Recipient
1	24/M	7	Spleen, liver, intestine	IV	3 338	DLCL	B/+	+	-
2	62/M	6	Intestine	IV	378	DLCL	B/+	+	-
3	54/F	37	LN	II	164	DLCL	B/+	+	+
4	58/M	26	Intestine	IV	150	DLCL	B/-	NA	+

Abbreviations: Diagn, diagnosis; DLCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; F, female; LDH, lactate dehydrogenase; LN, lymph nodes; M, male; NA, not available; PTLD, posttransplant lymphoproliferative disorder; Time to Diagn, time from transplant to diagnosis of PTLD

reduction/surgical reduction), only 2 patients out of 36 had rituximab therapy after initial diagnosis,¹⁹ which suggests that rituximab maybe underused as a potential treatment for PTLD. Until recently, patients with PTLD who did not respond to immunosuppression reduction were treated with cytotoxic chemotherapy. However, there is no prospective randomized trial comparing chemotherapy to rituximab in that setting. A recent retrospective study analyzed data of 35 PTLD patients who underwent treatment with rituximab, chemotherapy, or both. The findings confirmed that single agent rituximab and chemotherapy could be effective in patients who fail immunosuppression reduction.²⁷ While rituximab was well tolerated, 26% of patients who received chemotherapy died from treatment-related toxicities. An important observation in this study was that patients who failed treatment with rituximab could receive salvage chemotherapy later. In the same line, a recent prospective trial including patients (n=17) with PTLD and CD20-positive immunohistologic staining, demonstrated that rituximab alone yielded 53% (n=9) complete remission in that homogenous population. Of interest, 4 more patients had stabilization of the disease with rituximab and achieved complete remission with the adjunction of chemotherapy.²⁸ Whether, chemotherapy should be included initially with rituximab in all CD20-positive PTLD patients remains debatable.

Reports concerning the efficacy of rituximab in heart transplant recipient with PTLD are limited.²⁹⁻³⁷ Treatment options for PTLD after heart transplant are not standardized, usually sequential, starting with a reduction in immunosuppression. In a prospective

study including 13 heart transplant patients, aggressive reduction in immunosuppression (calcineurin reduction by 50% for 2 weeks and further 50% reduction for 1 week if not in complete remission), produced noncomplete remission and rejection was frequent.²⁹ Clearly, the initial strategy has limitations. Recently, a sequential approach was tried to avoid the significant risks of chemotherapy; however, those concerns do not apply to rituximab. Along with immunosuppression reduction, rituximab may induce complete remission or allow lowering of chemotherapy dosages in an attempt to reduce toxicity, particularly in pediatric patients. Of interest, in a recent study including 10 heart transplant patients, complete remission was 80% in the group of patients receiving rituximab alone, and 100% in patients receiving chemotherapy and rituximab.³⁰ The efficacy and durability of rituximab in different PTLD subsets remains to be fully defined, but it is clear that a significant number of patients will be in complete remission without the use of chemotherapy.

Clearly, treatment of PTLD is difficult and individualization of therapy is necessary. Some patients will respond to a reduction of immunosuppression, while others also will need rituximab and/or chemotherapy to obtain complete remission. Rituximab response rate in most studies are encouraging. Large prospective multicenter studies are needed to determine the more-appropriate therapy and understand the factors influencing response. When such characterization is done, a higher rate of cure will be obtained. Until then, based on this well-tolerated and effective profile demonstrated by this cases series and by others,

rituximab, along with immunosuppression reduction, should be considered as a first-line therapy for patients with CD20-positive PTLD.

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