

# Monotherapy with Anti-CD20 Monoclonal Antibody in a Heart Transplant Recipient with Sick Sinus Syndrome and Posttransplantation Lymphoproliferative Disorder: A Case Report

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## ABSTRACT

Posttransplantation lymphoproliferative disorder (PTLD) is a serious complication of organ transplantation, with an incidence of 0.8% to 20% in heart transplant (HTx) recipients, and standard treatment may be too toxic in some cases. Rituximab is an anti-CD20 monoclonal antibody that has demonstrated efficacy in patients with various lymphoid malignancies and has been demonstrated effective in combination with chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). Cardiotoxicity with CHOP remains a major concern for treating HTx recipients with PTLD, however. We present a case of an HTx recipient with sick sinus syndrome and PTLD who was successfully treated with rituximab alone, avoiding the cardiotoxicity of CHOP. The cardiotoxicity induced by CHOP should be kept in mind in HTx recipients with PTLD, especially when there is an existing heart problem in such recipients. Monotherapy with rituximab can be considered a safe choice.

## INTRODUCTION

Posttransplantation lymphoproliferative disorder (PTLD) is a serious complication of organ transplantation, with an incidence of 0.8% to 20% in heart transplant (HTx) recipients [Gao 2003]. Histologic categories of PTLD present from benign polyclonal lymphoid hyperplasia to aggressive monoclonal lymphoma. PTLD tends to be extranodal, and approximately two thirds of patients are in extended stage III or IV at the time of diagnosis [Oertel 2005]. Rituximab is an anti-CD20 monoclonal antibody that has demonstrated efficacy in patients with various lymphoid malignancies, including indolent and aggressive forms of B-cell non-Hodgkin's lymphoma.

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A pivotal trial has established rituximab as a first-line treatment option when combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy in untreated elderly patients with diffuse large B-cell lymphoma (DLBCL), the most common type of aggressive non-Hodgkin's lymphoma [Coiffier 2002]. The toxicity of the chemotherapy regimens remains a major concern, however. Doxorubicin, a compound in the anthracycline class, is well known for its cardiotoxicity, which has also been reported for cyclophosphamide. We present a case of an HTx recipient with sick sinus syndrome and PTLD who was successfully treated with rituximab alone, avoiding the cardiotoxicity of CHOP.

## CASE REPORT

A 61-year-old Asian man with dilated cardiomyopathy underwent orthotopic heart transplantation in June 2005. The recipient had IgG antibodies against cytomegalovirus and Epstein-Barr virus. The donor, a 51-year-old man, also had cytomegalovirus IgG antibodies. Polyclonal antithymocyte globulin (2.5 mg/kg per day for 5 days) and methylprednisolone (500 mg at operation) were used for induction immunosuppression. Maintenance immunosuppressive agents included cyclosporine (CsA) (5-10 mg/kg [350-450 µg/L prior to the morning dose] for the first 3 months), mycophenolate mofetil (MMF) (1-3 g/day; white blood cell count, 5000-7000 × 10<sup>3</sup>/µL) and prednisolone (0.4 mg/kg per day; total, 30 mg/day with tapering to 10 mg/day). Anticytomegalovirus antibody (250 U) (Cytotect; Biotest, Dreieich, Germany) was injected every 2 weeks to prevent cytomegalovirus infection.

An episode of acute cellular rejection (International Society for Heart & Lung Transplantation working classification grade II) that developed 3 months after transplantation was successfully treated with 3 daily doses of intravenous methylprednisolone (500 mg). The rejection reaction was grade IA to IB at 4, 6, 12, and 18 months after transplantation.

At 18 months after transplantation, the patient was admitted because of dizziness with a sensation of an accelerating or slowing heart rate. His basic rhythm was sinus rhythm with incomplete right bundle branch block and a tachybradycardia pattern. An electrocardiography evaluation with 24-hour

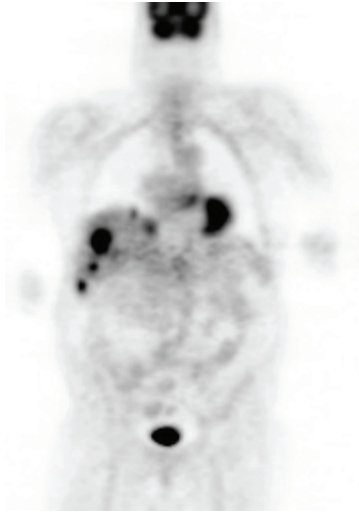


Figure 1. [<sup>18</sup>F]fluoro-2-deoxy-D-glucose activity in the left anterior mediastinal and inferior tracheobronchial lymphoid spaces and the liver.

Holter monitoring recorded paroxysmal atrial fibrillation with a maximum rate of 162 beats/min and some episodes of complete atrioventricular block with a minimum rate of 46 beats/min. The patient's blood pressure was 100-130/60-80 mm Hg. His echocardiogram revealed a left ventricular ejection fraction of 25%. An endomyocardial biopsy indicated rejection grade 1B. The maintenance immunosuppressive treatment was adjusted to 250 mg/day CsA, 500 mg/day MMF, and 10 mg/day prednisolone. A permanent pacemaker (VVIR; threshold, 0.2 V; impedance, 1368 Ω; R wave, 9.6 mV) was implanted for the sick sinus syndrome.

A sonographic examination of the patient's abdomen, scheduled because of liver function impairment (aspartate aminotransferase, 123 U/L; alanine aminotransferase, 98 U/L), showed 1 round, hypoechoic mass of approximately 3.2 × 3.4 cm over segment 7 of the liver. A computed tomography (CT) scan of the abdomen showed several low-density, poorly contrast-enhanced nodules in the right lobe of the liver. An ultrasound-guided biopsy was performed, and the presence of DLBCL was proved by pathology analysis. Diffuse positive immunohistochemical staining for CD20, CD45, and Bcl-2, and focal positive staining for LMP-1 were noted. Reactive T-cells stained positively for CD3. A positron emission tomography (PET) scan, which was scheduled for tumor staging, demonstrated intensive [<sup>18</sup>F]fluoro-2-deoxy-D-glucose activity in the liver (segments 4, 5, and 6) and mediastinum (left anterior mediastinal and inferior tracheobronchial lymphoid spaces) (Figure 1). Immunotherapy with rituximab (MabThera<sup>®</sup>; Roche Pharmaceuticals, Basel, Switzerland) was administered at a dose of 375 mg/m<sup>2</sup> for a total intravenous dose of 700 mg weekly for 8 weeks. MMF therapy was discontinued, and immunosuppressive treatment was reduced to 150 mg/day CsA and 10 mg/day prednisolone.

Two months later, a contrast CT scan of the patient's abdomen demonstrated a partial remission of the neoplasm. An echocardiogram revealed a left ventricular ejection fraction

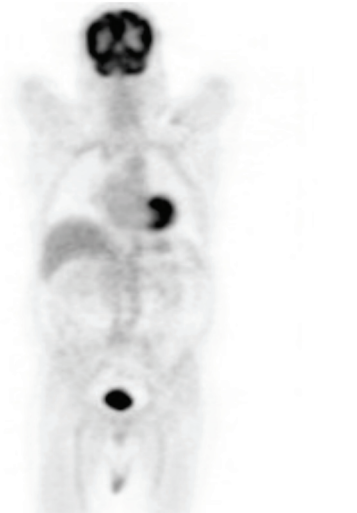


Figure 2. No evidence of significantly abnormal [<sup>18</sup>F]fluoro-2-deoxy-D-glucose uptake in any region of the body.

of 30%. Another 8-week course of rituximab immunotherapy (700 mg weekly) was administered. Overall, there were no major side effects during the 2 courses except for mild flu-like symptoms at the first 2 times of infusion. A sonogram of the abdomen at the 1-month follow-up showed complete remission. A PET/CT study demonstrated no residual tumor at the 1-year follow-up (Figure 2). An echocardiography evaluation revealed a left ventricular ejection fraction of 35%. The rejection reaction was grade IA to IB during immunotherapy and at the 1-year follow-up. The patient's heartbeat was a paced rhythm of 90 beats/min, and his blood pressure remained at approximately 110/70 mm Hg. He regularly visits the outpatient department for follow-up.

## DISCUSSION

PTLD after heart transplantation is a serious complication, and standard treatment may be too toxic in some cases. Among the PTLT, DLBCL is the most common type of aggressive monoclonal lymphoma. A randomized multicenter study conducted by Coiffier et al [2002] reported a high efficacy for a regimen of rituximab plus CHOP chemotherapy compared with CHOP alone in untreated elderly patients with DLBCL. Studies of rituximab monotherapy (typically 375 mg/m<sup>2</sup> once weekly for 4-8 doses) have generally been restricted to patients with relapsed or recurrent disease [Coiffier 1998; Igarashi 2002].

For HTx recipients with PTLT, cytotoxic drugs such as anthracyclines and cyclophosphamide can be a double-edged sword because of their cardiotoxicity [Schimmel 2004; Takemura 2007; Wallace 2007]. Doxorubicin has both acute and chronic effects on the cardiovascular system, including arrhythmias, ST-T segment changes, cardiomyopathy, and congestive heart failure [Takemura 2007]. Cyclophosphamide is a component of transplantation immunosuppressive regimens and is associated with acute cardiotoxicity [Schimmel 2004].

A number of studies have reported the use of methods (including echocardiography, radionuclide angiography, protective agents, and changes in delivery methods) to monitor, reduce, and prevent the development of acute or severe chronic cardiotoxicity [Gharib 2002; Lu 2005]. A variety of approaches to preventing cardiotoxicity have been tried, but the ability of these treatments to protect the heart from harmful side effects has thus far been limited. In some cases, the side effects are beyond prevention by the time defects are detected [Gharib 2002]. The ideal monitoring technique has yet to be determined.

At present, doxorubicin-induced cardiomyopathy and heart failure are refractory to conventional therapy [Hjalmarson 1994]. Risk factors for doxorubicin toxicity include combination therapy with other cardiotoxic antitumor drugs (such as cyclophosphamide), an increased age at exposure, and a history of cardiac disease [Takemura 2007]. Liposomal encapsulation may alter the tissue distribution and pharmacokinetics of an agent, leading to target specificity and a reduction in side effects. Studies have reported that the risk of anthracycline-induced cardiotoxicity is considerably lower with liposomal doxorubicin formulations than with conventional doxorubicin [Safra 2003; Rahman 2007], but there is insufficient evidence that liposomal doxorubicin provides safety for patients with heart problems. The long-term cardiac safety of these agents is unknown [Safra 2003].

Our case was of a 61-year-old HTx recipient who simultaneously received diagnoses of sick sinus syndrome and CD20-positive DLBCL. On the basis of the concerns discussed above, we used rituximab alone to treat the DLBCL. Partial remission was noted after completion of 8 rituximab doses, and another 8 doses was administered instead of CHOP to avoid the potential worsening of the heart problem by CHOP cardiotoxicity. The final outcome was not only complete remission but also no evidence of cardiotoxicity at the 1-year follow-up. In conclusion, the cardiotoxicity induced by CHOP should be kept in mind in HTx recipients with PTLT, especially when there is an existing heart problem in such recipients. Monotherapy with rituximab can be considered a safe choice.

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