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A comparison of desensitization methods: Rituximab with/without plasmapheresis in ABO-incompatible living donor liver transplantation

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ABSTRACT

Background: Plasmapheresis is a desensitization method used prior to ABO-incompatible (ABO-I) living donor liver transplantation. However, studies on its usefulness in the rituximab era are lacking.
Methods: Fifty-six adult patients underwent ABO-I living donor liver transplantation between January 2012 and October 2015. A single dose of rituximab (300 mg/m^2) was administered 2 weeks before surgery with plasmapheresis in all patients until February 2014 (RP group, $n=26$). Patients were administered rituximab only, without plasmapheresis between March 2014 and October 2015 (RO group, $n=30$).
Results: The 6-, 12- and 18-month overall survival rates were 92.3%, 80.8% and 76.9% in the RP group and 96.6%, 85.4% and 85.4% in the RO group, respectively ($P=0.574$). When the initial isoagglutinin titers < 16, neither group showed a rebound rise of isoagglutinin titers. For patients with initial isoagglutinin titers ≥ 16, the rebound rise of isoagglutinin titers was more prominent in the RP group. There was no difference in time-dependent changes in B cell subpopulations and ABO-I-related complications.
Conclusions: Sufficient desensitization for ABO-I living donor liver transplantation can be achieved using rituximab alone. This desensitization strategy does not affect the isoagglutinin titers, ABO-I-related complications and patient survival.
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Introduction

Since Starzl et al. [1] first reported 11 cases of ABO-incompatible (ABO-I) liver transplantation (LT) in 1979, there have been numerous advances. In countries with a severe lack of deceased donors, such as South Korea and Japan, ABO-I living donors have been crucial in expanding the pool of donors. Concerns about ABO-I-related complications, such as antibody-mediated rejection (AMR), biliary stricture, hepatic artery thrombosis, infection, poor graft and patient survival, have continually been raised [2–7]. However, the scope of applications for ABO-I LT has gradually broadened, and outcomes have improved considerably with the introduction of treatment strategies such as plasmapheresis, splenectomy, graft local infusion, rituximab, mycophenolate mofetil, and intravenous immunoglobulin, which can prevent AMR by lowering the titer level and inhibiting the production of anti-blood type isoagglutinin [8–13].

The most representative example of treatment strategies for ABO-I LT is rituximab with plasmapheresis. Rituximab is a monoclonal antibody targeting CD20 proteins on the surface of B cells. It was first introduced in Japan for prophylactic use in ABO-I LT patients during the early 2000s and used continuously for ABO-I LT at many centers, dramatically improving outcomes [10,14,15]. Plasmapheresis usually begins 1–2 weeks before ABO-I LT, with the aim of removing the preformed anti-blood type isoagglutinins.

Although plasmapheresis contributes to reducing anti-blood type isoagglutinin titers for ABO-I LT, there has been a lack of study on its usefulness in the rituximab era. This study aimed to evaluate the reliability, safety, and limitation of current desensitization protocols by comparing changes in anti-blood type isoagglutinin titers and peripheral blood B cells over time, patient survival, and ABO-I-related complications between a group undergoing rituximab only therapy and a group undergoing rituximab and plasmapheresis therapy in ABO-I LT.

Methods

Patients

This study was a single-center, retrospective study of 56 consecutive adult patients (18 years or over) who underwent ABO-I living donor liver transplantation (LDLT) at the National Cancer Center in Korea between January 2012 and October 2015. Between January 2012 and February 2014, 26 patients underwent desensitization

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with rituximab and several rounds of plasmapheresis (RP group) prior to ABO-I LDLT; 30 patients between March 2014 and October 2015 underwent preoperative desensitization with rituximab only, without plasmapheresis (RO group). Medical records, including demographics, anti-blood type isoagglutinin titers, CD19+ lymphocyte (B cell) subpopulations, and surgical outcomes such as patient survival and complications, were reviewed. This study was approved by our Institutional Review Board (IRB number: NCC2016-0157).

Desensitization and immunosuppression

A single dose of rituximab (300 mg/m^2) was administered approximately 2 weeks before surgery, but all patients prior to February 2014 also underwent plasmapheresis 1–2 weeks before the operation; patients from March 2014 onward were only administered rituximab. No other methods, such as splenectomy, graft local infusion (e.g. with prostaglandin E1, methylprednisolone, and gabexate mesilate), and preoperative mycophenolate mofetil, were used. Intravenous immunoglobulin (0.8 g/kg) was administered on postoperative days 1 and 4.

For induction therapy, basiliximab (20 mg) was administered on the day of the surgery and postoperative day 4. Immunosuppressive agents were a combination of tacrolimus, mycophenolate mofetil, and corticosteroids. Tacrolimus was started within 2 days after ABO-I LDLT with a goal trough of 8–12 ng/mL, and mycophenolate mofetil was started from postoperative day 2 at a dose of 1.5 g/day. The dose of corticosteroids was gradually reduced up to discontinuation 6 months after ABO-I LDLT.

Operation

In all cases, the right lobe of the liver donor was used. After full mobilization of the recipient's liver, the left and right portal veins were clamped before resection. The middle hepatic vein and left hepatic vein were resected with a surgical stapler, and the right hepatic vein was clamped before removing any diseased liver left in the peritoneal cavity after resection.

After the recipient's total hepatectomy, implantation began with right hepatic vein anastomosis using a modified right liver graft. In cases with an inferior right hepatic vein of at least 5 mm, that was directly anastomosed to the inferior vena cava. Based on its size and redundancy, the right portal vein of the graft was anastomosed to either the right or main portal vein of the recipient. Following reperfusion, hepatic artery anastomosis was achieved using surgical microscopy to anastomose the right hepatic artery of the graft with either the right or left hepatic artery of the recipient. Duct-to-duct biliary reconstruction was performed in all cases [16–21].

Perioperative management and follow-up

Apart from the desensitization methods, all other procedures were identical to ABO-compatible (ABO-C) LDLT, including routine laboratory and imaging tests such as computed tomography, magnetic resonance imaging, and positron emission tomography-computed tomography.

For patients with hepatitis B virus infection, hepatitis B immunoglobulin, and entecavir or tenofovir were used for hepatitis B prophylaxis after LDLT. In patients with suspected recurrence of hepatitis C virus, pegylated-interferon and ribavirin were used after confirming hepatitis C virus RNA levels and elevated liver enzyme levels. Other infection prophylaxis consisted of ticarcillin-clavulanate for 1 week, fluconazole for 1 month, and trimethoprim-sulfamethoxazole for 1 year.

Anti-blood type isoagglutinin titers were measured using the immediate spin technique [22,23]; these were measured immediately before rituximab administration, and continually from after the start of plasmapheresis until discharge. Following discharge, measurements were taken every week during the first postoperative month, and every 2 weeks to 1 month after that.

B cell (CD19+) subpopulations were measured by flow cytometry immediately before rituximab administration, and immediately before ABO-I LDLT [24,25]. Further measurements were taken twice a week from ABO-I LDLT to discharge, once a week from discharge to the end of the first postoperative month, and once per month after that.

In ABO-I LT, AMR can present in 2 broad forms: hepatic necrosis within the first postoperative week, or diffuse intrahepatic biliary stricture 1–2 months after transplantation [26,27]. Diffuse intrahepatic biliary stricture was considered if multiple strictures or sporadic dilatation of intrahepatic bile ducts was observed in computed tomography scans. AMR was suspected and a biopsy was performed in cases with a 4-fold or greater increase in anti-blood type isoagglutinin titers compared to surgery or anti-blood type isoagglutinin titers higher than 1:32, abnormal liver function test results exceeding normal values by 2–3-fold for serum aspartate aminotransferase, alanine aminotransferase, and total bilirubin, and a lack of abnormal findings by imaging tests. Also, in these cases, plasmapheresis was performed prior to liver biopsy results.

Statistical analysis

Continuous variables are given as mean ± standard deviation (SD) or median (interquartile range) and compared with a Student's *t* test or Mann–Whitney *U* test, depending on the normality of the distribution. For categorical variables, comparisons between groups were done with a Chi-square test or Fisher's exact test, as appropriate. Analyses for AMR, biopsy-proven acute cellular rejection, and other ABO-I-related complications between groups were made using a Mantel–Haenszel test stratified by the initial isoagglutinin titers 16. Cut-off values for continuous variables were defined as the point with the most significant (log-rank test) split using the "maxstat" and "survival" packages of R software. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Cox's proportional hazard model was used for multivariate analysis. A P value of less than 0.05 was considered statistically significant. All calculations were made using the SPSS 24.0 (IBM, Inc., Chicago, IL, USA) and R 3.3.3(https://www.r-project.org). The statistical methods were checked by the Biometric Research Branch, Research Institute and Hospital, National Cancer Center, Korea.

Results

Demographics

A total of 56 patients underwent ABO-I LDLT. These patients were divided into two groups according to the desensitization method, with 46.4% ($n=26$) in the RP group and 53.6% ($n=30$) in the RO group. The mean age of the recipients was 52.3 ± 8.1 years for the RP group and 54.3 ± 6.7 years for the RO group ($P=0.312$). The proportion of male and female recipients was 69.2% ($n=18$) and 30.8% ($n=8$) in the RP group, and was 60.0% ($n=18$) and 40.0% ($n=12$) in the RO group ($P=0.472$).

In terms of the ABO type of donor to recipient, the most common combination in the RP group was A to O in 23.1% of patients ($n=6$), while the most common combination in the RO group was AB to B in 30.0% of patients ($n=9$) ($P=0.413$). The median value for initial isoagglutinin titers prior to desensitization was 32 (8–32) in the RP group and 8 (4–16) in the RO group ($P<0.001$).

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