

ABO-Incompatible Living Donor Liver Transplantation

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Poor results after ABO-incompatible living donor liver transplantation (LDLT) are closely associated with severe hyperacute rejection due to the presence of anti-donor ABO antibodies during the early postoperative period. Nonetheless, ABO-incompatible LDLT has not been abandoned, and several different protocols have been proposed with the aim of avoiding acute graft necrosis and chronic biliary damage, both of which are recognized as major causes of poor outcome. Plasmapheresis to decrease anti-ABO titers and rituximab prophylaxis have been utilized to improve the outcome of ABO-incompatible LDLT. The lack of alternatives to LDLT provides a strong ongoing justification for performing ABO-incompatible LDLT in Korea.

Key Words: ABO blood-group system, Rituximab, Plasmapheresis, Treatment

중심 단어: ABO 혈액형, 리툽시맙, 혈장분리교환술, 치료 성과

Introduction

In Western countries where liver grafts from deceased donors are the main source of tissue, recipients are selected based on their ABO-compatible group. In Korea, sociocultural reasons limit the supply of organs from deceased donors, which has led to a patient waiting list several times large than the number of liver donors. Although living donor liver transplantation (LDLT) has been established as a treatment for patients with end-stage liver disease, donor selection is limited primarily to relatives and spouses. However, the growth of waiting lists and the urgency of liver transplantation have increased the drive to expand the donor pool by considering more unconventional and higher-risk techniques. These new strategies include transplantation from ABO-incompatible donors, which would normally be considered a barrier to transplantation.

Common Complications after adult ABO-Incompatible LDLT

ABO-incompatible liver transplantations are only performed in emergency situations, and the results are usually not satisfactory(1). The primary reason for the poor results associated with this approach is severe hyperacute rejection by anti-donor ABO antibodies. Specifically, attachment of anti-blood type antibodies to blood type antigens present on vascular endothelial cells results in damage to the endothelial cells. This phenomenon is mediated by the production of substances such as cytokines, chemotactic factors, and free radicals, and is accompanied by platelet and complement activation, thrombus formation, granulocyte and macrophage migration, and phagocytosis by granulocytes and macrophages(2,3). Moreover, hepatic necrosis and intrahepatic biliary complications are closely related to high perioperative anti-A or anti-B Ab titers(4).

Anti-A/B Isoagglutinin Titer

Most of the efforts to improve the outcome of ABO-incompatible LDLT have been directed toward the elimination of anti-blood type antibodies to prevent hyperacute rejection, antibody-mediated rejection, hep-

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atic necrosis, and intrahepatic biliary complications. The primary approach to reduce the abundance of preformed anti-donor ABO antibodies is apheresis performed before transplantation, and there are many published regimens for antibody removal. The main methods used for physically removing circulating antibodies are centrifugal plasma exchange (therapeutic plasma exchange, TPE)(5), double filtration plasma-pheresis(6), and immunoabsorption (IA) columns(7). In addition, splenectomy can be performed during the operation to reduce the source of antibody production. In published research, most approaches aimed to achieve IgM and IgG titers below 1:16 at the time of liver transplantation(8).

The median number of therapeutic plasma exchange (TPE) treatments of 8 (range, 6~18) enables the success of ABO-incompatible LDLT in patients with a high initial titer (IgM and IgG $\geq 1:256$). In addition, there are no statistical differences among clinical characteristics, infectious complications, biliary complications, vascular complications, or liver function tests after transplantation between groups with low and high initial titers(9).

Most of the current efforts to improve the outcome of ABO-incompatible LDLT have been directed toward the elimination of anti-blood type antibodies to a level considered safe before transplantation. In a recent study, the median number of TPE treatments was 4 in the low initial titer group and 8 in the high initial titer group; however, the median number of TPE treatments until the target level ($\leq 1:8$) was reached indicated that the median TPE number was 2 in the low initial titer group and 4 in the high initial titer group(9).

Rituximab

The spleen is the site of maturation of B lymphocytes. Splenectomy is often performed during LDLT to reduce the source of antibodies production. However, the spleen represents only 25% of the peripheral lymphoid tissue, and splenectomy compromises other immune functions of the spleen. Although these procedures have contributed to the success of transplantation

in pediatric patients, splenectomy has almost no effectiveness in adult patients(10,11).

Rituximab is a monoclonal chimeric human-murine anti-CD20 antibody that depletes the B cells by complement-dependent cytotoxicity, drug-induced apoptotic death, and antibody-dependent cellular cytotoxicity(2). Rituximab has been approved for the treatment of relapsed or refractory B-cell non-Hodgkin's lymphoma. Although splenectomy is required to remove B cells from the spleen, rituximab depletes CD20-positive B cells from the spleen. Egawa et al.(12) studied the timing of rituximab administration in ABO-incompatible LDLT recipients, and concluded that early prophylaxis with rituximab depletes B cells, including memory B cells, in the spleen and is associated with a trend toward lower antibody-mediated rejection rates. Thus, splenectomy is not always performed for cases of rituximab administration, and its necessity remains controversial in LDLT. Further, several recent studies on LDLT do not include the splenectomy in their protocols(9,13).

Systemic Infusion

Despite the dismal outcomes of initial ABO-incompatible LDLT, the application of local graft infusion treatment, which delivers protease inhibitors, prostaglandins and steroids through the portal vein or hepatic artery have increased the survival of ABO-incompatible LDLT to greater than 50%(11,14). However, such local graft infusions are associated with a high incidence of catheter-associated problems including vascular thrombosis, bleeding, and infection(11). Interestingly, despite the recent invention and application of rituximab, local graft infusion is still exclusively used in ABO-incompatible LDLT. Recently, an ABO-incompatible LDLT protocol without the use of local graft infusion was shown to be a safe and effective treatment modality(9,13).

Outcomes

The first ABO-incompatible LDLT was reported in the year 2000(15). ABO-incompatible liver transplanta-

tion is performed only in an emergency, and the results are not usually satisfactory with respect to patient and graft survival(16,17). Indeed, the current literature for Japanese patients indicates that the overall experience using ABO-incompatible LDLT for adult recipients is only slightly greater than 20% patient survival at 2 years. The main reason for this poor result is severe hyperacute rejection due to the presence of anti-donor ABO antibodies during the early postoperative period.

Recently, several studies have reported similar outcomes of ABO-incompatible LDLT compared with ABO-compatible LDLT(1,18,19). The largest cohort of the Japan Study Group for ABO-incompatible transplantation showed a significant decrease of AMR (antibody-mediated rejection) and increased survival between 2000 and 2006, owing to improved immunosuppressive treatment regimens and complication management(11). However, the high risk of complications after ABO-incompatible LDLT such as biliary complication, acute rejection, and hepatic artery thrombosis remains a vital issue for ABO-incompatible LDLT(8). Yoon et al.(18) reported that patient survival and biliary complications in ABO-incompatible LDLT are comparable with ABO-compatible LDLT. Further, meta-analysis results have shown that there are no statistically significant differences in pediatric graft survival rate among 1-year, 3-year, 5-year, and 10-year graft survival rates. However, the 1-year, 3-year, and 5-year graft survival rates for adult exhibit statistically significant differences between ABO-incompatible LDLT and ABO-compatible LDLT groups. Specifically, the graft survival rate of the ABO-compatible LDLT group is higher than for ABO-incompatible LDLT groups, but within each group the 1-year, 3-year, and 5-year patient survival rates are not significantly different. In addition, the rate of patient survival after ABO-incompatible LDLT is elevated mainly by retransplantation(8).

Conclusion

Rituximab and TPE may enable ABO-incompatible LDLT. With respect to long-term outcomes of ABO-incompatible LDLT, if acute antibody-mediated rejection and biliary dysfunction are overcome, survival after

ABO-incompatible LDLT can be expected to proceed without severe complications. Thus, we believe that ABO-incompatibility should not be considered an absolute contraindication to LDLT because good outcomes can be achieved. Going forward, it will be necessary to identify the immunological factors associated with desirable outcomes to better match donors and recipients.

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