COMMEMORATIVE LECTURE

Progress and future in living donor liver transplantation

Koichi Tanaka

Department of Transplantation and Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

(Received for publication on April 23, 2003)

Key words: liver transplantation, living donor, liver regeneration, immunosuppression, liver graft

Living donor liver transplantation (LDLT) is a new modality that has been developed to overcome the shortage of available cadaveric livers for transplantation. This modality now covers a wide range from newborn to advanced age. However, the evolution has revealed many unresolved problems such as liver anatomy, physiology, and immunology as well as social and psychological controversies. I'd like to discuss the progress in and future of LDLT.

Introduction of LDLT

After basic research, Thomas Starzl did the first cadaveric liver transplantation on a human being in 1963. The first success was in 1967 in Denver, Colorado. Owing to the dramatic increase in patient survival brought about by the immunosuppressant cyclosporine as well as the improvement of quality of life, liver transplantation was established as a treatment modality that spread in the 1980s (Fig. 1). Since then, the number on the waiting list has increased rapidly and the organ shortage is now the great concern although the availability of organs from brain-dead donors is gradually increasing in the United States. The liver has the specific characteristic of regeneration according to internal demand after partial resection. Also, vascular and alveoli structures systemically form each segment (Fig. 2). Based on these characteristics, I had an idea that liver transplantation using a part of liver from living donor could be a lifesaving treatment for end-stage liver disease in our country where the concept of brain-death has not yet been accepted. Feasibility test using the canine model have been studied since 1987 for future clinical application in our laboratory. Although such experiments were tried in Japan many years ago, they did not lead to clinical application in the past. The reduced-sized liver transplantation[1] in which only a lobe of the liver is used as a graft and the split liver transplantation[2] in which two recipients receive a graft from a single donor paved the way to LDLT. The first clinical LDLT was performed in Sao Paulo, Brazil in 1988,[3] and the first successful LDLT was reported in Brisbane, Australia, in July 1989.[4] In parallel, in Japan, the first LDLT was done in Shimane Medical College in November 1989,[5] followed shortly thereafter by the series of LDLT of Kyoto University[6] and Shinshu University. In LDLT, major advantages would include the good viability of a partial liver donated by a healthy individual; the careful selection of the timing of the transplantation; and the potential good tissue matching. Disadvantages are the risks to healthy donors and also that this modality is a potential psychological burden on a potential donor.

Overall Results

The annual and cumulative number of LDLTs has rapidly increased in our institute since 1990 (Fig. 3). We have performed 850 LDLTs until the end of October of this year. 2002 was the 13th year since the introduction of this modality to our institute. Seventy-five percent of the indications in children have cholestatic diseases, followed by congenital metabolic disease and fulminant hepatic failure. On the other hand, indications in adults are more variable. Cholestatic diseases including primary sclerosing cholangitis and primary biliary cirrhosis make up approximately thirty percent, but the majority is post-necrotic end-stage cirrhosis due to viral hepatitis with or without hepatocellular carcinoma (Fig. 4). The indication has been extended to ABO incompatible grafts, fulminant hepatic failure, which needs urgent informed consent, and re-transplantation. We started

---

Dr. Tanaka is the recipient of the 2002 Keio Medical Science Prize.

Presented at the Keio Medical Science Prize Symposium, November 29, 2002.

Reprint requests to: Dr. Koichi Tanaka, Department of Transplantation and Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

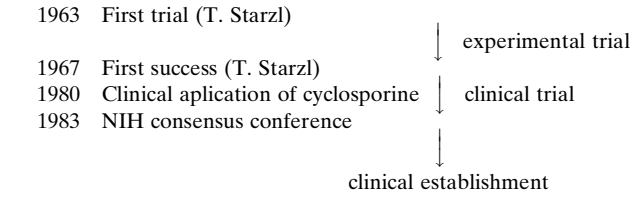

Fig. 1 Evolution in liver transplantation from brain dead donor.

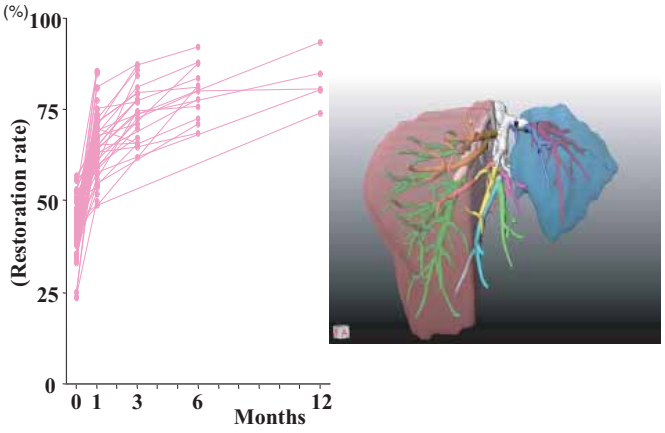

Fig. 2 Liver regeneration and segmentation of the liver.

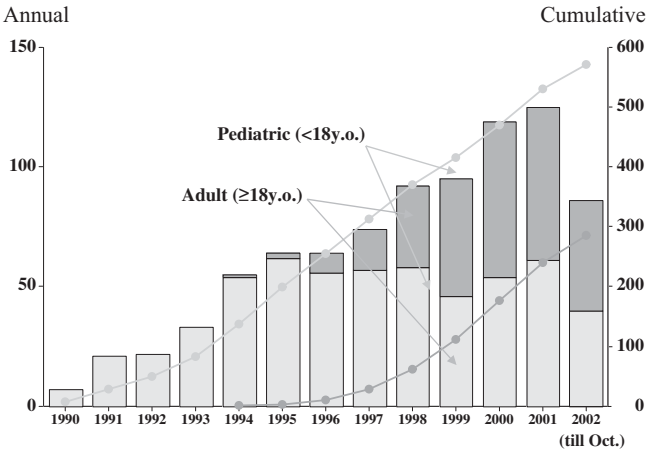

Fig. 3 Number of LDLTx cases (annual and cumulative).

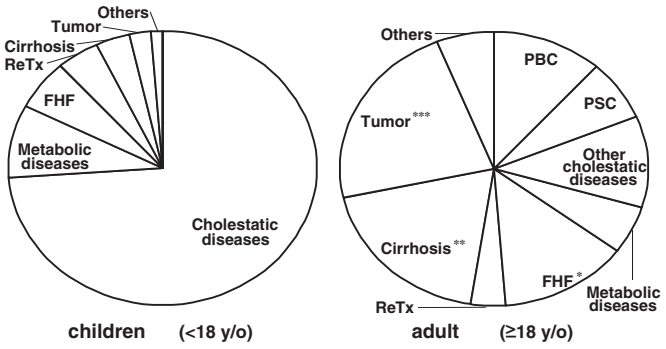

Fig. 4 Indications of LDLT.

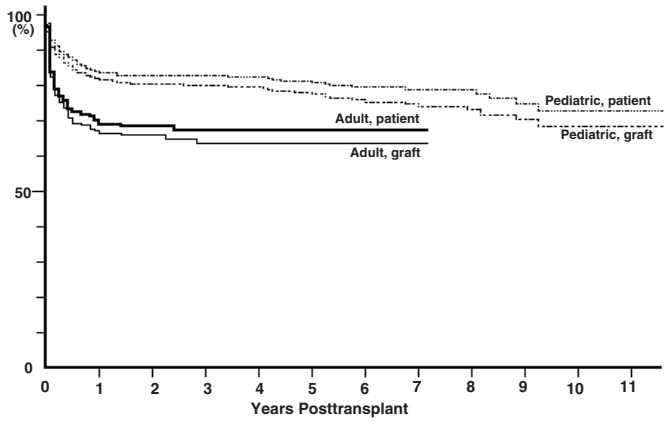

Fig. 5 Patient & graft survival rate.

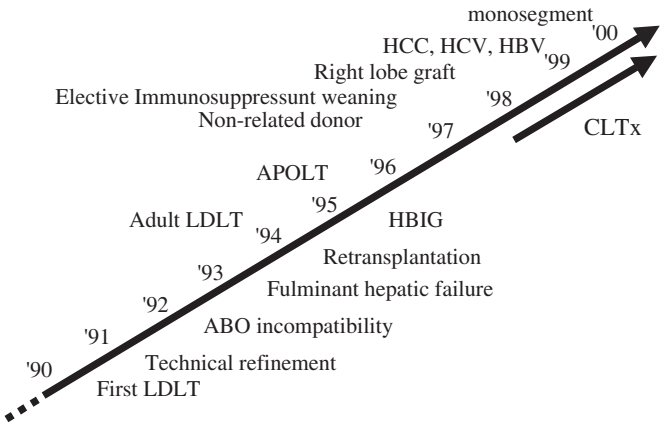

Fig. 6 Evolution in liver transplantation in Kyoto.

adult LDLT in 1984. After the introduction of the right lobe graft, the indication was expanded and adapted to patients with HCC and/or viral-related liver cirrhosis. Our overall cumulative survival rate is seventy percent in adults and eighty-five percent in children. Patient survival is higher than graft survival owing to the success of re-transplantation (Fig. 5). Since our first case in 1990, we have encountered many subjects and have put a lot of effort into their resolution (Fig. 6).

Surgical Techniques and Innovations

Regarding technical innovations, the major subjects were the safe liver resection in the donor and the reduction of technical complications in the recipient.[7] From the technical point of view, the incidence of hepatic artery thrombosis in cadaveric liver transplan-

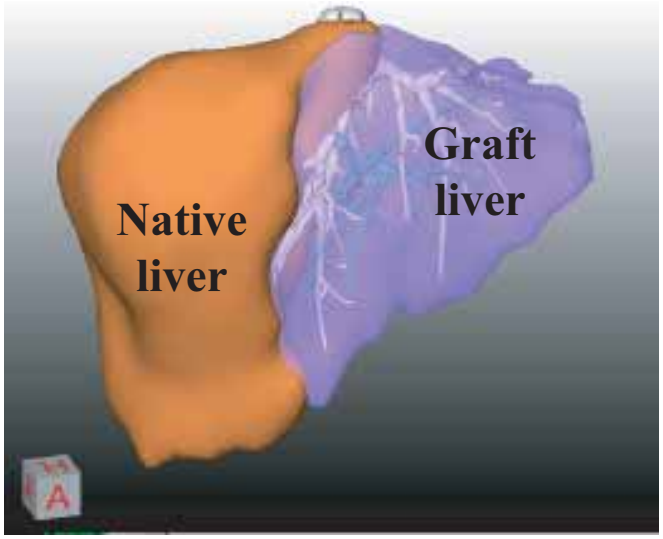

Fig. 7 Auxiliary partial orthotopic liver transplantation.

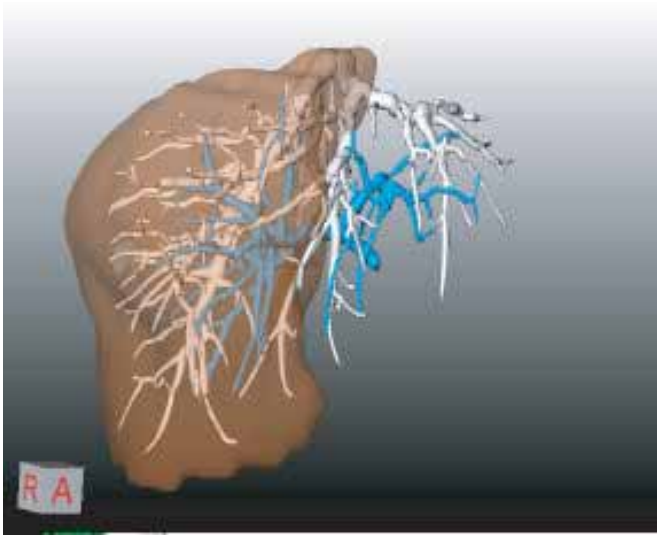

Fig. 8 Right lobe graft.

tation in children was reported to be as high as 15 to 20 percent. Most cases with hepatic artery thrombosis were reported to need retransplantation. Prevention of this complication is extremely important in our country where the backup system of re-transplantation using cadaver donors is difficult. To deal with this, we have introduced microsurgical artery reconstruction for the first time in the world,[8] which reduced the incidence to 1.5 percent, and many programs abroad have followed this technique. Auxiliary orthotopic liver transplantation, which is a technique of a partial resection of the diseased liver and implant of a graft orthotopically, is indicated for patients with metabolic liver disease, fulminant hepatic failure or too small sized grafts (Fig. 7). We introduced the right lobe graft,[9] which is about 60% of the whole liver, for adult LDLTs in 1998 (Fig. 8). The right lobe graft is divided into two types: the right lobe graft without the middle hepatic vein and the right lobe graft with the middle hepatic vein. The major concern is how much remnant liver is necessary for donor safety when the right lobe graft is used. From our experience, we think that less than 30% remnant liver is a risky volume for a donor, thirty to thirty-five percent is the marginal volume, and more than thirty-five percent remnant liver is the safe volume. We did one dual liver transplant from two donors. The patient, whose body weight was 72 kilograms, had a severely deteriorated liver disease. His two daughters were small in body weight. A right lobe graft of 500 grams from one donor and a left lobe graft of 210 grams from the other were used. The patient's post-operative recovery was uneventful and they are all enjoying life. The domino split liver transplantation using a liver from an amyloid neuropathy patient was introduced to expand the donor pool.

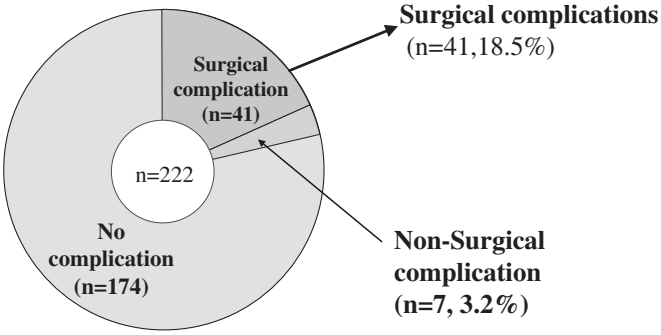

Fig. 9 Complications (right lobe donor: n = 222).

Donor Safety Issues

Donor safety, which is a priority in this modality, is obtained based on the confirmed volunteer and, without question, on good donor selection, skillful surgical expertise, sophisticated management and long-term follow up.[10] We have encountered 50 complications in 222 right lobe grafts, including surgical complications in 18.5 percent and non-surgical complications in 3.2 percent (Fig. 9). With surgical complications, each code is made in the mobility of the donor. Recently, there was one donor death at Mount Sinai, in the United States. So this time, the patient lived and the donor died. This was a very shocking report, which caused a reduction in the number of LDLTs in the United States, but there is always the possibility of encountering this problem in any healthy donor and in any society. Worldwide, at least four donor deaths directly related to donation have been confirmed and another four donor deaths are estimated. Specific prophylactic measures should be

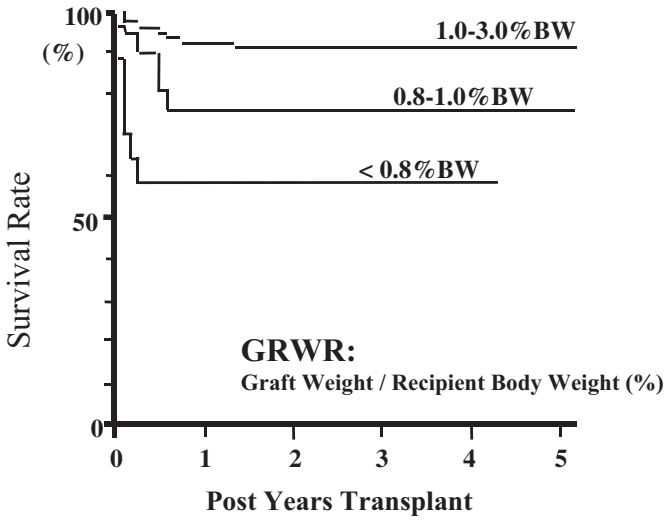

Fig. 10 Patient survival according to graft size over recipient body weight.

taken for donors in regard to general risks such as deep vein thrombosis leading to pulmonary embolism.

Strategies for Graft Size Matching

We use a lateral segment graft or left-lobe graft in children. We have developed a monosegment graft using segment 3 with the resection of segment 2 in situ in small infants because the graft must be small enough to accommodate in abdominal cavity and to be adequately perfused. Recently, we used a 100-gram graft after cutting down segment 2 and a part of segment 3 for a newborn patient with a 3.1-kilogram body weight. The biggest obstacle of the LDLT was size matching. The precise demand of the graft volume is seen as controversial. We have studied the impact of graft size on patient survival in ABO-compatible and elective cases. Grafts that were less than 0.8 percent of the recipient body weight show significantly poor results in patient survival (Fig. 10). In general, grafts larger than 0.8 to 1.0 percent of the recipient body weight are expected to result in a good outcome. However, safety criteria are still unclear and may be affected by many factors such as pre-transplant metabolic load, portal hypertension and latent infection in the recipient. In our experience, small-for-size grafts in patients cause them to suffer from persistent cholestasis, coagulopathy and massive ascites due to persistent portal hypertension, poor synthetic function and reduced bacterial clearance. Consequently, small-for-size grafts led to poor results. Donor and recipient factors also affect graft survival. Needless to say, liver size and graft quality are important factors in donor selection. I think the minimal graft ratio to recipient is 0.8 percent. However, the necessity of the liver volume also depends on graft quality and recipient factors. We have to decide how much liver volume is needed in individual situations. Aged liver, steatotic liver, and special anatomic variants have the possibility of a relatively poor graft quality. Recipient factors including metabolic load, surgical complications, preoperative latent infectious complications and also extra hepatic organ dysfunction have negative impact on graft survival (Table 1).

Table 1 Donor and Recipient Factors Influencing Graft Survival

Donor Factors
• Size
• Graft quality (aged liver, steatotic liver, special anatomical variants)
Recipient Factors
• Metabolic load (Pretransplant condition)
• Surgical complications
• Latent infectious complications
• Extrahepatic organ dysfunction

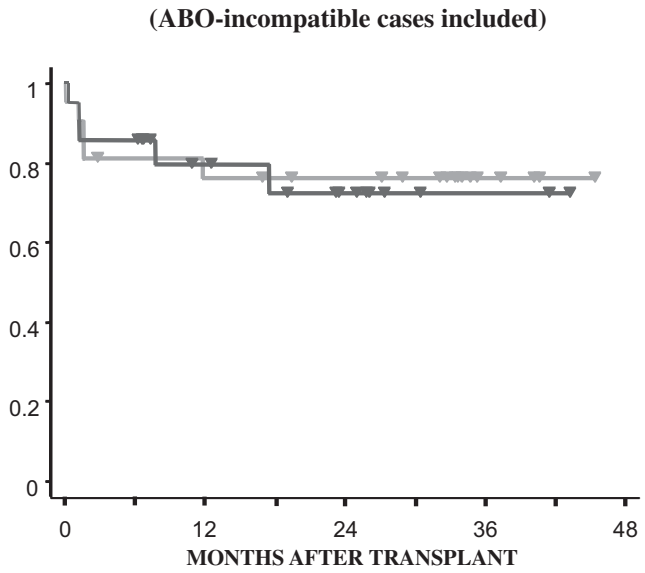

Fig. 11 Overall survival of LDLT for patients with chronic HBV.

Extension of Indications

With the introduction of the right lobe graft, the number of adult cases increased. The recurrence of original disease is a major concern in adult LDLT. Prophylaxis against hepatitis B viral recurrence using pretransplant Lamivudine and post-transplant lamivudine and hyperimmune globulin has, so far, been very successful and we have not yet encountered any persistent viremia or recurrence after LDLT for patients with

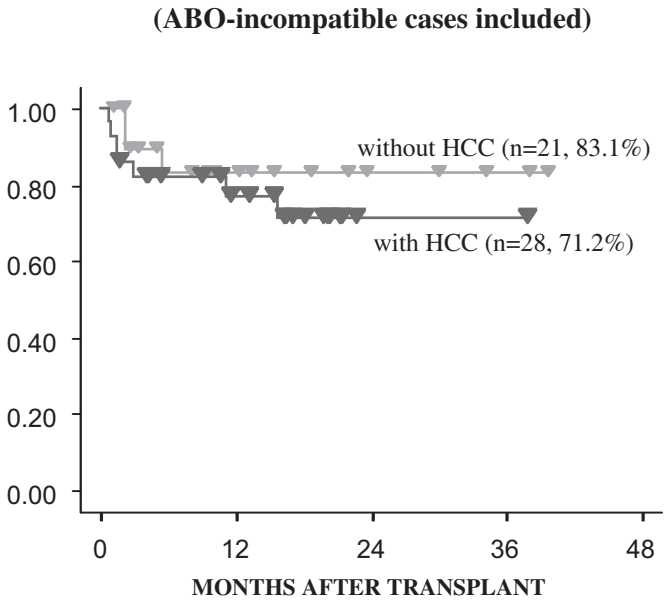

Fig. 12 Overall survival of LDLT for patients with chronic HCV.

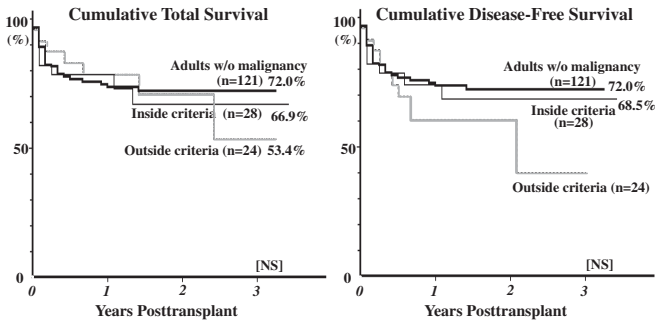

Fig. 13 LDLT for patients with HCC. Survival by PreTx Milan Criteria (ABO-compatible cases, n = 52).

Hepatitis B (Fig. 11). The hepatitis B core antibody positivity is observed in more than ten percent of the healthy Japanese population. The use of hyperimmune globulin after transplantation with a lower target level is useful for the prevention of disease transmission from hepatitis core antibody positive donors.[11] The next issue would be efficacy of vaccination. Fig. 12 is the overall survival rate of LDLT for patients with chronic hepatitis C disease with/without HCC. The recurrence of hepatitis C is a great concern after transplantation. But we have not had experience with the use of interferon and/or Ribavirin for prophylaxis of hepatitis C recurrence. I am anxious about the rapid replication of the hepatitis C virus with the regeneration of the new liver graft. For the next step, we have to analyze how the regeneration of the liver promotes the replication of the hepatitis C virus. Based on the understanding that the living donor graft is not a public resource but a private gift and on the established safety of the donor operation, we started a pilot study on LDLT for hepatocellular carcinoma in 1999 with the approval of Ethics Committee in our institute. The exclusion criteria are macroscopic vascular invasion or extra-hepatic metastasis irrespective of tumor size and number. In cadaveric liver transplantation, the indication had been expanded to the advanced HCC. However, with the learning curve, the Milan Criteria is now used for the organ allocation system for HCC patients. The Milan Criteria consists of a single tumor less than 5 cm or three nodules less than 3 cm in each nodule. If the patient meets these criteria, good results would be obtained after transplantation. But those histologically outside of the criteria show a little bit poorer results compared to those histologically within the Milan Criteria even if the clinical criteria is within Milan Criteria. Fig. 13 shows the patient survival rate after LDLT for HCC in ABO-compatible cases of 53. Patients meeting the Milan Criteria show good results, however, those outside of the criteria show poor results.[12] But patient survival is similar to that of LDLT for adults without malignancy. Up-to-date, significant data is available on patients with advanced cases compared to other treatments such as radio frequency or external re-injection therapy and rejection. I think liver transplantation should be indicated for those advanced cases, in which tumor cells are limited to liver parenchyma.

Immunosuppression and Tolerance

From the beginning of the program we have used tacrolimus, which was developed in Japan as a main immunosuppressant. Clinical reports were only from Pittsburgh when we started the program, because this drug was first put into clinical use at the University of Pittsburgh in the United States, and we had no information of pharmacokinetics or pharmacodynamics in a Japanese population. Therefore, the first subject was a study of optimal dose requirement and a drug monitoring system in our institute. Our investigation on the relationship between tacrolimus, trough level and the side effects in a clinical setting has revealed a good correlation.[13,14] This has furthermore led to the establishment of optimal dosing in pediatric and adult population through population analysis. Liver transplantation across the ABO-type barrier is contraindication or is only exceptionally performed as a rescue therapy in an emergency situation. Sixty-six transplants of ABO incompatible LDLT were performed in our institute from 1990 to 2000. The one year patient survival rate is 76%, 70%, 58% and 22% in patients of age <1, 1–7, 8–15 and >15, respectively. The administration of Methyl-

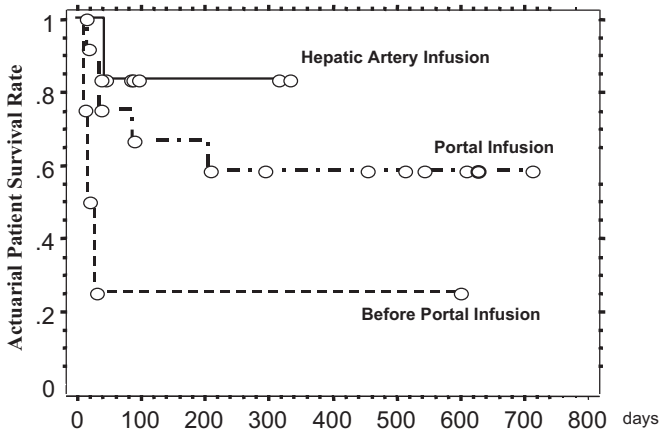

Fig. 14 Patient survival in adult LDLT from ABO incompatible donors.

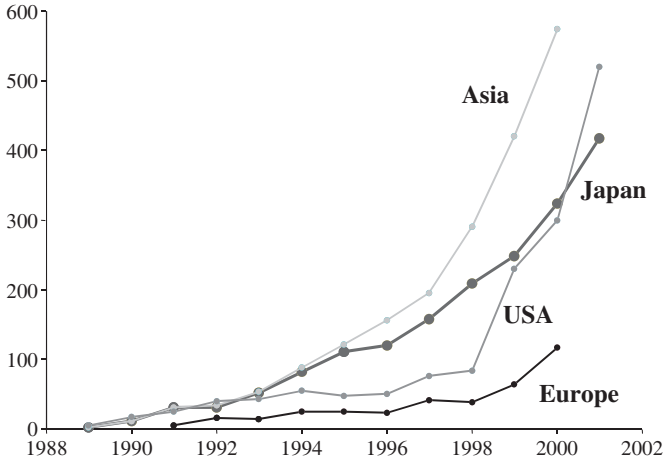

Fig. 15 Annual number of LDLTx.

prednisolone, Prostaglandin E_1, and Gabexate Mesilate through the portal vein was introduced by Keio University Hospital. Portal vein infusion therapy improved the 1 year survival rate at adult LDLT to 61%. To achieve the better outcome, hepatic artery infusion therapy was initiated which improved the patient survival rate to 86% (Fig. 14). With the use of hepatic artery infusion therapy, ABO incompatible liver transplantation would not be a contraindication in LDLT. The ultimate good of organ transplantation is to achieve an immunosuppression-free state with benefits derived from the return of natural immunity and a reduction of drug-related toxicity. We have some patients who maintained good graft function after either a forced or incidental withdrawal of immunosuppression. These experiences encouraged us to develop a novel weaning protocol for the long-term patients after transplantation.[15] We have selected patients and studied the prospective protocol for weaning them off an immunosuppressant agent. Entry criteria are as follows: informed consent, a stable liver function more than two years after transplantation, absence of rejection in the proceeding twelve months and close observation after reduction. Sixteen of the 67 patients on the schedule of weaning have achieved complete withdrawal, forty-three are under weaning and eight patients developed rejection. These results have overthrown the conventional concept and are expected to lead a new field of immunological tolerance research in transplant medicine. Further analysis of the tolerance mechanism and the active induction of tolerance are expected to lead to further developments in organ transplantation.

Future

These are visiting doctors from abroad to our Center. In Japan, many centers are sharing their message to the world. In severe donor shortage of cadaver organs, many centers in the United States introduced this modality by 1998, the year in which the right lobe graft was introduced. Since then, the number of LDLT has increased in the United States and also Europe. In Asia, where cadaveric organ donation is strictly limited, the numbers have been increasing (Fig. 15).

Japan is a very special country in the field of transplantation. Many liver transplant surgeons in Japan have made direct efforts in the establishment and the popularization of LDLT with the support of experts in many surrounding fields. However, there remain many problems that can be resolved only by the use of living donors. Further efforts should be directed to the development of cadaveric liver transplantation so that the patient can select from cadaveric and living donors.

References

1. Bismuth H, Houssin D: Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 1984; 95: 367–370
2. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, Bunzendahl H: Transplantation of a donor liver to 2 recipients (splitting transplantation): a new method in the further development of segmental liver transplantation. Langenbecks Arch Chir 1988; 373: 127–130 (in Germany)
3. Raia S, Nery JR, Mies S: Liver transplantation from live donors. Lancet 1989; 2: 497
4. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA: Successful liver transplantation from a living donor to her son. N Engl J Med 1990; 322: 1505–1507
5. Nagasue N, Kohno H, Matsuo S, Yamanoi A, Uchida M, Takemoto Y, Nakamura T: Segmental (partial) liver transplantation from a living donor. Transplant Proc 1992; 24: 1958–1959
6. Ozawa K, Uemoto S, Tanaka K, Kumada K, Yamaoka Y, Kobayashi N, Inamoto T, Shimahara Y, Mori K, Honda K, *et al*: An appraisal of pediatric liver transplantation from living rela-

tives. Initial clinical experiences in 20 pediatric liver transplantations from living relatives as donors. Ann Surg 1992; 216: 547–553
7. Tanaka K, Uemoto S, Tokunaga Y, Fujita S, Sano K, Nishizawa T, Sawada H, Shirahase I, Kim HJ, Yamaoka Y, *et al*: Surgical techniques and innovations in living related liver transplantation. Ann Surg 1993; 217: 82–91
8. Mori K, Nagata I, Yamagata S, Sasaki H, Nishizawa F, Takada Y, Moriyasu F, Tanaka K, Yamaoka Y, Kumada K, *et al*: The introduction of microvascular surgery to hepatic artery reconstruction in living-donor liver transplantation – its surgical advantages compared with conventional procedures. Transplantation 1992; 54: 263–268
9. Yamaoka Y, Washida M, Honda K, Tanaka K, Mori K, Shimahara Y, Okamoto S, Ueda M, Hayashi M, Tanaka A, *et al*: Liver transplantation using a right lobe graft from a living related donor. Transplantation 1994; 57: 1127–1130
10. Morimoto T, Ichimiya M, Tanaka A, Ikai I, Yamamoto Y, Nakamura Y, Takada Y, Inomata Y, Honda K, Inamoto T, *et al*: Guidelines for donor selection and an overview of the donor operation in living related liver transplantation. Transpl Int 1996; 9: 208–213
11. Uemoto S, Sugiyama K, Marusawa H, Inomata Y, Asonuma K, Egawa H, Kiuchi T, Miyake Y, Tanaka K, Chiba T: Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. Transplantation 1998; 65: 494–499
12. Kaihara S, Kiuchi T, Ueda M, Oike F, Fujimoto Y, Ogawa K, Kozaki K, Tanaka K: Living-donor liver transplantation for hepatocellular carcinoma. Transplantation 2003; 75: S37–S40
13. Uemoto S, Ozawa K, Tanaka K, Honda K, Mori K, Yamamoto E, Sano K, Fujita T, Shirahase I, Katoh H, *et al*: Experience with FK 506 in living related donor liver transplantation. Transplant Proc 1991; 23: 3007–3009
14. Inomata Y, Tanaka K, Egawa H, Uemoto S, Ozaki N, Okajima H, Satomura K, Kiuchi T, Yamaoka Y, Hashida T: The evolution of immunosuppression with FK506 in pediatric living-related liver transplantation. Transplantation 1996; 61: 247–252
15. Takatsuki M, Uemoto S, Inomata Y, Egawa H, Kiuchi T, Fujita S, Hayashi M, Kanematsu T, Tanaka K: Weaning of immunosuppression in living donor liver transplant recipients. Transplantation 2001; 72: 449–454