

Clinical intestinal transplantation in 1998 : Pittsburgh experience

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Introduction

The massive lymphoid content, and the heavy bacterial load of the gut provided formidable barriers to intestinal transplantation in humans until the clinical introduction of tacrolimus in 1989. After successful preclinical studies, large scale trials were successfully undertaken at our Institution in 1990. To improve outcome and cost effectiveness of the procedure, we conducted an outcome analyses trying to identify correctable risk factors. Several factors have been recently identified that significantly influenced patient and graft survival (1-2). Of these, four were major immunologic risk factors ; the number of episodes of intestinal allograft rejections, high blood tacrolimus trough levels, high dose steroid requirements, and the need for adjunct OKT3 therapy. The remaining significant risk factors were number of previous abdominal surgeries, operative and cold ischemia times, cytomegaloviral (CMV), and post-transplant lymphoproliferative diseases. In order to lower the immunosuppressive requirements and improve survival outcome, we declared a one year moratorium in 1994 (figure 1), pending the results of extensive clarifying investigations by Murase and associates in rats (3). When the program reopened, two major changes in management strategy were instituted. One was an attempt to avoid, when possible, the transplantation of organs from CMV-positive donors to CMV-negative recipients. The second change was to give perioperative adjunct donor bone marrow when this was available, in order to take advantage of the more tolerogenic profile of bone marrow cells compared to that of the intestinal passenger leukocytes (3-6). Other adopted strategies were careful patient selection, exclusion of the colon from the intestinal allograft, and monitoring of EBV infection by serial quantitative EBV-PCR measurements.

Materials and methods

We report here our overall long-term results with 121 intestinal transplantation in 115 consecutive patients that were transplanted between May 2, 1990 and October 8, 1998. Of these 68 (59%) were children and 47 (41%) were adults. The causes of intestinal failure were short gut syndrome (SGS) in 95 (82%), dysmotility syndrome in 11 (10%), intestinal neoplasm in 6 (5%),

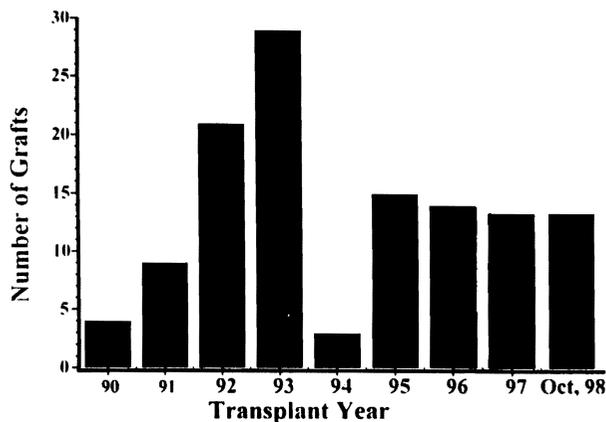


Fig. 1. — Number of intestinal transplants per year at the University of Pittsburgh.

and enterocyte dysfunction in 3 (3%). The leading causes of SGS were vascular occlusion ($n = 14$), Crohn's disease ($n = 11$), and trauma ($n = 7$) in adults and volvulus ($n = 20$), gastroschisis ($n = 16$), necrotizing enterocolitis ($n = 9$) and atresia ($n = 8$) in children. The intestine was engrafted alone ($n = 43$, 37%), or as part of a composite graft ($n = 76$, 63%). The composite visceral grafts were combined liver and intestine ($n = 59$) and multivisceral ($n = 17$). All of the isolated intestinal recipients were suffering from frequent central line sepsis (30%), vanishing central venous access (40%), and reversible TPN induced hepatic dysfunction (30%). Most combined liver recipients had TPN induced liver failure before transplantation. The donors were all ABO identical and HLA histoincompatible. The lymphocytotoxic cross-match was positive in 16 patients. No attempts were made to alter the graft lymphoreticular tissue with antilymphocyte preparations or other modalities. Of the last 61 recipients, 25 were infused with bone marrow, the distinction from the other 36 being the willingness of the donor family to permit the extra procurement procedure. The surgical techniques of the donor and recipient operation and details of bone marrow augmentation are fully described elsewhere (7-10).

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The management of the intestinal allograft recipients is fully described elsewhere (11). The immunosuppressive therapy was based on tacrolimus and prednisone. Cyclophosphamide was given to 23 patients after the moratorium at a dose of 2-3 mg/kg/day for 4 weeks and then switched to mycophenolate mofetil (15-30 mg/kg/day) or azathioprine. Daclizumab (Zenapax) was given as an induction therapy for the last 8 recipients in a dose of 1-2 mg/kg body weight every two weeks for a total of five doses. In a few cases, azathioprine was given as a third maintenance drug from the outset. The level of maintenance immunosuppression was individualized and adjusted based upon the clinical course of each patient with the intention to reduce the drug dosage and levels whenever possible. Episodes of rejection were treated with adjustments of tacrolimus dose and/or supplemental prednisone. OKT3 was given only as a rescue therapy. Upward dose adjustments of mycophenolate mofetil, azathioprine, or steroids, were frequently needed to compensate for tacrolimus dose reductions mandated by tacrolimus-related adverse effects. Patient/graft survival and curves of cumulative risks were generated using the Kaplan-Meier method and group comparisons were done using the log-rank test.

Results

Survival

The overall cumulative patient survival is 72% at one year and 48% at five years with a graft survival rate of 64% and 40% respectively (figure 2). With a mean follow-up of 40 ± 29 months (range : 1-94), 31 patients are alive with good nutrition beyond the third postoperative year and 18 are well beyond the 5-year milestone. The survival benefits of intestinal transplantation has been better (p = 0.57) achieved among children compared to adults with the best outcome among patients between 2 and 17 years of age, in whom the 5 year cumulative survival rate was 68%. Bone marrow

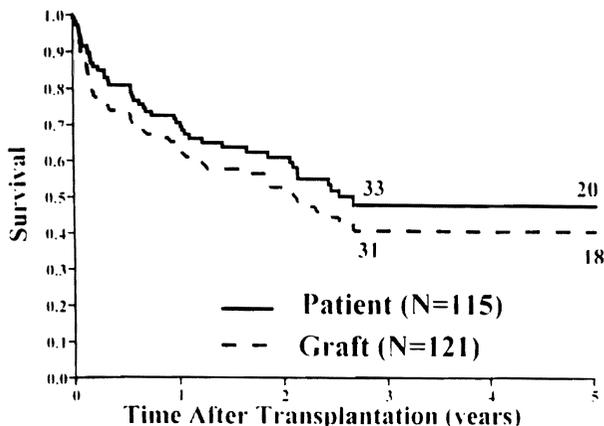


Fig. 2. — Patient and graft survival curves using the Kaplan-Meier method.

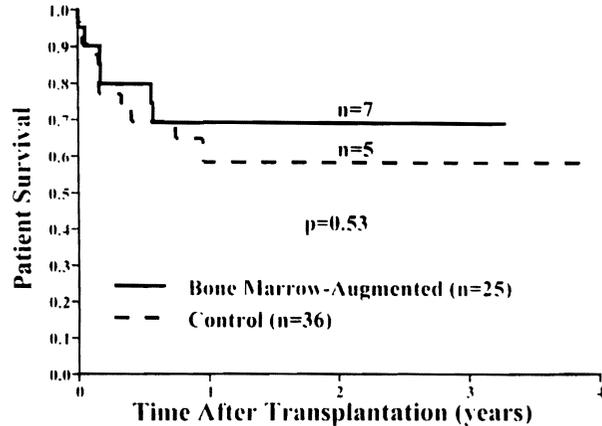


Fig. 3. — Patient survival and bone marrow augmentation.

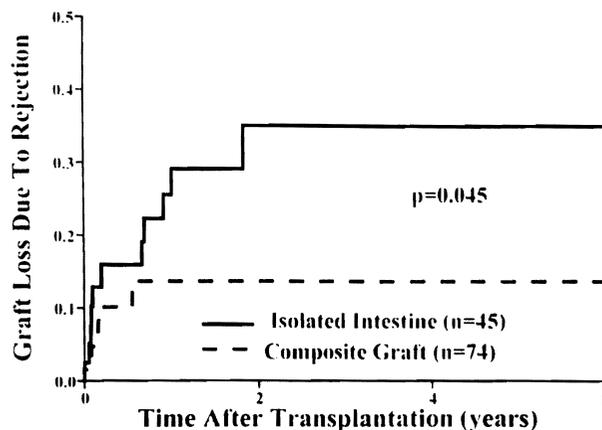


Fig. 4. — Cumulative risk of graft loss due to rejection among isolated and composite intestinal grafts.

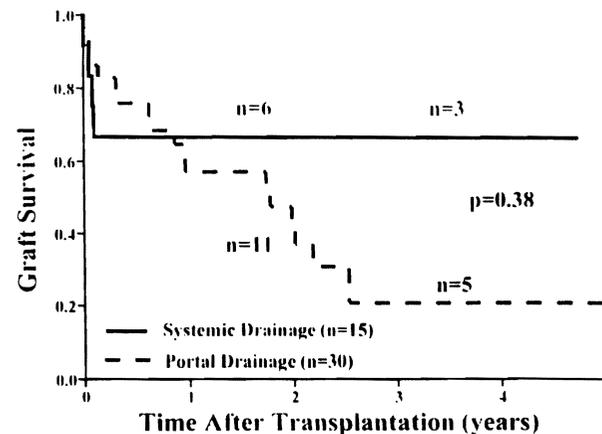


Fig. 5. — Effect of type of venous drainage on intestinal allograft survival.

augmentation did not significantly improve patient survival (figure 3). Although both the isolated intestinal and composite visceral grafts had similar (p = 0.72) survival rate, the cumulative risk of graft loss due to rejection was significantly (p = 0.045) higher among the isolated intestine (figure 4). Systemic venous drainage of the isolated intestine did not significantly affect graft survival (figure 5). The Kaplan-Meier graft survival

curves stratified according to the etiology of intestinal failure are depicted in figure 6. The best survival rates have been achieved among children with microvillus disease and gastroschisis and in adults with Crohn's disease and vascular thrombosis. Figure 7 illustrates the significant ($p = 0.04$) improvement in intestinal allograft survival during the last four years (after the moratorium) with a cumulative rate of 65% at four years. Such an achievement reflects further refinement in operative techniques, immunomodulation, and management strategies as described above.

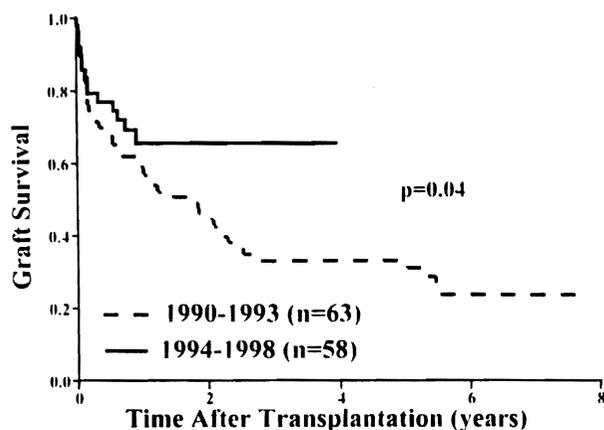


Fig. 6. — Graft survival before and after the 1994 moratorium.

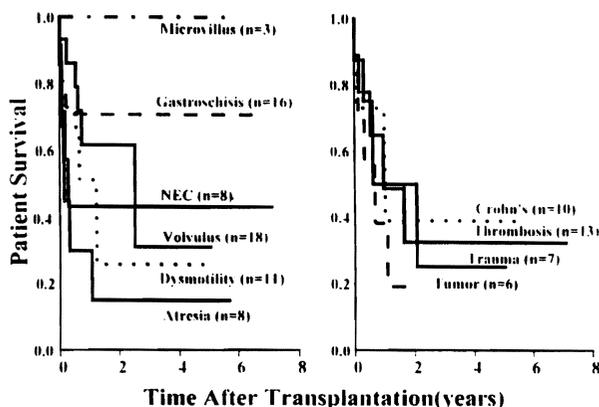


Fig. 7. — Causes of intestinal failure and patient survival.

Long-term rehabilitation

Fifty-eight (95%) of the 61 current survivors are home, fully active and completely off TPN with full nutritional autonomy. These individuals have reported improved quality of life measures in comparison to TPN dependency. The remaining three patients (5%) are receiving partial intravenous support while recovering from a recent episode of rejection ($n = 2$) or PTLD ($n = 1$). No clinical or histopathologic evidences of disease recurrence has been documented in our series during the 8 years of follow-up. To date, no attempts have been made to electively wean any of the intestinal recipients, including the bone marrow augmented cases, off immunosuppression.

Cost Analysis

The average cost of intestinal transplantation between 1990 and 1994 was \$203,111 for the isolated intestine, \$252,453 for the combined liver-intestine transplantation, and \$284,452 for the multivisceral procedure. This has been significantly reduced during the last four years to an average of \$132,285, \$214,716 and \$219,098, respectively. The use of intestinal transplant can be examined on a cost-effectiveness basis, due to the availability of chronic TPN as an alternative therapy for patients with irreversible gut failure. Based on the Medicare (USA) data, the average yearly cost of TPN in 1992 was above \$150,000 per patient not including the cost of frequent hospitalization, medical equipment, and nursing care (12). The total dollars spent on TPN are increasing every year because of the yearly increase in TPN cost and the cumulative increase of the home and hospital bound TPN population. Based upon these data, intestinal transplantation becomes cost-effective by the second year after transplantation.

Conclusions

Intestinal transplantation has become a life saving treatment for patients with irreversible intestinal failure who cannot be maintained on TPN, and a cost effective therapy for patients who still have the option of TPN. The long-term rehabilitation with all three kinds of intestinal transplantation is similar to that achieved with lung transplantation (13), and some other kinds of organ allografts. Therefore, it is justifiable, to currently consider intestinal transplantation as non-experimental procedure. Based upon the results of our most recent preclinical trials (14), further improvement in patient and graft survival is greatly anticipated with further immune modulation strategies (graft cytoreduction) that can be added to the bone marrow augmentation protocol.

References

1. TODO S., REYES J., FURUKAWA H., ABU-ELMAGD K., LEE R.G., TZAKIS A., RAO A., STARZL T.E. Outcome analysis of 71 clinical intestinal transplantation. *Ann. Surg.*, 1995, 3 : 270-282.
2. ABU-ELMAGD K., REYES J., TODO S., RAO A., LEE R., IRISH W., FURUKAWA H., BUENO J., MCMICHAEL J., FAWZY A.T., MURASE N., DEMETRIS A., RAKELA J., FUNG J.J., STARZL T.E. Clinical intestinal transplantation: New perspectives and immunologic considerations. *J. Am. Coll. Surg.*, 1998, 186 : 512-527.
3. MURASE N., STARZL T.E., TANABE M., FUJISAKI S., MIYAZAWA H., YE Q., DELANEY C.P., FUNG J.J., DEMETRIS A.J. Variable chimerism, graft-versus-host disease, and tolerance after different kinds of cell and whole organ transplantation from Lewis to Brown Norway rats. *Transplantation*, 1995, 60 : 158-171.
4. MURASE N., DEMETRIS A.J., WOO J., FURUYA T., NALESNIK M., TANABE M., TODO S., STARZL T.E. Lymphocyte traffic and graft-versus-host disease after fully allogeneic small bowel transplantation. *Transplant. Proc.*, 1991, 23 : 3246-3247.
5. MURASE N., DEMETRIS A.J., WOO J., TANABE M., FURUYA T., TODO S., STARZL T.E. Graft-versus-host disease after Brown Norway to Lewis and Lewis-to-Brown Norway rat intestinal transplantation under FK506. *Transplantation*, 1993, 55 : 1-7.

6. TANABE M., MURASE N., DEMETRIS A.J., HOFFMAN R.A., NAKAMURA K., FUJISAKI S., GALVAO F.H.F., TODO S., FUNG J.J., STARZL T.E. The influence of donor and recipient strains in isolated small bowel transplantation in rats. *Transplant. Proc.*, 1994, **26** : 4325-4332.
7. STARZL T.E., TODO S., TZAKIS A., ALESSIANI M., CASAVILLA A., ABU-ELMAGD K., FUNG J.J. The many faces of multi-visceral transplantation. *Surg. Gynecol. Obstet.*, 1991, **172** : 335-344.
8. CASAVILLA A., SELBY R., ABU-ELMAGD K., TZAKIS A., TODO S., REYES J., FUNG J.J., STARZL T.E. Logistics and technique for combined hepatic-intestinal retrieval. *Ann. Surg.*, 1992, **216** : 605-609.
9. FURUKAWA F., ABU-ELMAGD K., REYES J., NOUR B., FUNG J.J., TZAKIS A., TODO S., STARZL T.E. Technical aspects of intestinal transplantation. In : Surgical Technology International. Vol. 2. (BRAVERMAN M.H., TAWES R.L., eds) Surgical Technology International San Francisco : Universal Medical Press, 165-170, 1994.
10. FONTES P., RAO A., DEMETRIS A.J., ZEEVI A., TRUCCO M., CARROLL P., RYBKA W., RUDERT W.A., RICORDI C., DODSON F., SHAPIRO R., TZAKIS A., TODO S., ABU-ELMAGD K., JORDAN M., FUNG J.J., STARZL T.E. Bone marrow augmentation of donor-cell chimerism in kidney, liver, heart, and pancreas islet transplantation. *Lancet*. 1994, **344** : 151-155.
11. ABU-ELMAGD K., FUNG J.J., REYES J., CASAVILLA A., VAN THIEL D.H., IWAKI Y., WARTY V., NIKOLAIDIS N., BLOCK J., NAKAMURA K., GOLDBACH B., DEMETRIS A.J., TZAKIS A., TODO S., STARZL T.E. Management of intestinal transplantation in humans. *Transplant. Proc.*, 1992, **24** : 1243-1244.
12. HOWARD L., AMENT M., FLEMING R., SHIKE M., STEIGER E. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology*, 1995, **109** : 355-365.
13. HOSENPU D., NOVICK R.J., BENNETT L.E., KECK B.M., FIOL B., DAILY O.P. The registry of the international society of heart and lung transplantation : Thirteenth official report — 1996. *J. Heart Lung Transplantation*, 1996, **15** : 655-674.
14. MURASE N., YE Q., LEE R.G., DEMETRIS A.J., ABU-ELMAGD K., REYES J., STARZL T.E. Immunomodulation of intestinal transplantation with allograft irradiation and simultaneous donor bone marrow infusion. 24th Annual Scientific Meeting, The American Society of Transplant Surgeons, 1998.