CONFERENCIA MAGISTRAL

What's hot in liver transplantation

J.J. Fung

Cleveland Clinic Foundation. Cleveland. EE.UU.

INTRODUCTION

Prior to the development of liver transplantation (LTX), patients with end-stage liver failure had dismal prognosis. Since the first human LTX performed in 1963, survival outcomes have improved substantially with a resultant increasing demand for this procedure each year. According to the Scientific Registry of Transplant Recipients (SRTR) data, the current United States 1-year patient and graft survival rates after LTX are 87% and 80%, respectively. Unlike failure of kidney transplantation, failure of a liver graft results in a patient's death unless these patients undergo retransplantation. The risk factors associated with poorer outcomes at 1-year following LTX include: (1) older (>65 yr of age) recipient age; (2) repeat transplants; and (3) higher degree of medical illness at the time of LTX, including renal failure. For graft survival, the risk factors were similar, although very young (<1 yr of age) recipients and older donors (>65 yrs of age) are associated with lower graft survival. For several risk factors, the penalty in patient and graft survival appears to occur in the immediate post-transplant period, without disproportionate losses after the first 3 months, such as use of living liver donors, non-heart beating donors, high acuity recipients. Other factors are associated with short-term success and long-term decrement in survival, such as the transplantation of patients with hepatitis C, alcohol related liver disease, use of female donor livers. Long-term patient survival is currently projected to be over 60% at ten years. Allograft loss from acute and chronic rejection is rare. The majorities of late graft losses and deaths are related to: recurrence of disease; non-compliance; the development of de novo malignancies and age related concurrent medical conditions.

ORGAN AVAILABILITY

The shortage of available organs for transplantation continues to worsen and represents the single greatest challenge for established LTX programs. This has led to changing clinical practices and strategies to deal with the organ shortage. The implementation of an objective prioritization score, the Model for End-Stage Liver Disease (MELD), has helped to transplant sicker patients in a more timely fashion.

Expanded Criteria Donor (ECD) Use

The statement made by Dr. Thomas Starzl in 1963: "The provision of a viable and minimally damaged homograft is undoubtedly the most important single factor in the determinant of success," is as pertinent now as it was then. However, the changing characteristics of the cadaveric donor pool have forced a reassessment of what constitutes an ECD liver. An ECD is one in whom certain characteristics impart either real or perceived short and/or long term risks to the recipient, which in current practice would not be normally considered as a donor. In addition, there are differences in what types of risk are associated with their use, for example, a steatotic graft is at risk for early graft failure but not additional late graft failure, while a Hepatitis B core antibody donor would be at risk for late graft failure but not early. In practice, the Scientific Registry of Transplant Recipients (SRTR), using a limited data set, has characterized an ECD by several factors, age, cause of death, race, and split or non-heart beating donor. This has been taken into account in a formula called the Donor Risk Index and has the potential for being able to calculate the impact of donor characteristics on recipient outcomes.

Living Donor Utilization

Perhaps the most promising, yet still controversial, area of liver donation is in the area of living donor liver transplantation (LDLT). Due to relatively higher waiting list mortality in pediatric candidates, living adult-to-child left lateral segment LTX was developed almost two decades ago. The widespread adoption of this practice, combined with split LTX (a direct precedent to living lateral segment dona-

tion), has been successful in reducing mortality in this group of patients. However, with the increasing mortality in the adult candidates, the development of living adult-to-adult full lobar donation has generated greater interest due to a potentially larger beneficiary pool. The principal concern is the demand for technical skill and experience to minimize the substantially greater risk to the donor. At this time, a true assessment of the risk to the donor is still being refined, in part, because a standard approach to the collection and categorization of complications has not been achieved. In addition, the realization that LDLT has limitations in patients with advanced portal hypertension and with donor recipient combinations resulting in low graft weight/body weight ratios, increasing the risk of small-for-size syndrome (SFSS). Further research in this area may lead to strategies to minimize SFSS.

RECURRENT DISEASES

The impact of the various disease processes on long-term survival outcomes is becoming quite apparent. In the adult population, recurrent diseases such as: primary hepatic malignancies, steatohepatitis, recurrent alcohol abuse, viral hepatitis, Budd-Chiari syndrome, primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis, have been reported to occur and variably impact survival. Already application of the Milan criteria for selection of hepatocellular carcinoma (HCC) candidates has resulted in improved outcomes, however the advent of novel anti-angiogenesis factor agents, e.g. sorafenib (Nexavar), Avastin, and novel immunosuppressive agents, e.g. rapamycin, may allow transplantation of patients with more advanced HCC. HBV was once a poor indication for liver transplantation due to a high rate of HBV recurrence, however the advent of new nucleoside analogs and Hepatitis B immune globulin has decreased the recurrence rate to <10% with long-term outcomes that are no different than non-HBV indications. Recurrent diseases do not occur to the same extent in the pediatric population and partially accounts for the significantly better long-term survival in this population.

When long-term causes of graft failure and patient deaths are analyzed, the major cause of loss appear to be non-immunologic in nature. In patients transplanted for alcohol related liver disease, the majority of late deaths were related to de novo cancer, cardiorespiratory, and cerebrovascular events. The risk of death was 2.3 times higher for the alcoholic group of patients beyond 5 years post-LTx.

The impact of HCV following LTx can be assessed with more than 10-year follow-up since the introduction of routine HCV testing. The almost universal reinfection rate and a high incidence of clinical hepatitis (and cirrhosis in a small percentage of patients) is cause for concern. HCV infection after LTX does not significantly affect five-year survival based on several single center studies, but registry data and longer term follow-up analysis demonstrates significantly lower survival rates. Newer agents that interfere with HCV replication are being tested, although none have been utilized in the LTC population.

IMMUNOSUPPRESSION AND TOLERANCE

Immunosuppression

Advances in the understanding of the immune response to transplanted organs has led to a wealth of new immunosuppressive agents for the prevention and treatment of allograft rejection. The introduction of cyclosporine led to significant improvements in LTX patient survival and graft survival with reduction in the incidence and severity of rejection. The utilization of the more potent immunosuppressive agent, tacrolimus, has further reduced the frequency and severity of rejection in LTX and has been associated with improved patient and graft survival. Other immunosuppressive agents have been utilized in LTX, including mycophenolate mofetil, anti-IL-2 receptor antibodies, and sirolimus. While further reduction in acute rejection rates have been reported using some of these agents, there has been no further improvement in survival rates. Newer agents target novel pathways in the immune system, including costimulatory pathways and adhesion molecules.

Tolerance

The immunologic privilege of the liver, its ability to induce systemic hyporesponsiveness and to protect other organs from rejection, is still not delineated. It may lie in the relative abundance of migratory cells in the liver as compared with other organs, such as the kidney and heart. The importance of these cells to induce tolerance is shown in experiments where hepatic migratory cells are eliminated with subsequent loss of the tolerogenic potential of the transplanted liver. If this hypothesis is correct, then strategies can be developed to identify the cell type and the optimal source of these cells and to enhance the migration of these cells, in an attempt to accentuate the immunomodulating effect of these cells on the recipient immune response. On the other hand, peculiar features of the liver, such as the presence of hepatic stellate cells, may be responsible for triggering apoptosis of activated T cells and maintaining tolerance. The ability to wean select liver transplant patients from immunosuppression supports the concept of hepatic tolerance in humans, however the ability to predict which patients can be weaned is still in infancy. Immunologic assays, such as cytokine genotypes, proliferative assays, apoptosis of graft infiltrating cells, may shed light on basic mechanisms of tolerance, but more importantly, lead to achievement of the "holy grail" of transplantation - clinical tolerance.

CHALLENGES FOR THE FUTURE

Extracorporeal Liver Assist Device

Survival from advanced acute liver insufficiency due to fulminant hepatic failure (FHF) is poor without transplantation, particularly in patients suffering advanced encephalopathy with development of hepatorenal syndrome, systemic lactic

acidosis, and severe coagulopathy. FHF has a mortality rate of 60% to 95%, with higher mortality from viral and toxic exposure FHF, lower in patients with acetaminophen overdose. Management of FHF is challenging and aimed at prevention and treatment of complications including infections, brain edema, hemodynamic instability, pulmonary and renal failure, acid-base disturbances, and coagulopathy.

The concept of using biomechanical devices to maintain patients with FHF until transplantation or recovery is an attractive one. Dialysis and charcoal hemoperfusion are of limited benefit, because the multiple biochemical functions are not being replaced, and their use has not resulted in decreased mortality in patients with FHF. Several proposed systems have used a hybrid device containing metabolically active liver cells. Two sources of viable liver cells are being utilized, porcine hepatocytes and immortalized human hepatocyte lines. In both cases, human plasma or blood is separated from the liver cells by the cartridge membrane. Pilot studies suggest that these devices have demonstrable clinical effects, although diverse variables and outcomes of these studies make a definitive statement difficult.

Hepatocyte Transplantation

Intrasplenic hepatocyte transplantation has been shown to improve the survival of laboratory animals with liver failure and to lead to an improvement in associated physiologic liver-based abnormalities. Hepatocytes obtained from human livers considered unsuitable for transplantation have been utilized clinically as a potential option for LTX. The exact use of isolated hepatocytes and their human application is still to be determined - in several case reports, allogeneic hepatocytes can partially reversed inborn-error, metabolic liver diseases, including urea cycle deficiencies and Crigler-Najjar syndrome.

Xenotransplantation

Due to the difficult immunologic barriers associated with cross-species transplantation, the goal of achieving xenotransplanation has proven elusive. Technologic advances have helped create novel genetic manipulated pigs, bearing the transgene for human complement regulatory proteins, or even more recently, knocking out the genes that regulate expression of the of the Gal _(1-3)Gal epitope, the major target of preformed xenoantibodies. Whether the changes are sufficient to overcome the initial antibody barrier is being determined in primate studies.

CONCLUSIONS

The field of LTX has grown tremendously in the past 43 years since the first human liver transplant. A better understanding of the immune mechanisms that cause graft damage (and tolerance), as well as new immunosuppressive agents, has helped put transplantation in a therapeutic realm. Unfortunately, with the success of transplantation, the scarcity of donor organs remains one of the principal limitations for broader applications. Over 2,000 patients die every year while waiting for a liver; and in the US for every individual who receives a transplant, 2 others are placed in the waiting list. Efforts are constantly made to expand the donor pool, either by using expanded criteria donors to living donors and perhaps in the future to xenotransplantation.

Future advances in LTX will focus on mechanisms of tolerance induction, improving clinical outcomes by reducing the impact of recurrent diseases and improved monitoring for cancer and cardiovascular complications, and reducing the organ shortage, which will help to expand application of LTX for new indications.