Living Donor Liver Transplantation for Adults

Michael Abecassis, MD

Since the first successful living donor liver transplantation (LDLT) of a right hepatic lobe into an adult in 1997, medical and surgical developments have required modification of the procedure. In addition, ethical and regulatory issues have been raised that require further elaboration.

Medical and Surgical Issues

Unquestionably, right hepatic lobectomy constitutes a major surgical procedure with risks that include donor death. We have recently published our experience, highlighting the fact that complications must be quantified so that patients can make fully informed decisions about LDLT.

To this end, the National Institutes of Health (NIH) has initiated a seven-year prospective clinical trial, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), to analyze the effectiveness of the procedure, including donor risk.

Northwestern Memorial Hospital’s LDLT program is one of nine sites selected by the NIH to participate in A2ALL, currently in its second year. One objective of this study is to analyze all complications in a large multi-center cohort of living donors. Another objective focuses on recipient outcomes, comparing LDLT to deceased donor liver transplantation (DDLT).

A retrospective review of LDLT indicates that the slightly increased morbidity of the procedure is outweighed by the waiting list mortality for recipients who do not have a living donor.

The evaluation of potential donors, as well as the surgical procedures in both the donor and recipient are becoming standardized. Controversy persists about technical aspects of the donor procedure, particularly related to the need for middle hepatic vein reconstruction. Biliary and vascular complications are more prevalent in LDLT than in DDLT recipients. It appears that most centers require an experience with 10 to 20 LDLT procedures to eliminate learning curve events.

Ethical and Regulatory Issues

As the medical and surgical issues are resolved, there is an increasing need to focus on regulatory and ethical deliberations. It is important to consider that indications and contraindications for LDLT may be different from those for DDLT.

It is well established that liver transplantation is indicated in patients with hepatocellular carcinoma whose tumors meet the Milan criteria. The transplant community has established that patients within the Milan criteria receive an allocation advantage for DDLT, whereas patients who exceed the Milan criteria do not. Since LDLT does not impact the national donor pool, most centers have advocated the use of LDLT in patients who exceed the Milan criteria, as long as the risk of recurrence remains acceptable. Is it ethical to subject a living donor to unquestionable risks for anything less than an optimal outcome in the recipient?

The risk of either death or transplantation in right lobe donors is on the order of 0.5 percent. This raises significant ethical considerations. What is an acceptable risk to the donor?

Donor morbidity and mortality have also raised regulatory issues. Following a donor death in New York City, the state regulations require a review of the case to determine if the donor’s best interests were served.

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Emerging Therapies for Hepatocellular Carcinoma

Laura Kulik, MD

The incidence of hepatocellular carcinoma (HCC) has escalated over the past three decades and is predicted to continue to increase. By the year 2010, it is projected that the number of patients with HCC awaiting orthotopic liver transplantation will surpass the number of organs available for transplant. Newer effective therapies are therefore needed for the treatment of HCC.

TheraSphere® is a novel treatment for HCC. In 2000, the FDA granted a humanitarian device exemption for the use of TheraSphere in the treatment of unresectable HCC and as a bridge to transplantation. TheraSphere beads are nonbiodegradable glass microspheres with yttrium-90 (Y-90), a pure beta emitter, as an integral part of the glass matrix. Traditional radiation therapy for treatment of HCC has been limited by the inability to deliver effective doses of radiation secondary to the development of radiation-induced hepatitis. Due to the hypervascular nature of HCC, microspheres are preferentially trapped in the tumor capillary bed allowing higher doses of radiation to be delivered to a smaller hepatic volume, leading to a greater tumoricidal effect. At the same time, the exposure to the surrounding non-tumor tissue is minimized.

Phase 1 and 2 trials have demonstrated a positive safety profile for TheraSphere in patients with a bilirubin less than 2.0 mg/dL. Patients are generally discharged within six hours after the procedure is completed. The therapy is well tolerated, with minimal observed risk of post-embolization syndrome.

Data has demonstrated that there is a trend in increased survival observed in patients who have received more than 104 Gy. One-year survival rates are comparable to those in a randomized control of transarterial chemoembolization (TACE) vs. supportive care. However, to date there has not been a randomized control trial comparing TheraSphere to TACE.

TheraSphere beads are delivered via the hepatic artery in a similar manner to chemembolization by an interventional radiologist with training in radiation therapy. Prior to the administration of Y-90, a mesenteric angiogram is performed to determine the patient’s underlying anatomy, the proper catheter position and embolization of extrahepatic arteries, as needed, to avoid inadvertent delivery of microspheres to surrounding organs. In addition, a technetium-99 macroaggregated albumin scan (MAA) estimates the degree of intratumoral arteriovenous shunts. This enables the interventional radiologist to calculate the dose radiation that will be distributed to the lungs and refluxed into the gastrointestinal organs. A hepatopulmonary shunt resulting in greater than 30 Gy dose to the lungs or a failure to prevent blood flow into the gastrointestinal organs by embolization or catheter position might preclude therapy with Y-90.

The radiation dose is calculated based on the volume of the hepatic lobe to be treated (not the tumor volume) and the estimated lung shunt fraction. The target dose is 100 to 150 Gy. If there is bilobar disease present, the lobe with the higher tumor burden is treated first, followed by treatment of the other lobe at a later time. With each additional treatment, the angiogram and MAA must be repeated. A cumulative dose of 30 Gy to the lungs is the accepted threshold.

A repeat scan (CT or MRI) is performed 30 days after Y-90 therapy to determine the effect of the therapy. The maximal response may occur up to 80 days post-therapy. Patients who do not adequately respond to Y-90 therapy (based on decline in alpha fetoprotein and radiographic findings) may be evaluated for chemembolization. Treatment with Y-90 following TACE is not performed due to the inability of the microspheres to penetrate the tumor bed that has been embolized.

At Northwestern Memorial Hospital, patients are evaluated on a case-by-case basis by Transplant Hepatology, Transplant Surgery, Oncology and Interventional Radiology at weekly multidisciplinary HCC conferences. TheraSphere therapy is being used at Northwestern Memorial as both a bridge to transplant and as a down-staging procedure. Patients with adequate hepatic reserve, who have evidence of portal vein thrombosis, a transjugular portosystemic shunt or hepatic fugal flow on ultrasound are preferentially being treated with TheraSphere. Randomized control trials are awaited to further evaluate the efficacy of TheraSphere for the treatment of HCC.

REFERENCES:
Albumin Dialysis: Effective Treatment for Liver Failure?

Andres T. Blei, MD

The focus of this review is the current status of the Molecular Adsorbent Recirculating System (MARS) for the treatment of liver failure. It reflects my personal experience in the performance of a clinical trial using MARS, which allows an analysis of the rationale and experience with this device.

The search for effective methods to support patients with liver failure spans several decades of unsuccessful results.1 Artificial liver support has been mainly explored through the use of albumin dialysis, though sorbent dialysis also has undergone clinical testing. Bioartificial systems combine features of artificial liver support with the addition of biological elements, either pig or human-derived hepatocytes. Regardless of the system chosen, the need for such approaches has never been greater: Current guidelines for allocation of donor organs prioritize sick individuals, increasing the number of patients with severe hepatic insufficiency awaiting liver transplantation.

A Rationale for Albumin Dialysis

A dialysis system that eliminates protein-bound substances from the circulation was designed by Stange and Mitzner.1 Here, a double-sided albumin impregnated high-flux polysulfon dialyzer was used with a closed loop dialysate compartment containing albumin. Albumin was filtered and recycled via a separate circuit. Removal of both water-soluble and protein-bound substances was demonstrated.

A therapeutic use for albumin is well known. However, the effects of albumin on the vasculature are considerably more complex than the traditional view of its role as a volume expander. Albumin can be viewed as a scavenger of reactive oxygen/reactive nitrogen species generated in conditions of oxidative stress and tissue injury, especially prominent in sepsis.1 Neutrophil-derived reactive oxygen species are also scavenged by albumin. Bilirubin also may protect albumin from oxidant-mediated damage.

In liver failure, additional biological effects of albumin are suggested by the clinical experience in Barcelona focused on patients with cirrhosis, ascites and its complications. Albumin can prevent the development of post-paracentesis circulatory dysfunction, a phenomenon that reflects excessive arterial vasodilatation after the procedure. Albumin enhances the ability of vasoconstrictor agents to improve renal function in patients with hepatorenal syndrome, and it increases survival in patients with spontaneous bacterial peritonitis.

Effects of Albumin Dialysis on the Pathophysiology of Liver Failure

The pathophysiology of liver failure is complex. It includes the effects of hepatic synthetic failure as well as a multisystem organ derangement. A common thread for the latter is the presence of systemic vasodilatation, which can affect renal, pulmonary and brain function in liver disease. Accumulation of water-soluble and protein-bound toxins occurs. Reported effects of albumin dialysis on some of these parameters include the removal of toxins and support of circulatory function. A controlled evaluation2 showed a correction of the hyperdynamic circulatory state in patients with acute-on-chronic liver failure. Several groups have shown an increase in cerebral blood flow with MARS. Two groups have reported, in small preliminary studies, a striking reduction of portal hypertension in patients with cirrhosis. Several compounds implicated in the pathogenesis of hepatic encephalopathy appear to be removed by albumin dialysis. Ammonia, a water-soluble compound, can be removed through the dialytic process. Manganese has been implicated in the development of extrapyramidal signs, and while manganese has not been specifically examined, removal of other divalent cations, such as copper, has been well documented and can explain beneficial effects of this approach to patients with decompensated Wilson’s disease. Finally, exogenous benzodiazepines can precipitate hepatic encephalopathy and are bound to albumin. These drugs can probably be removed by albumin dialysis.

Clinical Experience

Use of an expensive therapeutic modality cannot be undertaken without evidence arising from well-designed controlled trials. There is a long history of enthusiasm with new approaches to liver support—which were ultimately refuted when subjected to the critical assessment of a controlled trial.

A number of publications report improved outcomes in several critical conditions with the use of albumin dialysis, including acute liver failure (ALF), alcoholic hepatitis, fulminant Wilson’s disease, post-hepatic resection, liver failure with graft-vs-host disease and intractable pruritus. Phenytoin toxicity also can be effectively treated. The reader is referred to a recent review on the topic.6

Three controlled studies have been completed since 2000,6,7, one of which was published in abstract form.8 They report effectiveness in treating the hepatorenal syndrome6 and improving hepatic encephalopathy.6 One of the studies noted improved survival rates in 23 patients with acute-on-chronic liver failure.6 While these studies are encouraging, more data is needed. Two European trials are currently underway, one in decompensated cirrhosis and the other in ALF. With further study, a complete picture of the usefulness of albumin dialysis will emerge.

REFERENCES:
4. Schmidt LE, Wang LP, Hansen BA, Larsen (Continued on Page 4)
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Liver Transplant Program Team

of New York established and implemented strict and comprehensive regulations. The United Network for Organ Sharing has established similar guidelines. However, definite criteria and policies have not yet been established for LDLT.

Conclusions
At Northwestern Memorial, we reserve the use of LDLT for those patients in whom DDLT is not a viable option, primarily because of low-priority status despite progressive and life-threatening liver disease. We perform LDLT in approximately 10 to 15 percent of liver transplant recipients. Our approach to LDLT consists of well thought-out surgical procedures combined with sound medical judgment. An ethics group meets weekly to discuss individual patients and issues related to living donation.

Finally, we think that through further prospective study in a multi-center setting (A2ALL), we will achieve a better understanding of some of these complex medical and social issues.

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2. www.nih-a2all.com

Albumin Dialysis

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The adult and pediatric teams of Northwestern Memorial Hospital and Children’s Memorial Hospital developed a program that brings together all the necessary components to treat intestinal failure patients through specialized nutrition and medical and surgical strategies. This multidisciplinary group of experts includes gastroenterologists, surgeons (GI and transplant), nurses, dietitians, infectious disease specialists, stoma therapists, interventional radiologists, psychiatrists and social workers.

“While we have significant expertise with intestinal transplantation, our ultimate goal is to avoid transplant in as many patients as we can,” says Jonathan Fryer, MD, surgical director of Intestinal Transplantation at Northwestern Memorial and associate professor of Surgery at the Feinberg School. “As a result, we are able to reverse complications in an increasing number of patients who initially meet transplant indications. We are achieving increasing success in improving or reversing the changes of liver disease and in many cases taking patients off TPN.”

Transplant surgeons on the medical staff at Northwestern Memorial and Children’s Memorial perform the full range of liver and intestinal procedures including autologous GI reconstructive techniques as well as all available intestine transplant procedures including intestine-only transplant, combined liver/intestine transplant and multi-visceral transplant. Transplants are performed using either deceased donors or living donors, although living donor transplantation is reserved for exceptional situations. Excellent outpatient programs and facilities enable some intestinal transplant recipients to experience hospital stays significantly below the national average. Candidates for intestinal transplant are patients who are unable to discontinue TPN and develop complications as a result. The complications listed by Medicare are liver injury, loss of vascular access, recurrent line infections and recurrent severe dehydration. Northwestern Memorial meets the national Medicare criteria for intestinal transplantation surgery. Early referral of intestinal failure patients to an intestinal rehabilitation program gives patients the best chance of rehabilitation and avoiding transplant.

“Unfortunately, most patients who get referred for transplant actually are referred too late,” says Dr. Fryer. “We recommend sending intestinal failure patients early so we can work on weaning them off TPN first. Then, if they cannot be weaned from TPN, and they face life-threatening complications associated with TPN, they can be transplanted in a timely manner so they avoid also needing a liver transplant.”

In particular, patients who have less than 100 centimeters of intestine should be referred early, as should those who develop any liver abnormalities. These groups are both at high risk for developing liver disease.