Invited Article

Management of Decompensate Cirrhotic Patients Awaiting Liver Transplantation and Early Post-transplant Care

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INTRODUCTION

The last resorts of definitive treatment for decompensate cirrhosis, acute liver failure and early-stage of hepatocellular carcinoma in end-stage liver disease is liver transplantation. From the two-year survival rate of 50% in decompensate cirrhosis, the one-year survival rate after liver transplantation goes beyond 90%. Deceased donor liver transplantation has been an established surgical procedure since the first liver transplantation performed by Thomas E Starzl in 1967. The discovery of highly effective immunosuppressive drug, cyclosporine A, opened a new era of organ transplantation. Subsequently, National Institutes of Health (NIH) issued a consensus statement that liver transplantation was no longer an experiment and should be accepted as a necessary procedure for selected patients with end-stage liver disease.

Indication of liver transplantation

Decompensate cirrhosis

From the policy of the United Network for Organ Sharing (UNOS) issued in 1997, Child-Turcotte-Pugh (CTP) score of 7 or higher was considered the minimal listing criteria for eligibility for liver transplantation. A CTP score of 7 or higher was translated to an estimated equal to or less than 90% chance of 1-year survival without liver transplantation. Since February 2002, the Model for End-Stage Liver Disease (MELD) score*, a risk predictive score of death at 3 months, has been utilized as an organ allocation measure in the United States and in many countries. Since the implementation of MELD, there has been a reduction of the number of death on the waiting-list and the number of new patients listed for liver transplantation. In addition, subsequent reports revealed that liver transplantation in patients with MELD scores <14 led to higher mortality than that of patients with the same MELD score but not transplanted[1]. Some conditions with certain clinical severity that cannot be depicted by MELD score or "MELD exception" such as hepatopulmonary syndrome, metabolic liver diseases are accepted criteria for undergoing liver transplantation[2].

Acute liver failure

Though King's College Hospital Criteria is widely known as a prognostic stratification measure for selecting patients with acute liver failure for liver transplantation, it is still not a perfect tool (Table 1)[3]. Some

Table 1. King's College Hospital Criteria[4]

Acetaminophen	Non-acetaminophen
Arterial PH < 7.3	Prothrombin time > 100 sec (or INR > 7.7)
Or	Or
All three of the following:- 1. Prothrombin time > 100 sec (or INR > 7.7) 2. Creatinine > 300 μmol/L (or > 3.4 mg/dL) 3. Grade III or IV encephalopathy	Any three of the following:- 1. Age < 10 or > 40 years 2. Etiologies:- non-A non-B or drug-induced hepatitis 3. Jaundice > 7 days before encephalopathy 4. Prothrombin time > 50 sec (or INR > 3.85) 5. Bilirubin > 300 μmol/L (or > 17.5 mg/dL)

*MELD score = $9.57 \times \log_e(Cr) + 3.78 \times \log_e(bilirubin) + 11.2 \times \log_e(INR) + 6.43$

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patients with acute liver failure who do not have the criteria of King's College Hospital do not recover spontaneously, and still need liver transplantation.

Hepatocellular carcinoma

Liver transplantation is indicated in hepatocellular carcinoma that has liver cancer staging within Milan criteria. The criteria requires a single lesion ≤ 5 cm in diameter or up to three lesions that are all ≤ 3 cm in diameter[4]. Some centers expand the HCC selection criteria by adopting the University of California San Francisco (UCSF) criteria, namely a single tumor ≤ 6.5 cm or up to three lesions that are ≤ 4.5 cm with the sum of all diameters of 8 cm or less. A few reports showed that the survival after liver transplantation under the UCSF criteria was not different from those who had liver transplantation for hepatocellular carcinoma within Milan criteria[5].

Contraindication of liver transplantation[6,7]

Patients with the following conditions should not undergo liver transplantation because of high morbidity and mortality.

1. Uncontrolled sepsis
2. Unstable hemodynamic status
3. Severe (or advanced) medical comorbidity
4. Acquired Immune Deficiency Syndrome (AIDS)
5. Brain death
6. Extrahepatic malignancy
7. Advanced hepatic malignancy
8. Active alcohol or substance abuse
9. Lack of psychosocial support

Pretransplant management

Ascites and refractory ascites

Once ascites develops in cirrhotic patients, the chance that patients will die in 2 years equals 50%. Ascites fluid tapping should be performed in new onset or recent onset ascites to work up for the cause of ascites and to exclude concomitant infection or malignancy. Serum ascites albumin gradient (SAAG) of > 1.1 U/L and ascites protein < 2.5 g/dL suggests cirrhotic portal hypertension as the cause of ascites fluid. Dietary salt restriction (less than 2 g/day) and diuretic drugs are the recommended treatment[8]. Ascites fluid is better controlled if the combined therapy of spironolactone and furosemide is given than being treated with sequential therapy of the drugs. The diuretic dose should be adjusted every 7 days, aiming to achieve 0.5 kg per day in patients without peripheral edema and 1 kg per day in patients with peripheral edema. All diuretics should be discontinued if the patients develop hyponatremia, acute kidney injury, hepatic encephalopathy or severe cramps[9]. Water restriction is not needed except when serum sodium falls below 120 or 125 mEq/L[8]. Patients should be assessed for the possibility of liver transplantation after the first presentation of ascites. Refractory ascites is defined when there is no clinical response to high dose diuretics or when the patients developed side effects from diuretics. Large volume paracentesis (LVP) with infusion of albumin 8 g per 1 L of fluid removal is the initial recommended treatment for patients with refractory ascites[8]. A recent meta-analysis revealed that transjugular intrahepatic portosystemic shunts (TIPS) was a more effective therapy for refractory ascites in preventing recurrence of ascites fluid than repeated LVP[10]. However, survival improvement was not different between the two groups and the incidence of hepatic encephalopathy increased significantly in the TIPS group[10].

Spontaneous bacterial peritonitis (SBP)

The diagnosis of SBP can be made when there is a positive ascites fluid culture or an elevated ascites fluid absolute neutrophil count ≥ 250 cells/mm^3 in a cirrhotic patient with signs and symptoms of infection. Empiric antibiotic therapy, for instance intravenous cephalosporin, should be given in 5-10 days[8]. Cirrhotic patients with SBP who have a serum creatinine > 1 mg/dL, BUN > 30 mg/dL or total bilirubin > 4 mg/dL should receive 1.5 g albumin per kg within 6 hours and 1 g per kg on day 3 to reduce the incidence of hepatorenal syndrome and mortality rate[8,11]. Short-term antibiotics prophylaxis for SBP is recommended in decompensate cirrhotic patients who develop upper gastrointestinal bleeding because short-term antibiotics can increase the survival rate and reduce the incidence of infection[12]. Long-term prophylaxis of SBP is suggested in those who have a prior history of SBP, and those who have low ascites fluid protein (< 1.5 g/dL) with at least one of the following criteria (creatinine ≥ 1.2 mg/dL, BUN ≥ 25 mg/dL, sodium (130 mEq/L or Child-Pugh ≥ 9 points with bilirubin ≥ 3 mg/dL)[8]. A recent study revealed that long-term prophylaxis of SBP in patients with low ascites fluid protein led to survival improvement, which was related to a reduced incidence of hepatorenal syndrome[13]. However, the emergence of drug-resistant organism problem calls for caution for the long-term use of antibiotic prophylaxis in patients with decompensate cirrhosis.

Hepatorenal syndrome

Pretransplant renal dysfunction is an important predictor of posttransplant survival and chronic renal insufficiency. Acute kidney injury (AKI) is highly prevalent in cirrhotic patients who are admitted to the hospitals. The common causes of AKI are sepsis, hypovolemia and nephrotoxic drugs. If serum creatinine still persists over 1.5 mg/dL after all causes are excluded and fluid volume is fully replaced, the diagnosis of hepatorenal syndrome (HRS) should be made according to a revised criteria of HRS[14]. Terlipressin (0.5 to 1 mg iv. every 4-6 hr) plus 1 g/kg of albumin infusion is the initial treatment of HRS type 1[9,14]. TIPS has a limited role in HRS type 1 and requires further studies[9,14]. TIPS can be used in HRS type 2 which has refractory ascites and renal insufficiency as its concomitant conditions[9,14]. Liver transplantation is the treatment of choice for both HRS type 1 and type 2. The patients who have end-stage liver disease coexisting with HRS should have expedited referral for liver transplantation[9].

Portal hypertension

Endoscopic variceal screening is recommended in all cirrhotic patients[16]. Patients with small esophageal varcies but who have the high-risk predictors of bleeding such as red wale marks, Child class C cirrhosis should be treated with nonselective beta-blockers (NSBB)[16,17]. NSBB or endoscopic band ligation is suggested for primary prophylaxis in patients with medium or large esophageal varices[17,18]. Isosorbide-5-mononitrate (ISMN) lacks of supporting evidence for use in the combined treatment of NSBB or endoscopic band ligation for primary prophylaxis[18]. For the treatment of acute variceal bleeding, vasoconstrictor (terlipressin, somatostatin and octreotide) should be used in combination with endoscopic band ligation; and the vasoconstrictor should be continued for up to 5 days[17,18]. Endoscopic therapy with N-butyl-cyanoacrylate is recommended for acute hemorrhage from isolated gastric varices (IGV), GOV1 and GOV2[17,18]. The combined use of endoscopic variceal ligation and NSBB is recommended for the prevention of recurrent variceal hemorrhage[17,18]. PTFE-covered TIPS is a salvage therapy for 10-20% of patients with variceal hemorrhage who fail medical treatment[17,18]. Beta-blocker is the drug of choice for bleeding from portal hypertensive gastropathy[17,18].

Hepatopulmonary syndrome (HPS)

HPS is found in 15-20% of cirrhotic patients who are on the list of liver transplantation[17,18]. Using a pulse oximeter as a screening tool to detect hypoxemia provides a sensitivity of 96% and a specificity of 76%[17,18]. Arterial blood gas (ABG) should be done to confirm hypoxemia which is detected from a pulse oximeter. If HPS is suspected, saline agitating contrast echocardiography should be carried out as the next step[17,18]. A macroaggregated albumin (MAA) scan is the most reliable diagnostic test for confirmation of HPS[17,18]. Liver transplantation is the only effective treatment for HPS and it can result in the complete resolution of HPS in nearly all patients[17,18].

Portopulmonary hypertension (PPH)

PPH is a unique pulmonary condition found in patients with cirrhosis. It is defined by the elevation of pulmonary artery pressure (PAP) > 25 mmHg, increased pulmonary vascular resistance > 240 dynes.s.cm^{-5} and normal pulmonary artery occlusion pressure[21]. PPH was present in 8% of cirrhotic patients on the waiting list[19]. Patients may be asymptomatic or have some symptoms such as fatigue, dyspnea and syncope. Doppler echocardiography is a practical screening tool for the diagnosis of PPH. Using a right ventricular systolic pressure (RVSP) cutoff of 40 mmHg, the sensitivity and specificity of doppler echocardiography are 80% and 96%[20]. Right heart catherization can further confirm the diagnosis PPH in those who have RVSP > 50 mmHg[21]. Cirrhotic patients with PAP greater than 50 mmHg should not undergo liver transplantation because of the high risk of perioperative mortality[21]. Although patients with PAP between 35 and 50 mmHg have an increased mortality if liver transplantation is performed, the patient condition may be improved from vasodilators such as prostanoid, endothelin receptor blockers and sildenafil[21].

Nutritional support

The prevalence of malnutrition among patients with decompensate cirrhosis who await liver transplantation is as high as 90-100%. End-stage liver disease patients on the list usually have frequent fasting periods because of hospitalization and the requirement to undergo a large number of investigations. Poor dietary intake because of salt restriction and the presence of hypermetabolic state are additional contributing factors of malnutrition in decompensate cirrhotic patients[22]. Nutritional deficiency affects survival rate, clinical course and complications of decompensate cirrhosis. The survival outcome and complications after

liver transplantation are also related to pretransplant nutritional status[22]. Increased infection episodes and prolonged ICU and hospital stays were related to poor pretransplant nutritional status[23]. Patients with decompensate cirrhosis should acquire dietary energy intake of 35-40 kcal/kg/day with a protein intake of 1.2-1.5 g/kg/day[24]. Late-evening or nighttime food intake yields more positive protein gain than daytime nutritional supplement in patients with cirrhosis[25].

Hepatic encephalopathy (HE)

The principal of HE management is to identify and eliminate the precipitating factors. Target protein intake in cirrhotic patients without HE or with grade 1 HE is 1.0-1.5 g/kg/day. Short-term protein restriction is recommended in acute hepatic encephalopathy. After the acute event, protein diet should be reinitiated at 0.5-0.6 g/kg/day, then increased by 0.25-0.50 g/kg/day, to the maximum requirement of 1.0-1.5 g/kg/day or the development or worsening of HE[26]. Nonabsorbable disaccharides (lactulose) have a better cathartic effect than other laxatives. The alternative drug is rifaximin, a nonabsorbable antibiotic[27]. Lactulose and rifaximin can prevent the recurrence of HE episodes[27]. Zinc supplementation may improve nutritional status and neuropsychological function of HE. Branched-chain amino acid (BCAA) has been widely evaluated in cirrhosis but the benefit of BCAA in HE was confirmed in cirrhotic patients with hepatic encephalopathy who cannot tolerate animal or vegetable protein[28].

Early posttransplant management

Laboratory monitoring

Immediately after surgery, continuous improvement of serum transaminases and resolving coagulopathy reflects the recovery of liver graft[29]. Optimum fluid management and electrolyte imbalance correction is crucial during this period. The deterioration of hepatic encephalopathy, marked rising of serum transaminases, worsening coagulopathy, oliguria, metabolic acidosis and hypoglycemia point toward the occurrence of severe liver dysfunction that can be caused by primary non-function, hepatic artery thrombosis, portal vein thrombosis or hyperacute rejection[30].

Immunosuppressive therapy

A bolus of intravenous methylprednisolone is commonly given at the time of transplantation as induction therapy[31]. Several steroid free regimens are under investigation and are used in some centers. Maintenance immunosuppressive regimen, which consists of steroid, calcineurin inhibitor with or without antimetabolite, is generally started in 48 hours of transplantation[32]. The calcineurin level, liver function test and renal function require closely monitored during the early posttransplant period. Immunosuppressive regimen with delayed, reduced-dose calcineurin and antimetabolite is favorably used in patients with pretransplant and peritransplant renal dysfunction[33].

Posttransplant nutritional support

Because of pretransplant malnutrition, stress of surgical procedure, protein catabolism, and the fasting period, it is recommended that normal diet or enteral tube feeding should be initiated in 12-24 hours of transplantation[24]. Liver transplant patients should receive 1.5-2 g of protein per kg with calories at 120-130% of calculated basal energy expenditure.

Infection prophylaxis

Hospital-acquired bacterial infection is the most common cause of infection at immediate early postliver transplant period. Intrabdominal surgical site infection, ventilator-associated pneumonia, catheter-related septicemia and urinary tract infection are the frequent primary sources of infection[34]. The timeline of the natural epidemiology of posttransplant infection directs the regimen and duration of prophylaxis, for instance TMP-SMX prophylaxis is given to prevent Pneumocystis carinii pneumonia in the first 6 months. For fungal prophylaxis, there have been contrasting guidelines of indications and regimens of antifungal therapy. By and large, antifungal prophylaxis should be considered on a case by case basis. High risks of fungal infection are acute liver failure, retransplantation, renal failure and longer operation[34]. For cytomegalovirus (CMV) prophylaxis, there are generally two strategies, namely universal prophylaxis and preemptive approach, for those who are not high risk of CMV infection.

CONCLUSION

Patients with decompensate cirrhosis awaiting liver transplantation have high incidence of coexistent medical illnesses and nutritional deficiency. Apart from donor liver graft quality and operative factors, pretransplant status of patients is also a crucial factor that can affect posttransplant outcome. The long-term survival of post-liver transplant patients is attributed by the appropriate care during pretransplant, peritransplant and posttransplant period.

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