Chapter

Introductory Chapter: Liver Transplant in the Current Era

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1. Introduction

The historical backdrop of liver transplantation (LT) is an intricate story to reveal. It is an adventure of extraordinary achievement and catastrophic disappointments. Throughout the history of LT, controversies and LT seem to be synonymous with each other.

To begin with the world's first liver transplant, which was done by Thomas Starzl on March 1963 in a 3-years-old boy with biliary atresia, and another five more LT were performed by Thomas Starzl in the following years, but none of them survived more than 23 days [1]. During that time, many called a liver transplant as an unethical procedure and condemned Starzl. After the discovery of cyclosporine A, the survival of LT patients significantly increased [2, 3]. Additionally, in recent years, the advancement in surgical techniques, new antimicrobials and immunosuppressant drugs, and cutting-edge interventional radiology have notably enhanced the outcomes of LT. At present, LT turned out to be the gold standard and only the cure for end-stage liver diseases. The outcomes of LT recipients have significantly enhanced throughout the years through therapeutic advances, including ameliorated surgical techniques, powerful antimicrobial treatment, effective immunosuppressive drug regimens, and cutting-edge interventional radiology. At present, LT turned out to be the gold standard and only the cure for end-stage liver diseases. Despite the improvements in results, LT is still facing lots of challenges, where demand is high and the resources, primarily concerned with donors, are very limited. Although the marginal supply of organ donors has been increased through different surgical and medical innovations [4, 5]. Nonetheless, there are many unsolved questions that need in-depth debate among the transplant society, primarily focusing on the question about the selection of patients that are in need of LT, best use of new drugs, and procedures in this area, which has quickly advanced in the course of recent decades [4–7]. It is believed that DCD-LT poses higher risks of graft failure and biliary complication in comparison with donation after brain death (DBD) LT, which are related to warm ischemia, early allograft dysfunction, and prolonged cold ischemia time [5]. Similarly, in the time of organ shortage, the strategy of salvage liver transplant (SLT) is used for patients with HCC in the case of recurrence after resection [6]. However, SLT still remains controversial in comparison to primary liver transplant (PLT) mainly due to surgical difficulties due to adhesions, increased rate of posttransplant complications, and poor long-term outcomes [6]. Likewise, the approach of ABOi LT was to increase the donor pool and to provide LT in emergency conditions. However, ABOi LT remains to be a controversial approach in comparison to ABO-compatible (ABOc) LT, mainly due to different risks associated with it, especially earlier graft

loss, acute cellular rejection (ACR), antibody-mediated rejection (AMR), vascular, biliary complications, and HCC recurrence [4]. Moreover, other concerns are related to timing, economic evaluations, and criteria of LT for acute decompensated liver and LT for severe alcoholic hepatitis as tools for decision-making and implications in clinical practice [8–10].

To review all the contentions in LT comprehensively is outside the sphere of this chapter. This chapter is principally aims at LT for Hepatitis C virus (HCV)-related cirrhosis and nutritional support for cachectic patients waiting for LT.

2. Liver transplant and hepatitis C virus (HCV)

Hepatitis C virus (HCV) infection accounts for approximately around 40% of all chronic liver diseases in the United States [11]. However, since the introduction of direct-acting antiviral (DAA) therapy, the number of cases has declined rapidly in recent years. Nonetheless, HCV-related cirrhosis is still the third most common indication for LT in the United States [12]. It is recommended that all the patients with HCV infection should be treated ahead of LT. If not treated in the pretransplant setup, there is a very high chance of HCV reinfection after liver transplant, and that can be the main cause of graft failure without effective antiviral therapy [13].

It is unclear if the HCV-positive patients with child grade C on the LT waiting list should be treated with antiviral drugs before liver transplant. It is seen that the practice varies largely in different regions and medical centers.

The primary consideration is the accessibility and utilization of HCV-positive livers. In regions where these organs are extremely common, the accentuation will probably be not to treat HCV-infected patients who are on the LT waiting list with the goal that HCV-positive livers can be available for such patients. Similarly, in the regions where HCV-positive livers are not as common, the focus will be toward treating HCV-positive patients before the LT. A recent study by Bowring et al., showed large variations in the centers using HCV-positive liver, which ranges between 0 and 40%. Indeed, roughly one-fourth of the medical centers by no means have used an HCV-positive liver, while at one medical center 40% of liver from HCV-infected donors were used [14]. Accordingly, there is a vast disparity in the utilization of HCV-positive livers. The choice to treat patients before the LT is situated to some extent on this issue.

Besides, the model for end-stage liver disease (MELD) score, before LT is an additional circumstance from above. In an HCV-positive patient with a low MELD score, physicians focus on treating such patients with DDA prior to transplant, which can make them virus-free with a sustained virologic response (SVR). However, in the patients whose MELD scores are more than 30, physicians are less likely to treat those patients with DDA prior to LT and place them in a situation called “MELD limbo” or “MELD purgatory.” Saying that refers to the patients who are not too sick to undergo LT, yet not in a good health to function satisfactorily. This has extensively been debated concerning why patients ought not to be treated [15].

The last reason to acknowledge is the patient’s capacity for *medication* adherence and completing the course of the DDA, which is normally 12 weeks. Most patients with decompensated liver fail to complete their course due to repeated hospitalization. Likewise, it has been found that the patients with decompensated liver have a lower SVR rate contrasted with less sick patients [16].

Despite, it is hard to generalize the treatment strategies of different centuries, overall most of the centers might say that patients with MELD scores of 20 or above

are likely not great candidates for HCV antiviral treatment. Whatever the reason, this practice greatly varies from hospital to hospital and geographical location, which depends on the physician's judgment, the availability of HCV-positive organs, and the MELD score of patients before LT.

3. Nutritional support for cachectic patients before liver transplant

Currently, frailty, and sarcopenia are have gained lots of concern in LT, as they have shown to *associated with* an increased risk of morbidity and mortality for the patient waiting for LT and post-LT [17, 18]. Frailty is evaluated through different performance-based parameters, such as grasp strength and gait speed, chair stands, and balance [19], whereas sarcopenia is regularly evaluated by estimating the psoas muscle zone on imaging or using whole-body bioelectrical impedance [20]. Nonetheless, presently there are many ongoing studies to properly identify these patients and appraise them for new treatments [18].

High mortality has been reported in the patients on the waiting list who are malnourished, and those on a low protein diet of less than 0.8 gm/kg body weight/day [21]. In a study by Le Cornu et al., found that nutritional advice together with oral nutritional supplements improved the mid-arm circumference and grasp strength of the patients compared to nutritional advice alone; nonetheless, mortality was similar in both groups [22]. Similarly, a pilot study by Plank et al., revealed that oral nutritional supplements fortified with omega-3 fatty acids, arginine, and nucleotides had lower infectious complications after LT than those on the standard nutritional intervention [23]. However, a successive randomized trial by Plank et al., did not find any significant benefits of perioperative immunonutrition in patients undergoing LT in terms of preoperative nutritional status or postoperative outcome compared to standard oral nutritional intervention [24]. Similarly, a meta-analysis found that perioperative use of immunonutrition, such as glutamine or omega-3 fatty acids, arginine, and ribonucleic acids, was significantly associated with a reduction in infectious complications and earlier recovery in liver function after LT; however, there was no significant difference in overall survival [25]. Kaido et al., also reported that patients who took oral immunonutrition, has less postoperative infectious complications after LT [26]. Surprisingly, preoperative branched-chain amino acid only showed better survival outcomes for patients with sarcopenic on the waiting list; however, it failed to improve survival in non-sarcopenic patients.

The molecular mechanisms of integral sarcopenia have been researched extensively and interpreted to some degree. In the meantime, a unique idea has developed, for example, the incidence of overweight and corpulence in cirrhotic patients [27]. This warrants both clinical consideration and further investigation. Lately, studies have provided initial information on the potential advantage of physical activity in cirrhotic patients [28–30]. However, these data need to be better defined and verified.

To conclude, liver glycogen is exhausted in patients with cirrhosis. Thus, it is prudent to take incredible consideration to minimize the interval without nutrient consumption, so as to dodge gluconeogenesis from muscle protein in previously protein-depleted patients. The interest to characterize and treat frailty and sarcopenia in patients waiting for LT is rapidly increasing. In spite of the fact that results from the studies cited above are encouraging, there is a lack of large, well-powered homogeneous groups of patients, and long-term observational studies that can provide the ideal treatment for anticipation or reversal of frailty and sarcopenia.

4. Future perspectives

In general, LT is an exhilarating field of research. It comprises with an opportunity a wide range of research areas, such as transplant immunology, transplant pharmacology, transplant oncology, infectious diseases, and cardiovascular diseases.

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