Digestive and Liver Disease Supplements 5 (2011) 2–5

Contents lists available at ScienceDirect

Digestive and Liver Disease Supplements

journal homepage: www.elsevier.com/locate/dld

Current challenges and future trends in liver transplantation

Manuel L. Rodríguez-Perálvarez, Jose Luis Montero, Manuel De la Mata García *

Digestive Diseases Department, Reina Sofía University Hospital, Córdoba, Spain

Abstract

In Liver Transplantation (LT) units the clinicians routinely deal with complex decision making situations that cannot always be solved with the available scientific evidence. They include selection of the best candidates for LT, minimizing mortality and drop-out rates within the waiting list (WL) and rationalizing donor–recipient matching. These topics constitute some of the current challenges in LT and they may drive a number of future research trends. Since the MELD implementation the organ allocation model has moved from a system based on length of time on the WL to a disease severity based policy, and thus to a more rational use of LT and a decrease in WL mortality. However, during the last decade several limitations of this system have been highlighted, and modifications of the MELD score have been proposed. Furthermore, patients with hepatocellular carcinoma do not fit inside the MELD system and the current strategy of prioritization based on number and size of nodules has not eliminated the drop-out risk, despite the use of locoregional ablative treatment while on the WL. A better understanding of tumour behavior, especially concerning microvascular invasion, is urgently needed to improve management of patients with hepatocellular carcinoma. Finally, the donor and recipient features maintain a complex relationship that affects outcome. The use of artificial neural network to find the most adequate recipient to each graft, may allow a more rationalized allocation policy.

Keywords: Donor–recipient matching; Hepatocellular carcinoma; Liver transplantation; Microvascular invasion; Waiting list

1. Introduction

Liver transplantation (LT) is a complex procedure which leads to serious dilemmas in clinical practice, not only in medical terms but also in terms of ethical relevance. The rising worldwide prevalence of advanced liver disease and the shortage of donors, render LT a precious therapeutic resource that deserves to be used within multidisciplinary experienced units on a rational and efficient basis. Waiting list management, liver allocation policy, donor selection and donor–recipient matching are currently difficult challenges for LT units all over the world. Furthermore, some indications for LT such as hepatocellular carcinoma (HCC) with expanded criteria or the presence of comorbidities such as HIV infection make the decision even more complicated in some patients. These issues are addressed in the present review, summarizing the available scientific evidence and future trends.

2. Access to the waiting list and prioritization

As a direct consequence of the imbalance between candidates to LT and donors, potential recipients are placed on a waiting list (WL) where they are given priority according to different allocation models. The incidence of the main etiologies of LT remains stable or even on the increase worldwide [1,2] while a trend towards donor shortage has been noticed during the last years. Although non-heart-beating donors, split and living donor LT have increased the pool of donors [3], the liver graft demand is far from covered. In Spain, the risk of mortality on the WL is 6–10%. To optimize WL management, a careful selection of candidates and an objective prioritization should be implemented. Indeed, the optimal candidate for LT is the patient with the highest potential benefit in terms of quality of life and survival. Patients with long life expectancy

* Address for correspondence: Manuel De la Mata García, PhD, FRCP, Digestive Diseases Department, Reina Sofía University Hospital, Córdoba, Cantueso n° 37. PC: 14012; Córdoba, Spain. CIBERehd, Instituto Carlos III.
E-mail address: mdelamatagarcia@gmail.com (M. de la Mata García).

1594-5804/$ – see front matter

without transplant or those with poor prognosis regardless of LT should not be transplanted according to this rational basis.

The implementation of the MELD model in the early 2000s, which had demonstrated the ability to predict short term [4] and WL mortality [5] in patients with advanced liver disease, led to an objective, dynamic and easy-to-apply WL management. A decrease in WL mortality, without affecting post transplant long term prognosis, has been reported [6–8]. Previous studies have shown that patients with MELD score <14 face higher mortality rates when they receive a liver graft as compared to the mortality risk on the WL [9]. It has become widely accepted that patients with MELD score lower than 15 need to be closely followed but LT should be avoided. Nevertheless the MELD system has failed to identify those patients too sick for LT. In clinical practice, LT in cirrhotic patients with severe liver failure, requiring intensive care, haemodialysis, artificial ventilation or inotropic drug support, is very likely to be futile.

The MELD score entails a number of limitations that may lead to variability in daily practice. Firstly, it is important to keep in mind that the MELD score was designed to predict mortality in candidates to TIPS [10]. Subsequently the United Network for Organ Sharing (UNOS) introduced empirical modifications to facilitate its application on LT candidates. The specific weight of each parameter included has been extensively criticized because of the major importance given to serum creatinine in detriment of liver function parameters (bilirubin and INR). The identification of new variables with independent prognostic capability could improve the accuracy of the MELD model, being serum sodium one of the most widely studied. It has been proposed that adding serum sodium may improve the MELD's ability to predict WL mortality [11], especially for patients with MELD <20. Sharma et al. [12] showed that re-weighting MELD coefficients by enhancing liver function tests (i.e. bilirubin and INR) improves the accuracy in mortality prediction, but serum sodium was not included in this study. Recently, Leise et al. [13] developed a modification of the MELD model and validated it over a large cohort of patients. The main changes included were: serum sodium was added, coefficients were re-weighted (by highlighting bilirubin and downgrading creatinine and INR) and upper and lower bounds for creatinine were modified (to 3 and 0.8 mg/dl respectively). The 90 days WL mortality was reduced and 29 deaths (of 324 with the classic MELD) would have been avoided. These results are promising and deserve further investigations to reproduce them in other geographic areas.

None of the previous studies have demonstrated that MELD score accurately predicts mortality after LT. A high number of variables related to the graft, intraoperative period, early and late postoperative stages may condition the final results on survival. On the other hand, MELD parameters do not consider many other aspects which may impact on outcomes, such as cardiopulmonary comorbidities, insufficient family support or lack of adherence.

One of the most controversial comorbidities is the HIV infection. The presence of HCV and HIV co-infection is common in clinical practice and it represents an extremely difficult clinical scenario. Since the introduction of highly active antiretroviral therapy (commonly known as HAART), a long life expectancy has been achieved and complications of liver disease has become the first cause of death in this group of patients. Several series of LT in HIV positive patients have been reported in the last decade. HIV–HCV coinfection is the main indication for LT. The high frequency and severity of HCV recurrence after LT have determined a lower survival rate in most of the series published so far. Although absolute contraindication for LT in HIV patients has been eliminated in most centers, LT for HIV–HCV cirrhosis is currently highly controversial, particularly in patients with HCV viraemia [14]. In Spain [15] a cohort of monoinfected HCV patients (n = 252) has been compared to a group of coinfected HIV–HCV patients (n = 84) who received a LT. The five years survival in the HCV monoinfected and the HCV-HIV group were 71% and 54%, respectively (p = 0.008) [16]. Thus the selection of HIV–HCV coinfected candidates for LT requires a careful evaluation of HIV status and the application of appropriate prophylactic measures to prevent opportunistic infections. Further investigations are needed in this subgroup of patients before considering HIV as a formal exclusion criterion for LT.

3. Liver transplantation for HCC: the drop-out problem

HCC is the first cause of death in patients with cirrhosis and LT is a potentially curative treatment both for HCC and cirrhosis. Selecting HCC candidates is currently one of the most difficult challenges to be solved. From an ethical perspective, LT should be offered for HCC treatment whenever the expected survival after transplant is comparable to other etiologies. The Milan criteria [17] (one nodule <5 cm or up to three nodules <3 cm each, without major vascular invasion or extrahepatic disease) have turned out to be useful in selecting HCC candidates to LT with excellent survival results and a low rate of recurrence.

The Milan criteria are currently followed in most LT centers. There have been many attempts to expand Milan criteria proposing to raise the number of nodules, the size of the main nodule or both. Nevertheless results are not as good as those originally reported following Milan criteria. On the other hand, we now recognize that many other factors, apart from size and number of nodules, determine the biological tumour behavior and can affect prognosis after LT. A key factor, repeatedly confirmed in different studies, is microvascular invasion, a microscopic pathological finding which can dramatically affect disease-free and overall survival [18–23]. Microvascular invasion is a not consensually defined histological parameter which implies that the tumour cells are sufficiently evolved to degrade the lamina propia of parenchyma vessels and to access the bloodstream, leading to intra and extrahepatic tumour spreading. Mazzaferro et al. [22] analyzed the outcome after LT of patients under Milan criteria as compared to those beyond Milan criteria but under the so-called up-to-seven criterion (the sum of the