Frontiers in liver transplantation

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Several changes in disease epidemiology, treatment options and techniques to manipulate graft quality are changing the prospects of liver transplantation (Fig. 1). Liver cirrhosis from viral hepatitis B and hepatitis C (HCV) infection has been the leading indication for orthotopic liver transplantation (OLT) worldwide. As this patient population also has a particularly high incidence of hepatocellular carcinoma (HCC), this represents an additional indication for OLT in some. Historically, patients with HCV infection who received a liver transplant remained carriers of the virus and, as a consequence, a substantial proportion of patients relapsed into cirrhosis, particularly those with older donor grafts. Newer direct-acting antiviral agents have sustained response rates of 97–100 per cent, irrespective of viral genotype; this has had a major impact on indications for OLT. Organs from HCV-positive donors were traditionally accepted only for HCV-positive recipients, but antiviral treatment after OLT is so effective that transplants from virus-infected donors to HCV-naïve recipients have been described. Although the transfer of HCV is almost universal, recipients can be cleared of the virus within weeks and the therapy is well tolerated.

Emerging trends in public health and disease developments may influence the prevalence of chronic liver failure as well as the quality of available donor organs. Alcoholic liver disease and other lifestyle-associated disorders currently outnumber viral hepatitis as indications for OLT in the Western world. Sedentary lifestyle coupled with a high-calorie diet and processed food intake has led to increasing rates of non-alcoholic fatty liver disease as an indication for OLT in high-income countries. The epidemic change in liver pathology has consequences for the donor pool owing to the impact of associated steatosis and fatty liver disease on graft quality.

Currently, the demand for OLT far exceeds the number of available organs in most countries. Hence, the graft acceptance criteria have been extended to include donation after circulatory death. The use of marginal organs is associated with early allograft dysfunction or primary non-function, hepatic artery thrombosis, ischaemic cholangiopathy with biliary strictures, and impaired patient and graft survival. Transplantation has inescapable periods of organ ischaemia–reperfusion injury and marginal grafts tolerate the cold ischaemia less well than healthy livers. This has led to organ perfusion strategies in situ (in the donor), ex situ (or extracorporeal), at varying temperatures with or without oxygenation, and with an array of perfusates. It seems that machine perfusion has advantages over static cold storage (Fig. 1). Cold machine perfusion may be combined with gradual rewarming and normothermic perfusion to improve allograft dysfunction, ischaemic cholangiopathy and marginal graft survival. Hypothermic oxygenated perfusion can actually recharge mitochondrial adenosine 5′-triphosphate levels.

The ability to assess graft viability during perfusion is an important feature in fine-tuning OLT. Some organs may require more extensive and time-consuming interventions for reconditioning, as described for lung transplants. This strategy could open up a whole new scenario for extracorporeal therapy and regenerative medicine.

Liver transplantation for malignant disease has been considered an attractive option representing the ‘ultimate R0 resection’, but the initial outcomes were poor. To justify the allocation of liver grafts to patients with cancer, OLT survival rates must be comparable to those for non-malignant indications. This can be achieved by applying stringent tumour-specific criteria and good patient selection. Essentially, transplant criteria for patients with malignant tumours aim to predict the ill defined term ‘tumour biology’, which is highly variable between tumour types and patient groups. One might hypothesize that, given a favourable tumour biology, many patients with various non-resectable liver tumours could benefit from OLT. The International Liver Transplant Society has formed a special interest group in transplant oncology, and the first consensus conference was held in 2019. HCC and hepatoblastoma in children are well established indications, as is unresectable cholangiocarcinoma (with pretransplant chemoradiotherapy) in adults. Attempts at transplanting patients with secondary liver tumours have met with variable outcomes. During the past 10 years,
accumulating evidence suggests that selected patients with extensive, otherwise unresectable, liver-only metastases from neuroendocrine tumours and colorectal cancer can be offered OLT with very good survival outcomes comparable to those for conventional indications. A common feature of transplant criteria for both these secondary tumours is a clear demonstrable response to oncological treatment and disease stability over a prolonged observation time before listing for OLT. The significance of treatment response is also underscored by good experiences with downstaging of HCC tumours, allowing expansion of the original strict morphologically based Milan criteria. Preliminary results from a recent trial suggest that a similar approach can be used to select patients with intrahepatic cholangiocarcinoma for liver transplantation; this tumour has usually been considered an absolute contraindication.

Transplant oncology is an emerging field that will undergo more refinements as understanding of cancer biology is improved. Coupled with the more fundamental changes in epidemiology of liver disease and progress in organ preservation, reconditioning
and regenerative medicine technology (Fig. 1), this particular subgroup is likely to expand in the future.

Disclosure

The author declares no conflict of interest.

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