Editorial

The future of liver transplantation in Singapore

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Liver transplantation was first performed in the USA by Thomas Starzl in 1963[1]. In the early years, the mortality rate was extremely high[2] as surgical techniques and immunosuppressive therapy had not evolved sufficiently. In this millennium, liver transplantation stands as the final and accepted form of treatment for end-stage liver disease, with impressive one- and ten-year survival rates[3]. The results of the Singapore National Liver Transplant Programme are as good as published survival rates from the largest centres in the US and European Community.

In this recent era, we have seen improvements in all aspects of liver transplantation. For instance, transplantation for chronic hepatitis B has only recently become successful due to the availability of nucleoside analogues such as lamivudine and adefovir dipovoxil, without which high mortality occurs. Transplantation for chronic hepatitis C still results in relapse of infection in the new graft but the clinical course appears to be quite variable, and some patients are even cured with treatment after transplantation. Transplantation for hepatocellular carcinoma (HCC) has remained successful largely due to patient selection.

Overall, the success of the Singapore Liver Transplant Programme is to be lauded[4-10]. Nonetheless, real challenges remain. Despite such good results, mortality can still be improved further with better immunosuppressant regimes. The long-term complications of transplantation, particularly renal impairment, diabetes mellitus, malignancy and heart disease, continue to be major problems that lead to reduced long-term survival. Such complications can partly be addressed by improved immunosuppression that has less nephrotoxicity, and in the future development of targeted immunosuppression that can knock out specific immune cells involved in rejection. However, the main problem that remains is the increasing shortage of donor organs for an ever-increasing list of patients waiting for new livers. Our waiting list mortality is poor and the overall transplant rate is only 20.3% of referred patients.

One method of addressing the donor shortage is through an opt-in method that relies on increasing public awareness and organ donation drives, a method highly successful in Spain, so much so that the donation rate remains the highest in the world[11]. Singapore has taken the opt-out method by passing the Human Organ Transplant Act (HOTA)[12]. Since August 2004, only five liver grafts have been realised under the new act. The majority of offered livers were found unsuitable because of problems with the donors or graft steatosis. It does seem from this preliminary data that HOTA cannot answer Singapore's need for increased numbers of livers for patients on the waiting list for liver transplantation.

An alternative method has been to utilise right lobe living-related donor transplants. This type of transplant is offered by numerous centres worldwide. In the development of right lobe living-related transplantation, significant morbidity was found[13], but the surgical techniques and pre-transplant evaluation have matured to the stage where such complications for the recipient match that of cadaveric transplantation. However, there is and will always be a risk of donor mortality. Unfortunately, only a minority of patients can benefit from living donor transplantations, as the recipients have to rely on having suitable and willing relatives to donate part of their liver. While the ethics and morals can be debated, the fact is that only 14-15% of patients on the waiting lists for liver transplants appear to be able to utilise this option due mainly to issues of donor suitability[14,15].

In Hong Kong, the transplant programme has successfully utilised living-related adult liver transplantation to the extent that it contributes 47.7% to the adult transplant waiting list[16]. At the National University Hospital, Singapore, of a total of 41 patients on the waiting list over the last 18 months, less than 5% of these patients have a suitable related donor willing to proceed with right lobe living-related transplant. One problem may

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be due to the familial transmission of hepatitis B, making potential family members unsuitable due to their chronic hepatitis B carriage. However, there is certainly room for improvement in the adult living-related donation rate in Singapore.

Other transplant methods, such as split liver transplantation, should be utilised whenever possible, but this method largely benefits paediatric recipients. The future of liver transplantation relies on the development of new technology that can provide the breakthrough needed to fulfill the increasing demand for liver transplants. One possibility is xenotransplantation using a porcine model. Recently, the identification that rejection was targeted against porcine Galalpha (1,3) Gal resulted in the development of knockout transgenic pigs against this antigen with human complement regulatory protein and decay-accelerating factor (hDAF), and permitted survival of pig hearts in baboons for 76 days[17]. The most serious problem to overcome is rejection. Tissue engineering and transgenic models still have a long way to go even before clinical trials can start. Moreover, the discovery of chronic viral infections in the liver of these animals raises the possibility of zoonoses, and in the immunosuppressed state, disseminated viral infection in the human recipient[18]. Such biosafety concerns have yet to be suitably addressed.

Extracorporeal bioartificial liver devices have been used to bridge patients to transplant, provided a suitable liver can be found within a few days. In Singapore, the low liver donor rate makes this a somewhat futile exercise, unless a living-related donor is found rapidly. A true artificial liver device is the aim of many commercial companies and researchers, but no device has yet been accepted for routine clinical care[19-20]. Another experimental approach is liver cell transplant, either using isolated adult hepatocytes or foetal hepatocytes[21]. This type of approach is very promising for those with acute liver failure, or with metabolic disease where liver architecture is still preserved. In patients with cirrhosis, this method may run into problems.

In conclusion, although there is an increasing demand for new livers, supply has been unable to fulfill this demand. Even HOTA has failed to deliver a sufficient supply to reduce the waiting time in Singapore. Existing surgical techniques and procedures have been refined, but even right lobe living-related transplants, if optimised, cannot fulfill the demand for new livers. We need to look at new technology in the future to cater for such needs: a fully functional bioartificial liver device, liver cell transplantation and a safe xenograft model are needed. SMJ

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