Research Assessment Exercise 2020
Impact Case Study

University: The University of Hong Kong (HKU)
Unit of Assessment (UoA): 03 - Clinical Medicine
Title of case study: Improving worldwide survival of adult-to-adult right living donor liver transplantation

(1) Summary of the impact

In 2000, The University of Hong Kong (HKU) researchers reported the world-first adult-to-adult right living donor liver transplantations to ease the problems of small-for-size syndrome in areas where deceased organ donation is very low. We demonstrated that excellent control of chronic Hepatitis B virus infection without the use of Hepatitis B Immunoglobulin (HBIG) in post-transplant recipients have significant contributions to the world. Since 2017, the HKU HBIG-free approach has been incorporated in global clinical guidelines (European, Pan Asian and American) and adopted by many Asian centres. Cost-effectiveness analysis showed that use of HBIG-free approach could decrease at least 50% of cost.

(2) Underpinning research

Key HKU Department of Surgery researchers:
Prof Fan Sheung Tat (Professor of Surgery, 1993 – 2011, Emeritus Professor 2012- present)
Prof Lo Chung Mau (Professor of Surgery, 1999- present; Hospital Chief Executive of HKU-SZ Hospital, 2016 - present)
Prof Chan See Ching (Professor, 2011 –2016)
Dr Liu Chi Leung (Clinical Associate Professor, 2002 –2005)

Since performing the first successful liver transplant in Hong Kong, the Liver Transplant Service at Queen Mary Hospital has developed into one of the largest programmes of its kind in China and Southeast Asia. In 2000, HKU researchers published the pioneering application of liver transplants to adult patients using a world's first right lobe graft (3.1). We have shown that the ground-breaking innovative techniques provides life-saving options for desperately ill patients in the face of severe scarcity of deceased donor liver grafts (3.2). The study demonstrated actuarial patient and graft survival rates of 84% and 81%, respectively. Traditionally, Hepatitis B Immunoglobulin (HBIG) was the standard of care after liver transplantation for Hepatitis B related disease. The use of HBIG-free regimen was initially reported by our center in 2001 in 31 Asian chronic Hepatitis B (CHB) patients treated with lamivudine monotherapy only, with a low virological breakthrough rate of 3.8% (3.2). The disadvantage is the development of viral resistance. For these patients with resistance to lamivudine, we also demonstrated the efficacy of implementing add-on adefovir dipivoxil therapy (3.2). Five patients died of causes unrelated to hepatitis B, and 26 patients were alive at a median follow-up of 16 months (range 6–47) after transplantation. One (3.8%) patient developed recurrent hepatitis B resulting from viral breakthrough at week 53 and survived after retransplantation using adefovir and hepatitis B immune globulin treatment. The remaining 25 surviving patients had no biochemical or histologic evidence of recurrent hepatitis, and serum hepatitis B virus DNA remained negative. In six patients, hepatitis B surface antigen (HBsAg) persisted or reappeared in serum. Among 19 patients who became negative for HBsAg from 5 to 431 days after transplantation, 13 developed anti-HBsAb that lasted a median of 6 months (range 1–21). None of the patients with hepatocellular carcinoma developed recurrence. It showed good outcome after liver transplantation using lamivudine prophylaxis.

In 2011, we reported the efficacy of newer nucleoside analogue using entecavir as monotherapy without HBIG in CHB liver recipients, demonstrating high rates of hepatitis B surface antigen seroclearance and complete viral suppression in 80 patients transplanted between 2007 and 2009 (3.3).

The long-term survival of using a completely HBIG-free regimen was also demonstrated in 362 patients using oral antiviral therapy alone as prophylaxis after liver transplantation, with an excellent 8-year survival of 83%, and without any mortality related to hepatitis B recurrence (3.4). At the time of transplant, the median log HBV DNA level was 3.5 copies/mL (range, 1.54–8.81); 21 patients (26%) had undetectable levels of HBV DNA. The cumulative rate of hepatitis B surface antigen (HBsAg) loss was 86% and 91% after 1 and 2 years, respectively. Ten patients had reappearance of HBsAg. Eighteen patients (22.5%) were HBsAg positive at the time of their last examination; 17 of these had undetectable levels of HBV DNA, and the remaining patient had a low level of HBV DNA (217 copies/mL). There was no evidence of mutations. Entecavir monotherapy is effective after liver transplantation for chronic hepatitis B.

(3) References to the research

3.1 Fan ST, Lo CM, Liu CL. Technical refinement in adult-to-adult living donor liver transplantation using right lobe graft. Ann Surg. 2000 Jan;231(1):126-31. DOI: 10.1097/00000658-200001000-00018

3.2 Lo CM, Cheung ST, Lai CL, Liu CL, Ng IO, Yuen MF, Fan ST, Wong J. Liver transplantation in Asian patients with chronic hepatitis B using lamivudine prophylaxis. Ann Surg. 2001 Feb;233(2):276-81. DOI: 10.1097/00000658-200102000-00018

3.3 Fung J, Cheung C, Chan SC, Yuen MF, Chok KSH, Sharr W, Dai WC, Chan ACY, Cheung TT, Tsang S, Lam B, Lai CL, Lo CM. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. Gastroenterology. 2011 Oct;141(4):1212-9. DOI: 10.1053/j.gastro.2011.06.083

3.4 Fung J, Wong T, Chok K, Chan A, Cheung TT, Dai JWC, Sin SI, Ma KW, Ng K, Ng KTP, Seto WK, Lai CL, Yuen MF, Lo CM. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: Results up to 8 years. Hepatology. 2017 Oct;66(4):1036-1044. DOI: 10.1002/hep.29191

Key Funding

- Research Grants Council: Hepatitis B virus-specific immune response after liver transplantation for chronic hepatitis B using lamivudine prophylaxis (PI, Prof Lo CM; 2002-2006; HK$109,662)
- Croucher Senior Medical Research Fellowships: Prophylaxis and treatment of recurrent hepatitis B after liver transplantation (PI, Prof Lo CM; 2004-2005; HK$767,650)
- Health and Medical Research Fund: Mechanisms of antiviral drug-resistant in liver transplant recipients with HBV and HCC recurrence (PI, Prof Lo CM; 20015-2017; HK$960,820)

(4) Details of the impact

Impacts include: health and welfare, economy, practitioners and services, public policy

Main beneficiaries include: patients, practitioners, international policy makers

CHB virus infection remains a major global health issue, affecting up to 350 million people worldwide. Patients with CHB virus infection are at significantly increased risk for the development of cirrhosis, hepatic failure, and hepatocellular carcinoma. Liver transplantation is now a well-established treatment for liver failure and hepatocellular carcinoma. In order to overcome the graft size limitation often faced with adult-to-adult living donor liver transplantation (LDLT), we published the first report of right liver adult-to-adult LDLT. Since then, right liver adult-to-adult LDLT have been adopted in various centres around the world.

Patients, Clinicians, Health Policy and Cost-Effectiveness

In Hong Kong, where hepatitis B infection remains endemic, the cost of life-long HBIG for patients transplanted for CHB would have been prohibitive. With the approval of entecavir, a nucleoside analogue with a high barrier to drug resistance, HKU was the first to adopt this as a

standalone prophylactic agent. The significantly lower resistance rate meant that perhaps the use of entecavir as monotherapy without HBIG would be more acceptable for centers still subscribing to the use of HBIG. Indeed this was the case when we published our initial result and subsequent long term experience in 2018 on entecavir monotherapy [A]. In the more recent Asia Pacific Association for the Study of the Liver (APASL) hepatitis B guidelines published in 2016 [B], the use of HBIG-free regimen is now part of the recommendation, with specific reference to our study [C]. Also the latest American Association for the Study of Liver Diseases (AASLD) guideline in 2018 also recommended our approach [D].

Our long-term survival data has shown that there is no additional benefit to graft and patient survival with the use of HBIG. In fact, some centers adopting a completely HBIG-free approach like our own, including those in New Zealand, Australia, Singapore, and the United States [E]. Cost effective analysis showed that the use of Entecavir monotherapy could reduce the cost by at least 50% with compared with those needing HBIG [F].

Worldwide adoption of clinical practice, training and development

The application of right liver graft for adult to adult liver transplant is a revolutionized measure to ensure recipients' outcome with good donors' safety profile. As a result, 144 visitors from all different continents came to the Department of Surgery to learn our donor and recipient workup policy, techniques of donor right hepatectomy, hepatic venoplasty and implantation of right lobe liver grafts over the years [G]. In Asia countries, right living donor liver transplantation accounts for more than 90% of all transplant activities. We helped in the development of several LDLT programs in the world such as in Mainland China (Zhejiang University, Zhejiang, China), Philippines (Medical City Hospital, Manilla, Philippines), Malaysia (University of Malaya, Kuala Lumpur, Malaysia) and Sri Lanka (University of Kelaniya, Sri Lanka) since then. (attached two letters of appreciation from two of the visitors [H])

In Asia, right living donor liver transplantation accounts for more than 90% of all transplant activities due to the scarcity of organ donation. Korea has done 4000 cases per year since 2013 and the main indication for transplant was chronic HBV infection. The 5-year survival rate was more than 83% [I].

In Egypt, where there was severe discrepancy between supply and demand of organs, the LDLT program was initiated as they adopted our right liver living donor policy in order to overcome the graft size issue. The main indication for liver transplant was chronic Hepatitis C infection (HCV) which was highest incidence in the world (around 14%). The total number of LDLT (mostly right lobe) reached more than 2400 in 2014 and would further increase in future. The 5-year survival was around 70% and was mainly limited by the failure of HCV treatment before and certainly would be better in the era of new medication [J].

In the USA, despite the relatively good deceased donation rate in the US, it never met the demand. This innovative procedure had been adopted and it was the useful adjunct for patients on the waiting list. The latest published *Nature Reviews* commented that it might potentially eliminate those wait-list mortality for patients with end-stage liver disease [K].

(5) Sources to corroborate the impact

[A] Fung J, Cheung C, Chan SC, Yuen MF, Chok KS, Sharr W, Dai WC, Chan AC, Cheung TT, Tsang S, Lam B, Lai CL, Lo CM. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. Gastroenterology. 2011 ct;141(4):1212-9. doi: 10.1053/j.gastro.2011.06.083.

[B] Sarin SK et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1-98. DOI: 10.1007/s12072-015-9675-4 (P. 51-53).

[C] Wang P et al. Is hepatitis B immunoglobulin necessary in prophylaxis of hepatitis B recurrence after liver transplantation? A meta-analysis. PLoS One. 2014;7:9(8):e104480. DOI: 10.1371/journal.pone.0104480

[D] Terrault et al. Update on Prevention, Diagnosis and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018; Apr;67(4):1560-1599. DOI: 10.1002/hep.29800 Practice guideline. (P. 1599)

[E] Wang B et al. Management of chronic hepatitis B before and after liver transplantation. Frontline Gastroenterology 2018;9:79-84. DOI: 10.1136/flgastro-2016-100768

[F] Hu TH, Chen CL, Lin CC, Wang CC, Chiu KW, Yong CC, Liu YW, Eng HL. Combination of entecavir plus low-dose on-demand hepatitis B immunoglobulin is effective with very low hepatitis B recurrence after liver transplantation. Transplantation. 2014 Apr 27;97 Suppl 8:S53-9. DOI: 10.1097/01.tp.0000446278.43804.f9

[G] List of visitors coming to Dept of Surgery to learn the donor and recipient workup policy, techniques of donor right hepatectomy, hepatic venoplasty and implantation of right lobe liver grafts over the years

[H] Two letters of appreciation from Universiti Malaya, Kuala Lumpur and University of Kelaniya-Sri Lanka

[I] Lee SG. A Complete Treatment of Adult Living Donor Liver Transplantation: A Review of Surgical Technique and Current Challenges to Expand Indication of Patients. Am J Transpl 2015;15:17-38. DOI: 10.1111/ajt.12907

[J] Amer KE, Marwan I. Living donor liver transplantation in Egypt. Hepatobiliary Surg Nutr. 2016; 5(2):98-106. doi: 10.3978/j.issn.2304-3881.2015.10.03. Review. DOI: 10.3978/j.issn.2304-3881.2015.10.03

[K] Fisher RA. Living donor liver transplantation: eliminating the wait for death in end-stage liver disease? Nat Rev Gastroenterol Hepatol. 2017(14). DOI: 10.1038/nrgastro.2017.2