Living-donor liver transplantation from second generation children for atomic bomb survivors

Susumu Eguchi,[1] Mitsuhisa Takatsuki,[1] Masahiro Nakashima[2] and Takashi Kanematsu[1]

[1]*Departments of Surgery,* [2]*Division of Scientific Data Registry, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Japan*

Correspondence: Dr Susumu Eguchi, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E mail:sueguchi@net.nagasaki-u.ac.jp

Running title: LDLT for A-bomb survivor

Abstract

No report has been available regarding organ transplantation for atomic bomb survivors, even with renal graft. We experienced a living donor liver transplantation for two atomic bomb survivors using grafts from second-generation children. Post transplant course was uneventful without any systemic disorders under regular immunosuppression schema during 3-year follow up. The detailed results are herein reported for the first time in the literature.

INTRODUCTION

After sixty years since atomic bomb exploded in Nagasaki, those survivors became old enough to suffer from end-stage liver disease, which required liver transplantation[1,2]. However, no report has been available regarding organ transplantation for atomic bomb survivors, even with renal graft. It has been reported that atomic bomb survivor might have significant immunological alteration, especially T cell function such as interleukin-2 production[3]. We recently performed living donor liver transplantation (LDLT) for 2 atomic bomb survivors. The detailed results are herein reported for the first time in the literature.

CASE REPORT

Of 93 patients who had undergone LDLT in Nagasaki University Hospital (Nagasaki, Japan) between 1997 and October 2008, 2 patients (2.2%) were atomic bomb survivor. A survivor was defined in the present study as a person who received the 'Atomic Bomb Survivor's Health Handbook' produced by Nagasaki city authorities since the establishment of the Atomic Bomb Survivors' Medical Treatment Law in April 1957. All

information, including exposure distance, had been recorded before the present study.

The initial indication for LT was hepatocellular carcinoma in decompensated cirrhotic liver due to hepatitis B with model for end-stage liver disease (MELD) score of 19 in one patient, while it was due to hepatitis C in other patient with MELD score of 12 with intractable pleural effusion. The detailed information was described in Table 1. Since they were A-bombed in their childhood, both patients did not remember the wartime. Therefore, their psychiatric status before LDLT was stable. Usual thorough systemic survey was performed for both recipients, which included no specific additional screening. LDLT was performed with a right lobe graft without the middle hepatic vein for first patient in June, 2005 and with extended left lobe graft with middle hepatic vein for second patient in September, 2005. The living donors were a second generation son and a daughter of the recipients. HLA mismatches were 3 and 2, respectively. The first patient had been treated with tacrolimus based immunosuppression with trough level of 8-12 mg/dl during first 3 months and 5-8 ng/ml thereafter. The second patient had been on cicrosporine with trough level

around 150 ng/ml within first 3 months and subsequent interferon treatment for hepatitis C recurrence[4]. Both patients have experienced neither acute cellular rejection nor fatal infection throughout the posttransplant course. Both patients have been well with normal liver function tests 3 years after the LDLT. Both recipients have undergone close follow-up using computed tomography, magnetic resonance imaging and bone scintigram for systemic survey.

DISCUSSION

We feel it is responsible for medical doctors in Nagasaki to report the result of our intervention for atomic bomb survivors. By now, our both 2 patients have been well after liver transplantation with the allografts from living donor, who are second generation children. Since atomic bomb survivors have higher risk of multiple primary cancer development[5], longer follow-up might be needed to ensure subsequent development of new cancer, on the top of susceptibility to cancer development in patients under immunosuppression. No immunological derangement or fetal infectious complications occurred after LDLT under

regular regimen of immunosuppression probably because our patients did not have T cell dysfunction as shown in Table 1. Since LDLT were performed in our case using allograft from second-generation children, we also need to make careful observation in the graft liver, which might also have a risk with genetic instability[6]. Therefore, careful surveillance for simultaneous cancer and follow-up after LDLT are needed for those patients.

The exposure distance was used as a substitute for the estimated irradiated dose. Several unique epidemiological studies on Nagasaki survivors have already been documented with exposure distances[5]. In general, survivors who were less than 1.5 km from the hypocenter were exposed to a significant dose of radiation. The estimated doses in Nagasaki survivors who were not shielded at the time of explosion are: 924.7 cGy at 1.0 km, 120.7 cGy at 1.5 km, 17.9 cGy at 2.0 km, and 2.9 cGy at 2.5 km from the hypocenter[5]. In our patients, the distance from the hypocenter was 2.5 and 3.3 km. Since the distance was not too close, the influence between those patients and eradiation might not be strong. Latent period to develop hepatocellular carcinoma in case 1 patient was not unusual as compared to regular population of its development.

Usually, OLT might not be indicated for a patient with impaired T cell function. For example, patients with T cell dysfunction with human immunodeficiency virus sometimes can not be indicated for OLT to avoid opportunistic infection[7]. Therefore, if function of T cell is impaired in atomic bomb survivors, LDLT should not be done for the risk of infectious complication. Function of T cell could also decrease with aging, various stress and drugs etc. It needs further evidence for optimal immunosuppressive therapy for atomic bomb survivors.

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Table 1. Patient demographics and peripheral blood lymphocyte activation of the patients

	Case 1	Case 2
Age	59	64
Gender	M	F
Age at A-bomb	0	4
Distance from A-bomb	3.3km	2.5km
Indication for LDLT	HCC/LC-B	LC-C
Living donor (Age)	son (32)	daughter (34)
CD4(%)/CD8(%)	35.0 / 43.4 (ratio 0.8)	28.0 / 32.9 (ratio 0.9)
T cell function tests		
Con-A stimulation	57,430	64,535
SI (Con-A)	354.6	136.7
Control	162	472
PHA stimulation	140,234	100,830
SI (PHA)	865.6	162
Control	162	472

A-bomb: atomic bomb, LDLT: living donor liver transplantation, HCC: hepatocellular carcinoma, LC-B: liver cirrhosis due to hepatitis B, LC-C: liver cirrhosis due to hepatitis CA-bomb: atomic bomb, LDLT: living donor liver transplantation, Con-A: concanavalin-A, PHA: phytohemagglutinin,
SI: stimulation index, Normal range of SI 74.7-1793.2