Low incidence of malignancy in heart-transplant recipients in Taiwan: an update and comparison with kidney-transplant recipients

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Abstract

Objective: Malignancy is the leading cause of death among heart transplant recipients. There is a higher incidence of post-transplant malignancy in heart-transplant recipients than in kidney-transplant recipients. This study sought to assess the incidence of malignancy in heart-transplant recipients in Taiwan. Methods: This is a retrospective chart review. Results: From 1987 to 2008, 291 patients who underwent heart transplantation and survived for more than 1 month were enrolled. Seventeen patients (5.8%) developed de novo malignancies including skin cancers (three), post-transplant lymphoproliferative diseases (seven) and solid-organ malignancies (seven). Solid-organ malignancies affected prostate, liver, urinary bladder, kidney, lung, larynx, pancreas and brain in seven patients. Malignancy was responsible for 7% and 13% of all death for heart-transplant recipients who lived for more than 1 year and more than 5 years. The cumulative incidence of 1.03% at 1 year, 4.2% at 5 years and 8.1% at 10 years in our patients was much lower than the incidences reported in the multicentre registry of the International Society for the Heart and Lung Transplantation and in the Western series. The incidence was especially low for skin cancers. Compared with previous reports of kidney-transplant recipients in Taiwan, the incidence of post-transplant malignancy was not significantly increased. Conclusions: The incidence of post-transplant malignancy was low in Chinese heart-transplant recipients compared with heart-transplant recipients in Western countries. It resulted from a relative rarity of skin cancers in the Chinese population.

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Keywords: Malignancy; Heart transplantation; Kidney transplantation; Chinese population

1. Introduction

Long-term survival of heart transplantation is severely limited by cardiac allograft vasculopathy and the complications produced by the toxicities of maintenance immunosuppression (e.g. malignancy, infection and chronic renal failure) [1]. Cardiac allograft vasculopathy, chronic renal failure and malignancy, as expected, increase over time. The Cardiac Transplant Research Database data have shown, and International Society for Heart and Lung Transplantation Registry data suggest, that malignancy is the leading cause of death among long-term heart-transplant survivors [2].

The incidence of post-transplant malignancy depends on the type of organ transplantation and the length of time after transplantation [3–5]. Previous reports have demonstrated a higher incidence of post-transplant malignancy in heart-transplant than in kidney-transplant recipients. This considerable discrepancy in malignancy frequency is probably due to the more intense immunosuppression used to prevent and treat allograft rejection in the heart than in the kidney [3–5].

In Asia, the first clinical heart transplantation was performed by Wada in 1968. Because of poor result, no active heart-transplant programme was done for almost 2 decades. In July 1987, the first heart transplantation was started in Taiwan. Although Taiwan is a small island with a population of 23 million, most of the heart transplantation performed on the Chinese population is done in Taiwan [6]. We have reported a low incidence of malignancy in Chinese heart-transplant recipients [7]. However, this report is limited by small case number and limited time of follow-up. The case distribution of solid-organ malignancies is also not clear. This study is an update of 135 patients to our previously reported 156 patients [7]. Data are compared to the previous reports of heart-transplant recipients in Western countries and Chinese kidney-transplant recipients in Taiwan.

2. Patients and methods

2.1. Patients

From July 1987 to July 2008, 316 heart transplants were performed in our hospital. There were 262 males and 54 females with the mean age at transplantation of 44.8 ± 16.3
years (range, 6 months to 71 years). Heart transplantation was indicated by the following heart diseases: dilated cardiomyopathy in 172 patients (54%), ischaemic cardiomyopathy in 91 patients (29%) and other cardiac diseases in 53 patients (17%). Twenty-five patients who died within 1 month of transplantation were excluded from this study. Thus, a total of 291 patients were enrolled in this study.

2.2. Immunosuppression

All patients received triple-drug immunosuppressive therapy according to our heart-transplantation protocol [7–9]. Since 1995, we began using rabbit antithymocyte globulins for induction therapy. Azathioprine (4 mg kg\(^{-1}\)) was given 1 h before the operation. Solumedrol (1000 mg) was infused during the release of the aortic cross-clamp. Rabbit antithymocyte globulin 1.5–2.5 mg kg\(^{-1}\) day\(^{-1}\) was given after transplantation for 5 days. Cyclosporine was started orally within 5 days of transplantation or after the recovery of renal function. Cyclosporine dose was adjusted according to renal function and serum cyclosporine level, which was maintained at the trough level of 300–500 ng ml\(^{-1}\) during the first 3 months after transplantation and 200–300 ng ml\(^{-1}\) year after transplantation. Azathioprine was given at 1–2 mg kg\(^{-1}\) day\(^{-1}\) after transplantation, with the dose adjusted to maintain a white blood cell count of 4000–6000 mm\(^3\) [3]. Prednisone (0.5 mg kg\(^{-1}\) day\(^{-1}\)) was started on the second postoperative day and tapered to 0.2 mg kg\(^{-1}\) day\(^{-1}\) by the first month after transplantation. Tacrolimus (FK-506) and mycophenolate mofetil (Cellcept) were used for recurrent rejection or severe adverse reactions to cyclosporine and azathioprine.

All patients were followed up monthly at a special cardiac transplantation clinic. Standard chest roentgenogram, blood tests, electrocardiogram and physical examinations were routinely performed at regular intervals.

We evaluated the post-transplant course of the 291 heart-transplant patients to determine the incidence and specific type of post-transplant malignancies. The mean follow-up duration was 62.2 ± 49.0 months (range, 1–200 months; median, 46.6 months). None of them was lost to follow-up.

2.3. Statistical analysis

The results are expressed as means ± standard deviation or as frequencies for the categorical variables. The survival curve and cumulative incidence of post-transplant neoplastic diseases was plotted by the Kaplan–Meier method.

3. Results

3.1. Causes of death

Of the 316 heart-transplant patients, 141 patients died after heart transplantation. The causes of death were categorised by time post-transplant. Within the first 30 days post-transplant, infection accounted for 60% of the deaths in 25 patients, followed by surgical bleeding (20%) and acute rejection (12%). From 31 days to 1 year after transplant, infection accounted for 40% of the deaths in 35 patients, followed by acute rejection (26%), sudden death (14%) and non-specific acute graft failure (9%). From 1 year to 5 years after transplant, sudden death accounted for 24% of the deaths in 51 patients, followed by infection (22%), cardiac allograft vasculopathy (22%), non-specific acute graft failure (16%), acute rejection (8%) and malignancy (4%). After 5 years, cardiac allograft vasculopathy accounted for 30% of the deaths in 30 patients, followed by sudden death (27%), infection (13%), malignancy (13%) and non-specific acute graft failure (7%). In general, malignancy was responsible for 7% of all death for heart-transplant recipients who lived for more than 1 year and for 13% of all death for recipients who lived for more than 5 years.

3.2. Incidence of de novo malignancy

For 291 heart-transplant patients, the 1-year, 3-year, 5-year, 10-year and 15-year patient and graft survival rates were 87.6 ± 1.9%, 75.4 ± 2.6%, 65.8 ± 3.1%, 45.7 ± 3.8% and 35.9 ± 7.4%. Among the 291 heart-transplant patients, 19 patients suffered from 20 malignant neoplasms. Two patients with the history of malignancies had recurrent diseases. There were 18 de novo malignancies in 17 patients (5.8%). There were skin cancers in three (1%), post-transplant lymphoproliferative diseases in seven (2.4%) and solid tumours in seven patients (2.4%). There was no Kaposi’s sarcoma. The cumulative incidence of de novo malignancy was 1.03 ± 0.59% at 1 year, 2.6 ± 1.0% at 3 years, 4.2 ± 1.3% at 5 years and 8.1 ± 2.2% at 10 years after heart transplantation.

3.3. Comparison with Western series

The comparison of patient characteristics and incidence of post-transplant malignancy is listed in Table 1. The crude incidence of all-cause malignancy in the Western series ranged from 6.7% to 48.1% [10–19]. Only those series published after 1992 have been listed for comparison.

The incidences of all-cause malignancy and solid-organ malignancy were compared between this study and Crespo-Leiro’s series of Spain [18] because both groups had similar age at transplantation, mean follow-up duration and complete data of cumulative incidence by years. In this study, there was a lower incidence of all-cause malignancy (5.8% vs 14.4%). The incidence was especially low for skin/lip cancers (1.0% vs 7.3%) and solid-organ malignancies (2.4% vs 5.7%). In addition, there was a lower 5-year (4.2% vs 11.35%) and 10-year (8.1% vs 30.4%) cumulative incidence of all-cause malignancy, in spite of no difference in 1-year incidence (1.03% vs 1.87%).

The cumulative incidence of 1.03% at 1 year, 4.2% at 5 years and 8.1% at 10 years in this study was also lower than the incidence of 2.9% at 1 year, 15.1% at 5 years and 31.9% at 10 years in the multicentre registry of the International Society for the Heart and Lung Transplantation (data obtained from http://www.ishlt.org). The low cumulative incidence in our patients was significant at 5 years and 10 years.

The case distribution of solid-organ malignancies after heart transplantation is listed in Table 2. In this study, solid-organ malignancies affected the prostate, liver, urinary bladder, kidney, lung, larynx, pancreas and brain in seven
patients. One patient had double cancers affecting liver and urinary bladder. Lung cancer was the main cause of solid-organ malignancies after heart transplantation in the Western series [10—19]. However, only one of our patients had lung cancer after transplantation. Urological malignancy was the most common solid-organ malignancy in our patients.

3.4. Comparison with kidney-transplant recipients in Taiwan

The comparison of patient characteristics and incidence of post-transplant malignancy is listed in Table 3. Only those series published after 1992 was listed for comparison [20—24]. The crude incidence of all-cause malignancy in Chinese kidney-transplant recipients in Taiwan ranged from 4.5% to 8.8%. There was no difference in the incidence of all-cause malignancy and solid-organ cancers between Chinese heart-transplant and kidney-transplant recipients. The incidence of skin cancers and lymphomas was only slightly increased in heart-transplant patients. There was a particularly high incidence of urological cancers and liver cancers in the Chinese kidney-transplant recipients than in the heart-transplant recipients (75—91% vs 50%).

4. Discussion

4.1. Incidence of post-transplant malignancy

The incidence of de novo malignancy after organ transplantation ranges from 2.3% to 31%. The differences in incidence between these series are basically explained by the different length of follow-up durations. The multicentre registry of the International Society for the Heart and Lung Transplantation reported in 2008 that the cumulative incidence of malignancy was 2.9%, 15.1% and 31.9% at 1 year, 5 years and 10 years after heart transplantation (data obtained from http://www.ishlt.org). Malignancy is responsible for nearly 33% of all death for heart-transplant recipients who live for more than 5 years [2]. In this current series of 291 Chinese heart-transplant recipients who lived for more than 1 month after transplant, there was a significantly low incidence of de novo malignancy. Although the frequency of malignancy increased over time, malignancy was responsible for only 13% of the death for recipients who lived for more than 5 years. Both findings indicated that the incidence of post-transplant malignancy was low in Chinese heart-transplant recipients.
Skin cancers are the most frequent malignancies, accounting for 40–50% of all malignancies after transplantation [3–5]. Their high frequency is determined by the interaction of multiple factors including genetic or racial factors, the effect of immunosuppression, the infection by papilloma virus and the exposure to ultraviolet radiation. The incidence of Kaposi’s sarcoma after heart transplantation varied from 0.63% to 11%. Among the solid-organ malignancies after heart transplantation, lung cancer was particularly common, accounting for up to 50% of cases [10–19]. In this study, most patients had induction therapy with antithymocyte globulins and triple maintenance immunosuppression. There was no difference in age, sex, aetiology of heart disease and follow-up duration between our patients and most of the Western series (Table 1). The low incidence of post-transplant malignancy in this study results from a relative rarity of skin cancers and Kaposi’s sarcoma in the Chinese population. The ethnic factor, skin type and possible virus factor contributed to the low incidence of skin cancers in Chinese heart-transplant recipients. The distribution of solid-organ malignancies after heart transplantation was also different between this study and the Western series. It probably resulted from the different frequencies of cancers in the general population between Taiwan and the general populations of the Western countries [7]. The five most-common cancers in Taiwan are lung cancers, liver cancers, colorectal cancers, breast cancers and gastric cancers (data obtained from http://www.doh.gov.tw).

### 4.2. Heart versus kidney transplantation

Striking differences in the incidence of post-transplant malignancy are observed in heart-transplant recipients when compared with kidney-transplant patients. The most significant increase was in the incidence of lymphomas in heart-transplant versus kidney-transplant recipients. Moreover, a twofold greater increase of all malignancies was found in heart recipients, with nearly a sixfold increase in solid-organ malignancies [3–5].

Previous studies have reported a high incidence of hepatocellular carcinoma and urological malignancy in Chinese kidney-transplant recipients [20–24]. Compared with the reports from Western countries [4,5], the distribution pattern of cancer after kidney transplantation was different in Taiwan, with very low incidence of skin cancers [20–24]. In this study, there was no increase in the incidence of all-cause malignancy and solid-organ malignancy, and the incidence of skin cancers and lymphoma was slightly increased. Hepatocellular carcinoma and urological malignancy are responsible for 75–91% of solid-organ malignancies in Chinese kidney-transplant recipients of Taiwan (Table 3). In this study, solid-organ malignancy affected prostate, kidney, urinary bladder or liver in only four of eight solid-organ malignancies (50%). Patients with chronic kidney disease or end-stage renal disease are suggested to be at greater risk of cancers, especially those of the genito-urinary tract and kidney [25]. Contrary to Western countries, where renal cell carcinoma is the most common urinary-tract malignancy in patients with end-stage renal disease, transitional cell carcinoma is the most common malignancy in dialysis patients of Taiwan. The reason for such a high incidence is still unknown. It is considered to be related to the use of Chinese herbal drugs or compound analgesics [25]. Hepatocellular carcinoma is another one of the most common malignancies in Taiwan, an endemic area of hepatitis B virus infection. Kidney-transplant recipients with hepatitis B virus infection showed a high incidence of hepatocellular carcinoma [20–24].

In this study, compared with the previous reports in Chinese kidney-transplant recipients of Taiwan, the incidence of malignancy in heart-transplant recipients was not significantly increased. It probably resulted from a particularly high incidence of liver cancers and urological cancers after kidney transplantation in Taiwan.

### 4.3. Study limitations

The major limitation of this study was relatively small case number and short follow-up time. The incidence might be decreased in a small cohort and short follow-up time and increased in a large study and long follow-up duration.

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**Table 3**

Comparison of studies reporting malignancy in Chinese heart and renal transplant recipients.

<table>
<thead>
<tr>
<th>Lead author</th>
<th>Hsu</th>
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<th>Wu</th>
<th>Feng</th>
<th>Hung</th>
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<td>Year</td>
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<td>Kidney</td>
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<td>560</td>
<td>730</td>
<td>283</td>
<td>108</td>
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<td>84%</td>
<td>72%</td>
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<td>51%</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>62.2 ± 49.0</td>
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<td>97.6 ± 64.6</td>
<td>72.2 ± 54.4</td>
<td>79.6 ± 45.1</td>
<td>89.6 ± 35.1</td>
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</table>

**PtLD**: post-transplant lymphoproliferative disease; and NA: not available.
However, this study is the largest case series reporting post-transplant malignancy in Chinese heart-transplant recipients.

4.4. Conclusions

The incidence of post-transplant malignancy was low in Chinese heart-transplant recipients compared with heart recipients in Western countries. It resulted from a relative rarity of skin cancers in the Chinese population.

References


