Malignancy After Heart Transplantation

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Background: The purpose of this study was to assess the incidence and type of malignancies after heart transplantation at a medical institute in Taiwan.

Methods: From January 1987 to December 2008, a total of 66 patients who survived more than 30 days after transplantation were enrolled in this study.

Results: Of the 66 heart transplant recipients, 8 (12.1%) post-transplant malignancies were diagnosed: 5 post-transplant lymphoproliferative diseases (PTLD), 1 prostate cancer, 1 lung cancer, and 1 squamous cell carcinoma of the cheek. The clinical presentations were diverse, and the diagnoses were confirmed by biopsy. Only 1 patient died of PTLD and subsequent multiple organ failure.

Conclusion: Cancer is a limiting factor for long-term survival after heart transplantation. The most common type in this study was PTLD. Early detection and aggressive treatment results in good response and preserves the allograft. [*J Chin Med Assoc* 2009;72(11):588–593]

Key Words: heart transplantation, malignancy, post-transplant lymphoproliferative disorder

Introduction

Heart transplantation remains a gold standard of treatment for patients with end-stage heart disease. With the evolution of potent immunosuppressive agents and post-transplant management, the survival rate of the patient and graft survival has improved significantly. Thus, long-term complications have become an issue of concern. One of the complications is post-transplant malignancy. According to the registry of the Internal Society for Heart and Lung Transplantation (ISHLT) in 2008,[1] the cumulative prevalence of malignancy in heart transplantation recipients at 1 year is 2.9%, and at 10 years is 31.9%. The most commonly reported tumors are skin cancer and post-transplant lymphoproliferative disorder. The aim of this study was to investigate the incidence and types of malignancies in heart transplant recipients at our institute.

Methods

Patient population

From January 1987 to December 2008, a total of 78 patients received heart transplantation at our institute. Patients who died within 1 month after transplantation were excluded from this study. A total of 66 patients were enrolled. Eight patients who developed malignancies were identified. Their medical records were reviewed and patient data, including cancer type, treatment modality, and survival, were collected.

Immunosuppression

All patients were treated with standard calcineurin inhibitor-based triple immunosuppressive agent therapy. In the early days, we used azathioprine for induction therapy. After 1999, rabbit antithymocyte globulins (RATG) replaced it. RATG 0.75–2.0 mg/kg was given 1 hour before the operation, and the

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infusion was pretreated with the administration of 5 mg chlorpheniramine and 100 mg hydrocortisone. Then, 500 mg methylprednisolone was infused during release of aortic cross-clamp, followed by methylprednisolone 125 mg, 62.5 mg, and 31.25 mg every 8 hours for the 1st, 2nd and 3rd postoperative days, respectively. After transplantation, RATG at a dose of 1.5–4.0 mg/kg/day was administered for 3 days. Oral prednisolone (0.5 mg/kg/day tapered to 0.1 mg/kg/day), cyclosporine and azathioprine were given after the patient resumed enteral feeding. After 1999, mycophenolate mofetil gradually replaced azathioprine, and tacrolimus replaced cyclosporine as first-line immunosuppressive agents for our heart transplant recipients. Tacrolimus dose was adjusted according to the serum trough level. In most patients, it was maintained between 5 and 15 ng/mL.

Results

Eight patients (2 pediatric, 6 adult) developed malignancies after heart transplantation, with a prevalence of 12.1%, at our institute. Patient characteristics at the time of diagnosis of malignancy, clinical findings and treatment modalities are listed in Table 1. The median age at diagnosis was 57.5 years (range, 6–68 years). Among the 6 adult patients, the median age at diagnosis was 63 years (range, 37–68 years). The median time from transplantation to the diagnosis of malignancy was 12 months (range, 7–106 months).

Five patients were diagnosed to have post-transplant lymphoproliferative diseases (PTLD). One patient developed PTLD at 106 months after transplantation, and another patient after 13 months. Others were diagnosed with early PTLD (< 1 year). The clinical symptoms varied, and included anemia and tarry stool passage, neck lymphadenopathy, bloody stool passage, and shortness of breath. Diagnosis was made via imaging studies and subsequent tissue biopsy. Monomorphic diffuse large B-cell lymphoma was the most common subtype. All these patients received immunosuppression reduction as their first-line treatment. Three of them achieved complete remission, 1 had partial remission, and another died of multiple organ failure 3 weeks after the diagnosis of PTLD.

A 58-year-old male patient experienced frequency and nocturia 5–6 times 11 months after transplantation. Digital rectal examination revealed induration of both lobes of the prostate, and there was elevated prostate-specific antigen level. Transrectal ultrasound biopsy showed adenocarcinoma of the prostate, Gleason 4+3. Whole body bone scan showed no metastasis. Radical retropubic prostatectomy was performed smoothly, after which the patient was in stable condition with normal prostate-specific antigen level.

Another 68-year-old male was accidentally found to have an ill-defined nodule in the left upper lobe of his lungs on chest X-ray 3 years after transplantation. Chest computed tomography (CT) revealed a 0.8-cm soft tissue nodule over the left upper lobe without calcification. Another pleura-based soft tissue density at the left lower lobe was also found. A chest surgeon performed wedge resection of the left upper lobe nodule and resection of the involved left 4th and 5th ribs. The pathological report was squamous cell carcinoma (SCC), pT3N0M0, stage IIb. The patient recovered uneventfully, and follow-up chest CT performed 6 months later showed no evidence of recurrence.

The third patient, a 67-year-old male, was accidentally found to have 2 soft tissue masses in his left cheek and sternal notch 3 years after transplantation. Incisional biopsy of the left cheek mass was performed by a plastic surgeon, and the pathological report revealed SCC. Thus, wide excision of both masses with a 0.5-cm safe margin was done. The pathological reports all showed SCC. Now, the patient is in stable condition.

Discussion

With the improvement in graft and patient survival, long-term complications such as coronary allograft vasculopathy and post-transplant malignancy have become significantly challenging. Penn and Starzl[2] first described the association between cancer and post-transplant immunosuppression in 1972. El-Hamamsy et al[3] reported a 21% incidence of malignancy in 207 heart transplant recipients with a mean follow-up of 99 ± 57 months. In the series of O'Neill et al,[4] 18% of heart transplant patients developed post-transplant malignancy at any time during the follow-up period, and 14% developed malignancy within the first 5 years post-transplant. Roithmaier et al[5] reported an 11.27% incidence of post-transplant malignancy in heart and/or lung transplant recipients, and a 7.1-fold increase in incidence compared with the non-transplant population. An overall incidence of 14.4% among Spanish heart transplant patients with a median follow-up time of 5.2 years was reported by Crespo-Leiro et al.[6]

The incidence of all-cause post-transplant neoplasm in our series (12.1%) is similar to the above data. It is also similar to the 15.1% incidence among 5-year survivors in the 2008 ISHLT Registry report.[1] Hsu et al[7] reported a lower incidence of post-transplant

Table 1. Patient characteristics

Patient	Age (yr)/Sex	Organ transplanted (reason)	Induction therapy	Immuno-suppressive agents	Median tacrolimus level* (ng/mL)	Median WBC count*	Median CD4 count*	Malignancy type
1	56/M	Heart/kidney (DCM/ESRD)	Azathioprine + methylprednisolone	Tacrolimus + MMF	12.6	4,800	183	PTLD
2	68/M	Heart (ICM)	Azathioprine + methylprednisolone	Tacrolimus + MMF + prednisolone	7.3	5,714	146	PTLD
3	59/M	Heart (ICM)	RATG + methylprednisolone	Tacrolimus + mycophenolic acid	5.2	3,863	387	Prostate cancer
4	6/M	Heart (DCM)	RATG + methylprednisolone	Tacrolimus + mycophenolic acid + prednisolone	10.3	4,471	376	PTLD
5	6/M	Heart (severe MR + DCM)	RATG + methylprednisolone	Tacrolimus + mycophenolic acid + prednisolone	7.3	8,187	759	PTLD
6	68/M	Heart (ICM)	RATG + methylprednisolone	Tacrolimus + MMF	6.7	3,700	194	Lung cancer
7	37/M	Heart (ECM + AMI)	Azathioprine + methylprednisolone	Tacrolimus + MMF	3.4	5,533	660	PTLD
8	67/M	Heart (DCM)	RATG + methylprednisolone	Tacrolimus + MMF + prednisolone	6.6	7,630	278	Skin

**6-month period before the diagnosis of malignancy; †EBV serum marker (immunofluorescent antibody to viral capsid antigen [VCA]); ‡at the time of diagnosis of malignancy; cardiomyopathy; AMI = acute myocardial infarction; RATG = rabbit antithymocyte globulin; MMF = mycophenolate mofetil; PTLD = post-transplant lymphoproliferative disease; Barr virus; HTx = heart transplantation; CR = complete remission; MOF = multiple organ failure; PR = partial remission.*

neoplastic disease in Chinese heart transplant recipients. The cumulative incidence of malignancy was 2.1% at 1 year, 3.6% at 5 years, and 10.1% at 10 years after transplantation. No skin cancer or Kaposi's sarcoma was reported in that series.

Skin cancer is the most common malignancy in heart transplant recipients, comprising about 42–50% in recent studies in the Western world.[3,4,7] SCC is the most common form, occurring 65–250 times as frequently as in the general population, and basal cell carcinoma occurs 10 times as frequently.[8] The pathogenesis of skin carcinoma is multifactorial. Ultraviolet radiation appears to be the most important cause, since the highest incidence of skin cancer is in countries with the highest sun exposure.[9] Hsu et al attributed the low incidence of post-transplant malignancy in Chinese heart transplantation recipients to a relative paucity of Kaposi's sarcoma and skin cancer.[7] In our series, the finding was proven again. Only 1 SCC over the left cheek and anterior chest was diagnosed among the 8 patients with post-transplant malignancies.

PTLD is a well-known complication of transplantation due to the use of potent immunosuppressive agents. Epstein-Barr virus (EBV) is strongly associated with PTLD. EBV is a herpes virus that infects more than 90% of the adult population, and causes self-limiting illness in childhood. It is believed that the transformation of EBV-infected B lymphocytes due to suppression of cytotoxic T cell functions allows uncontrolled proliferation and eventual malignant change.[10] However, PTLD is diagnosed in the absence of EBV in about 10% of cases, which have increased 10-fold since 1991.[11] According to the World Heath Organization classification, PTLD is divided into 3 categories: early lesions, polymorphic PTLD, and monomorphic PTLD. Pre-transplant EBV seronegativity and subsequent conversion after transplantation is a significant risk factor for the development of PTLD.

Diagnosis after transplant (mo)	Location	Histology	EBV serum marker† pre-HTx		EBV serum marker post-HTx†		Initial treatment	Response	Current condition§
			IgG	IgM	IgG	IgM			
13	Mass at allograft kidney	Plasma cell & lymphocyte	1:160	<1:10	NA	NA	Immunosuppression reduction	CR	Died due to acute rejection 5.5 yr after HTx
7	Gastric lymphoma & pericardial mass	M-DLBCL	1:640	<1:10	1:160	<1:10	Immunosuppression reduction	Died due to MOF	Died due to PTLD-related MOF 8 mo after HTx
11	Right lobe of prostate	Adeno-carcinoma	1:40	<1:10	NA	NA	Radical retropubic prostatectomy	Stable	Stable 2.5 yr after HTx
8	LAP at neck, occipital area, mediastinum, retropharyngeal space, spleen	M-DLBCL	<1:40	<1:10	1:160	<1:10	Immunosuppression reduction	PR	Stable 1 yr after HTx
11	Colonic lymphoma	M-DLBCL	<1:10	<1:10	1:640	<1:10	Immunosuppression reduction	CR	Stable 1.5 yr after HTx
35	LUL, ribs	SCC	1:160	<1:10	NA	NA	LUL wedge resection + rib resection	Stable	Stable 3.5 yr after HTx
106	LAP at axillary region, mediastinum, mes-entery,retroperitoneum	NA	NA	1:10	1:320	<1:10	Immunosuppression reduction	CR	Stable 10 yr after HTx
38	Mass lesion at left cheek & sternal notch	SCC	1:40	<1:10	NA	NA	Wide excision	Stable	Stable 4.3 yr after HTx

§till December 2008. DCM = dilated cardiomyopathy; ESRD = end-stage renal disease; ICM = ischemic cardiomyopathy; MR = mitral regurgitation; ECM = eosinophilic LAP = lymphadenopathy; LUL = left upper lobe; M-DLBCL = monomorphic diffuse large B-cell lymphoma; SCC = squamous cell carcinoma; NA = not available; EBV = Epstein-

So, young age, especially < 5 years, is a risk factor for the development of PTLD.[12] Our 2 pediatric heart transplant recipients developed PTLD within 1 year postoperatively. One of them had extremely high EBV viral load (9.3×10^5 copies/μg DNA). We assumed that his PTLD was induced by high EBV viral load.

Most PTLD in cardiac recipients occurred in the 1st year after transplantation,[13] as seen in our patients. The incidence of developing PTLD following a solid organ transplantation is the highest in intestinal (31%), lung (3.8–11.7%) and liver (6.8–13.1%) transplants, with the lowest risk in kidney transplant recipients (1.2–9.0%).[13] The incidence of PTLD in heart transplantation patients is about 1.5–11.4%, which is higher than many other types of allograft.[14] However, as can be seen in the report of Hsu et al[7] and our study, PTLD comprised 62.5% and 66.7%, respectively, of post-transplant malignancies in the Chinese population. Hoshida et al[15] reported that the most common cancer after kidney transplantation in Japan was renal cancer (32.6%), followed by gastric cancer (13.0%), malignant lymphoma (10.9%), and uterine cancer (8.7%). The distribution of post-transplant malignancies is different in Western and other Asian countries.

In our series, only 3 different types of solid organ malignancies were diagnosed after heart transplantation. Due to the small sample size, it is difficult to assess if they were related to immunosuppressive therapy. However, considering their age, immunosuppressive dosage and CD4 count, we believe that these 3 solid organ malignancies were just incidental occurrences.

Of the 6 adult patients, 1 developed PTLD 106 months after transplantation. Recent studies have demonstrated that late-onset PTLD is frequently monoclonal neoplasms, usually falling into subtypes of non-Hodgkin's lymphoma, lacks EBV genome

sequences, responds poorly to reduction or discontinuation of immunosuppression, and is generally believed to have poorer outcome compared to early-onset PTLD.[13,16,17] However, 8 months after immunosuppression reduction, the patient in this study achieved complete remission of his PTLD. Further investigation is warranted for the treatment modalities of Chinese PTLD patients.

Among our heart transplant recipients, 30 patients received cyclosporine (45.5%) as their immunosuppressive agent, and none of them developed post-transplant malignancy. Thirty-six (54.5%) patients were maintained on tacrolimus and 8 (22.2%) of them developed post-transplant malignancy ($p=0.006$). The more intense the immunosuppression used to prevent and treat rejection, the higher the incidence of adverse effects and the risk of post-transplant malignancy in heart transplant recipients.[18]

Cyclosporine was associated with higher incidence of lymphoma and Kaposi's sarcoma, but there has been no convincing evidence that cyclosporine increased the risk of tumors as compared with other immunosuppressive regimens, in particular conventional azathioprine-based regimens.[19,20] Several studies have even suggested that cyclosporine might produce a lower incidence of cancers.[21,22] A recent *in vitro* and *in vivo* study indicated that cyclosporine might promote tumor growth by a nonimmune mechanism that would act on the tumor itself by production of transforming growth factor-β.[23] The clinical relevance of these rather provocative data awaits further careful clinical confirmation.

Tacrolimus has similar immunosuppressive properties and is more potent than cyclosporine. Penn in 2000 also reported a similar incidence and pathological features of tacrolimus-induced post-transplant cancers to those observed with other immunosuppressive agents, in particular cyclosporine.[24] A comparative study failed to identify significant differences between tacrolimus-based and cyclosporine-based regimens.[25]

Whether or not a specific immunosuppressive drug or regimen is more strongly associated with the risk of cancer remains controversial, because of the frequently used combination regimens. In our series, although the use of tacrolimus carried a significantly higher risk of post-transplant malignancy, the number of cases was still very small. However, we may try to shift tacrolimus to cyclosporine instead of immunosuppression reduction in the PTLD group to see if disease remission can be achieved.

Since half of the 8 patients developed malignancy within 1 year of transplantation, especially those with PTLD, we recommend that chest and abdominal CT or magnetic resonance imaging be performed every 6 months in the 1st postoperative year, followed by every 1 year.

In conclusion, the long-term outcome of heart transplantation is strongly affected by the occurrence of malignancy in immunosuppressed transplant recipients. The incidence of post-transplant malignancy in the Chinese population is similar to that in Western countries, but the types of malignancies are different. PTLD is the most common malignancy and responds well to immunosuppression reduction. Since post-transplant malignancy is commonly seen after heart transplantation, routine screening for malignancy is mandatory.

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