Journal of Cardiology 73 (2019) 255–261

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

De novo malignancy in heart transplant recipients: A single center experience in Japan

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ARTICLE INFO

Article history:
Received 28 September 2018
Received in revised form 12 November 2018
Accepted 23 November 2018
Available online 23 December 2018

Keywords:
Malignancy
Heart transplantation
Risk factor
Prognosis

ABSTRACT

Background: Because of aggressive immunosuppression, heart transplant recipients have a high risk of de novo malignancy, which is a major cause of death and worse prognosis, regardless of the type. However, the impact of de novo malignancy on Japanese heart transplant recipients is unknown.
Methods: We analyzed 103 Japanese heart transplant recipients over 18-years-old at the time of transplantation between April 1999 and April 2017. Patient characteristics and prognosis were compared between heart transplant recipients with or without de novo malignancy after heart transplantation (HTx). Additionally, univariate and multivariate analyses for the risk factors of de novo malignancy after HTx were performed.
Results: De novo malignancy developed in 7 patients (6.8%; post-transplant lymphoproliferative disorders, $n = 3$; Bowen's disease, $n = 1$; colon cancer, $n = 2$; bladder cancer, $n = 1$). Follow-up time and previous antibody mediated rejection (AMR) $\geq$ grade 1 were risk factors of de novo malignancy after HTx in multivariate analysis (OR: 1.19, 95% CI: 1.00–1.42, $p = 0.043$; and OR: 10.7, 95% CI: 1.37–83.68, $p = 0.038$, respectively). History of malignancy was a potential risk factor, albeit not significant (OR: 23.05, 95% CI: 0.99–534.53, $p = 0.071$). The survival rates in patients with de novo malignancy was significantly lower than in those without de novo malignancy (3-year survival rate: 100% versus 67%, $p = 0.0025$).
Conclusions: Long follow-up time and previous AMR $\geq$ grade 1 were risk factors of de novo malignancy after HTx. Japanese heart transplant recipients with de novo malignancy have worse prognosis; therefore, screening examinations are important for early diagnosis.

Introduction

Heart transplantation (HTx) is an established and effective treatment for advanced heart failure [1]. The long-term prognosis after HTx has continuously improved as a consequence of reduced early post-transplant mortality [2]. In Japan, the survival rates at 5, 10, and 15 years after HTx are 92.7%, 89.6%, and 81.8%, better than those in Europe and the USA [3]. However, the incidence of de novo malignancy increases in the late period and is one of the major causes of death after HTx [4]. Malignancy negatively impacts the prognosis after HTx, regardless of the type of malignancy [5]. The risk of de novo malignancy in heart transplant recipients was reported to be 2–4 times higher than that in the general population [5–7]. Additionally, heart transplant recipients have a 4 times higher risk compared to renal transplant recipients due to their intensive immunosuppression therapy [5,6]. There are several

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https://doi.org/10.1016/j.jjcc.2018.11.011
0914-5087/

reports investigating de novo malignancy after HTx in Western countries [5–7]. However, in the Japanese national survey on de novo malignancy after solid organ transplantation [8], most cases were kidney and hepatic transplant recipients (49.9% and 45.9%, respectively) and the proportion of heart transplant recipients was only 0.5%. However, the incidence of de novo malignancy after HTx is expected to increase as it has been 20 years from the start of HTx in Japan. Therefore, early diagnosis and treatment of de novo malignancy after HTx are critically important, whereas the de novo malignancy in Japanese heart transplant recipients is not well known. With this in mind, we performed this study to elucidate the risk factors and prognosis of de novo malignancy after HTx in Japan.

Methods

Patient population and data collection

This retrospective study was conducted using the medical records of 91 consecutive Japanese patients who underwent HTx at the National Cerebral and Cardiovascular Center (NCVC) and 12 who underwent HTx in the USA and Germany after assessment at NCVC between April 1999 and April 2017. Patients under the age of 18 years at the time of transplantation were excluded. Patient characteristics and prognosis were compared between heart transplant recipients with or without de novo malignancy after HTx (malignancy group or no-malignancy group). The patients were followed up for more than 1 year after HTx. Patient characteristics evaluated included age, sex, etiology of heart failure, comorbidity, history of malignancy before HTx, family history of malignancy, history of smoking, viral status [cytomegalovirus (CMV) and Epstein-Barr virus (EBV)], and administration of statin. Additionally, the risk factors of de novo malignancy were identified. In the malignancy group, the type of malignancy, primary symptoms, time until malignancy was diagnosed, diagnostic examination results, immunosuppression therapy, and course of treatment were evaluated.

Immunosuppressive regimens and evaluation of rejections

For immunosuppression, a triple drug regimen including a corticosteroid, a calcineurin inhibitor (CNI; tacrolimus or cyclosporine), and an anti-proliferative immunosuppressant [mycophenolate mofetil (MMF) or azathioprine] was administered. Induction therapy was performed with muromonab-CD3 (OKT3) or anti-CD25 receptor monoclonal antibody (basiliximab) for patients with high panel reactive antibody or renal dysfunction. Due to modification of our immunosuppressive protocol, the initial CNI was changed from cyclosporine to tacrolimus since 2005 and OKT3 was used until 2010. Daclizumab was administered for induction to 1 patient in the no-malignancy group who underwent HTx in the USA. In patients with renal dysfunction or coronary allograft vasculopathy, MMF was switched to everolimus in combination with a reduced dose of CNI starting from March 2007.

Graft rejection was monitored by endomyocardial biopsy of the right ventricle at 1, 2, 3, 5, 7, and 11 weeks after HTx; every 6 weeks until the 6th month; every 3 months until the 1st year; every 6 months until the 5th year; yearly until the 10th year; and yearly or biennially thereafter. The diagnosis and grading of graft rejections were performed according to the 1990 International Society for Heart and Lung Transplantation (ISHLT) consensus statement [9]. When acute cellular rejection (ACR) $\geq$ grade 1B was present, optimization of maintenance immunosuppression, pulse steroids, or plasmapheresis were considered based on cardiac function or hemodynamics. Similarly, when antibody mediated rejection (AMR) $\geq$ grade 1 was present, optimization of maintenance immunosuppression, intravenous gamma globulin (IVIG), pulse steroids, or plasmapheresis were considered depending on the presence of graft dysfunction, complement-binding antibodies, or hemodynamic abnormalities.

Ethics

The research protocol was approved by the institutional review board of the National Cerebral and Cardiovascular Center according to the ethical guidelines of the 1975 Declaration of Helsinki and its amendments (M30-070). Since this was a retrospective study, the need for written informed consent was waived and the patients' records and data were anonymized before analysis.

Statistics

Continuous variables were expressed as means $\pm$ standard deviations or medians and interquartile range (IQR). Categorical variables were expressed as numbers and percentages. When comparing the two groups, Pearson's chi-square test or Fisher's exact test was used for categorical variables and the unpaired *t*-test or Wilcoxon rank-sum test was used for continuous variables, as appropriate. Univariate and multivariate analyses for the risk factors of de novo malignancy after HTx were performed, and the odds ratios (OR) and 95% confidence intervals (CI) were computed using the log-rank test. The variables included in multivariate analysis were selected using stepwise selection. Patient survival rates were computed by the Kaplan–Meier method and compared using the log-rank test. Time zero for the malignancy group was defined as time at malignancy diagnosis and that for the no-malignancy group was defined as the mean time of malignancy diagnosis in the former group (2971 days). A p-value <0.05 was considered statistically significant in all analyses. Statistical analyses were performed using JMP software, version 10 (SAS Corp., Cary, NC, USA).

Results

Patient characteristics

The final cohort included 103 Japanese patients, 91 who underwent HTx at NCVC and 12 who underwent HTx in other countries (USA and Germany), which were classified into a malignancy group ($n = 7$) and a no-malignancy group ($n = 96$). The clinical characteristics of the patients are summarized in Table 1. The prevalence of a history of malignancy was higher in the malignancy group (1/96, 1% versus 1/7, 14%; $p = 0.014$). There were no significant differences in other patient characteristics, including the viral status (previous infection with EBV, EBV mismatch, and CMV mismatch). Additionally, the prevalence of positive EBV-DNA one-year after HTx was not different between the groups. The follow-up time was longer in the malignancy group (6.0 years, IQR: 2.5–11.1 years; versus 10.7 years, IQR: 9.7–13.2 years; $p = 0.029$).

Immunosuppression therapy and graft rejection

There were no significant differences in initial maintenance therapy after HTx between the groups; however, the use of tacrolimus at the end point of this study was less common in the malignancy group than in the no-malignancy group (84/96, 88% versus 4/7, 57%; $p = 0.028$) (Table 2). However, the target trough concentrations of CNI were not different between the groups (Table 3). As the follow-up time after HTx was significantly longer in the malignancy group, the use of OKT3 was correspondingly more common (5/96, 6.2% versus 2/7, 29%; $p = 0.018$), while the use of basiliximab was not significantly different (Table 2).

Table 1
Clinical characteristics of patients.

	All $n = 103$	No-malignancy group $n = 96$	Malignancy group $n = 7$	p-Value
Age [mean (SD), years]	39.6 ± 12.6	39.8 ± 12.6	36.9 ± 14.2	0.56
Male sex [n (%)]	79 (77)	73 (76)	6 (86)	0.56
Etiology [n (%)]				0.63
DCM	69 (67)	63 (66)	6 (86)	
DHCM	12 (12)	12 (12)	0 (0)	
ICM	6 (6)	6 (6)	0 (0)	
Others	16 (15)	15 (16)	1 (14)	
Diabetes mellitus [n (%)]	15 (15)	13 (14)	2 (29)	0.28
Previous history of malignancy [n (%)]	2 (1.9)	1 (1)	1 (14)	0.014
Family history of malignancy [n (%)]	9 (8.7)	9 (9.4)	0 (0)	0.4
Smoking [n (%)]	44 (43)	40 (42)	4 (57)	0.42
Previous infection of EBV [n (%)]	93 (90)	87 (91)	6 (86)	0.67
EBV mismatch [n (%)]	10 (9.7)	9 (9.4)	1 (9.7)	0.67
CMV mismatch [n (%)]	18 (17)	18 (19)	0 (0)	0.21
Administration of statin [n (%)]	99 (96)	92 (96)	7 (100)	0.58
Follow-up time [median (IQR), year]	6.1 (3.1–11.4)	6.0 (2.5–11.1)	10.7 (9.7–13.2)	0.029

SD, standard deviation; DCM, dilated cardiomyopathy; DHCM, dilated phase of hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IQR, interquartile range.

In terms of graft rejection, there was no difference in the prevalence of ACR ≥ 1B, but AMR ≥ 1 was significantly more common in the malignancy group (4/96, 4.2% versus 2/7, 29%; $p = 0.008$) (Table 2). Additionally, pulse steroids were more frequently administered for graft rejection in the malignancy group, although the difference was not statistically significant (23/96, 24% versus 4/7, 57%; $p = 0.054$).

Patient characteristics and therapeutic course in the malignancy group

The overall incidence of de novo malignancy during the follow-up period (median 6.1 years, IQR: 3.1–11.4 years) was 6.8%. The individual characteristics of each patient in the malignancy group are shown in Table 4. The types of malignancy observed were post-transplant lymphoproliferative disorders (PTLD; $n = 3$), including Burkitt's lymphoma ($n = 1$) and diffuse large B cell lymphoma (DLBCL; $n = 2$); Bowen's disease ($n = 1$); and solid cancer ($n = 3$), including colon cancer ($n = 2$) and bladder cancer ($n = 1$). All patients developed malignancy at least 5 years after HTx, except for patient 3 who developed PTLD. The initial symptoms were variable even in patients with the same malignancy. Patients 5 and 7 were asymptomatic and suspected of malignancy after screening examinations (urinary cytology and fecal occult blood test, respectively). All patients with PTLD had B cell lymphoma and, therefore, received chemotherapy including rituximab. Additionally, patient 2 received everolimus as a substitute for tacrolimus and MMF. Patient 3 underwent additional radiation therapy and anti-EBV therapy with valganciclovir and IVIG. However, the DLBCL recurred and chemotherapy and autologous stem cell transplantation was performed. The patient eventually died of progression of DLBCL. On the other hand, in patients with skin and solid cancers, surgical resection was performed depending on the type and stage of the malignancy. Patient 6 had sigmoid colon cancer and

Table 2
Immunosuppression therapy and graft rejection.

	All $n = 103$	No-malignancy group $n = 96$	Malignancy group $n = 7$	p-Value
Initial maintenance therapy [n (%)]				
PSL	103 (100)	96 (100)	7 (100)	–
CYA	20 (19)	18 (19)	2 (29)	0.53
TAC	83 (81)	78 (81)	5 (71)	0.53
MMF	100 (97)	93 (97)	7 (100)	0.64
AZA	2 (1.9)	2 (1.9)	0 (0)	0.7
JAN	1 (1)	1 (1)	0 (0)	0.79
Maintenance therapy at the end point [n (%)]				
PSL	27 (26)	25 (26)	2 (29)	0.88
CYA	8 (7.8)	6 (6.3)	2 (29)	0.091
TAC	88 (85)	84 (88)	4 (57)	0.028
MMF	38 (37)	36 (38)	2 (29)	0.64
EVL	67 (65)	62 (65)	5 (71)	0.71
Induction therapy [n (%)]	41 (40)	38 (40)	3 (43)	0.86
Basiliximab	33 (32)	32 (33)	1 (14)	0.3
OKT3	7 (6.8)	5 (5.2)	2 (29)	0.018
Daclizumab	1 (1)	1 (1)	0 (0)	0.79
Heart rejection [n (%)]				
ACR ≥ 1B	14 (14)	13 (14)	1 (14)	0.95
AMR ≥ 1	6 (5.8)	4 (4.2)	2 (29)	0.008
Pulse steroids [n (%)]	27 (26)	23 (24)	4 (57)	0.054

PSL, prednisolone; CYA, cyclosporine; TAC, tacrolimus; MMF, mycophenolate mofetil; AZA, azathioprine; JAN, sirolimus; EVL, everolimus; OKT3, muromonab-CD3; ACR, acute cellular rejection; AMR, antibody mediated rejection.

Table 3
Target trough concentration of calcineurin inhibitors after heart transplantation.

	All	*n*	no-Malignancy group	*n*	Malignancy group	*n*	*p*-Value
Cyclosporine [median (IQR), ng/mL]							
3 months after HTx	300 (300–350)	15	300 (300–350)	13	325 (300–350)	2	0.95
1 year after HTx	250 (225–325)	13	250 (250–300)	11	275 (200–350)	2	0.96
3 years after HTx	200 (158–200)	8	200 (180–200)	7	150	1	0.1
5 years after HTx	200 (150–200)	7	200 (150–200)	6	200	1	0.58
Tacrolimus [median (IQR), ng/mL]							
3 months after HTx	10 (10–10)	88	10 (10–10)	83	10 (10–11)	5	0.45
1 year after HTx	8 (4–10)	89	8 (4–10)	84	10 (6.5–11)	5	0.15
3 years after HTx	6 (3–8)	70	5.5 (3–8)	64	8 (3.8–9)	6	0.45
5 years after HTx	5 (3–6.5)	53	5 (3–6)	48	5 (4–9)	5	0.21

n, number of patients; HTx, heart transplantation.

underwent laparoscopic colectomy and lymph node dissection with postoperative adjuvant chemotherapy 7.5 years after HTx. However, the colon cancer relapsed with peritoneal dissemination 1 year later and the patient died despite additional chemotherapy and reduction of immunosuppression.

The risk factors of de novo malignancy after HTx and prognosis

In univariate analyses, the factors associated with increased risk of malignancy were follow-up time and previous AMR $\geq$ 1 (OR: 1.18, 95% CI: 1.02–1.39, p = 0.03; and OR: 9.2, 95% CI: 1.10–61.39, p = 0.042, respectively). Additionally, history of malignancy, the use of OKT3 as induction therapy, and pulse steroids therapy were potential risk factors, although the differences were not significant. In multivariate analysis, follow-up time and previous AMR $\geq$ grade 1 were risk factors of de novo malignancy after HTx (OR: 1.19, 95% CI: 1.00–1.42, p = 0.043; and OR: 10.7, 95% CI: 1.37–83.68, p = 0.038, respectively). History of malignancy was a potential risk factor, albeit not significant (OR: 23.05, 95% CI: 0.99–534.53, p = 0.071) (Table 5).

During the follow-up period, 1 patient in the no-malignancy group died from sudden death and 2 died from sepsis caused by pneumonia and ileus. In the malignancy group, 2 patients died due to recurrence of colon cancer and progression of PTLD. The survival rates in the malignancy group were significantly lower than those in the no-malignancy group (3-year survival rate, 100% versus 67%; p = 0.0025) (Fig. 1).

Discussion

The main findings of this study are as follows: (1) the overall incidence of de novo malignancy after HTx was 6.8% during the follow-up period (median 6.1 years), and PTLD and colon cancer were more common than skin cancer in Japanese recipients; (2) the risk factors of de novo malignancy after HTx were long follow-up time and previous AMR $\geq$ 1; and (3) Japanese heart transplant recipients with de novo malignancy have an equally poor prognosis to those from Europe and the USA.

In the present study, the overall incidence of de novo malignancy after HTX was 6.8%, and PTLD (3/7; 43%), colon cancer (2/7; 29%), bladder cancer (1/7; 14%), and skin cancer (1/7; 14%) were observed. There were no patients with lung cancer, which had been reported to be common and associated with poor prognosis after HTx [10,11]. Additionally, the prevalence of PTLD, which was reported to be common in pediatric heart transplant recipients [12], and colon cancer were higher and that of skin cancer was lower compared to data from Western countries (PTLD, 7.7–17%; colon cancer, 2.4–8.6%; and skin cancer, 41.5–61%) [5,6,13,14]. These differences might be caused by differences in ethnicity, diet, environment, and viral status. For example, skin type II and sunlight exposure >30,000 h, which were reported to increase the risk of skin cancer (hazard ratios, 2.7 and 7.6, respectively) [15], are not common in Japan and may explain the low prevalence of skin cancer. In addition, Kaposi's sarcoma and malignancies of the vulva, anus, and lip, which were infection-related malignancies, are not common in Japan according to the national survey of de novo malignancy after solid organ transplantation [8].

Heart transplant recipients have an elevated risk of de novo malignancy because of aggressive immunosuppression. The etiology of malignancy involves impaired immunosurveillance; dysregulation of signaling pathways, DNA repair mechanisms, and apoptosis; and decreased anti-viral immune activity [16]. Age, male sex, smoking, and history of malignancy were reported as risk factors of de novo malignancy after HTx, similarly to the general population [5,6,11,13–15,17]. CNI exhibits pro-carcinogenic potential by inhibition of DNA repair mechanisms and apoptosis [16]. After diagnosis of malignancy, reduction of CNI dosage is recommended [16]. Therefore, tacrolimus was switched to everolimus after the diagnosis of malignancy and the use of tacrolimus at the end point of this study was less common in the malignancy group. Everolimus exerts a dual role through immunosuppression and anti-malignancy activity [16]. Furthermore, everolimus inhibits increase in infected cells by EBV causing PTLD [18]. In terms of induction therapy, OKT3 was shown to increase the risk of de novo malignancy compared to basiliximab [5,13,16]. Subsequently, OKT3 use has discontinued and has been replaced by basiliximab [13]. Additionally, viral infections such as CMV, EBV, human papillomavirus, and human immunodeficiency virus, were reported to increase the incidence of skin cancer or PTLD [5,8,15,19]. However, in the current study, the prevalence of CMV mismatch, EBV mismatch, and EBV-DNA one-year after HTx did not affect the development of de novo malignancy.

In the current study, long follow-up time and previous AMR $\geq$ 1 were the identified risk factors in multivariate analysis. Additionally, history of malignancy, induction therapy with OKT3, and the use of pulse steroids were also potential risk factors. These findings in Japanese heart transplant recipients were compatible with the risk factors previously reported [5,10,13,15,19]. The long follow-up time is related to advancing age and prolonged use of immunosuppression, which increases the risk of de novo malignancy after HTx. Additionally, if graft rejection is diagnosed, maintaining high blood levels of immunosuppressants or administering additional immunosuppression therapy, such as pulse steroids, are needed [15]. This intense immunosuppression results in an increase in the risk of de novo malignancy. Therefore, adequate diagnosis and treatment of graft rejection is critical.

Previous studies have demonstrated a reduced survival rate in patients with de novo malignancy, regardless of the type [5,11,13]. Similarly, the current study showed that de novo malignancy worsened prognosis in Japanese heart transplant

Table 4
Detailed data of patients in the malignancy group.

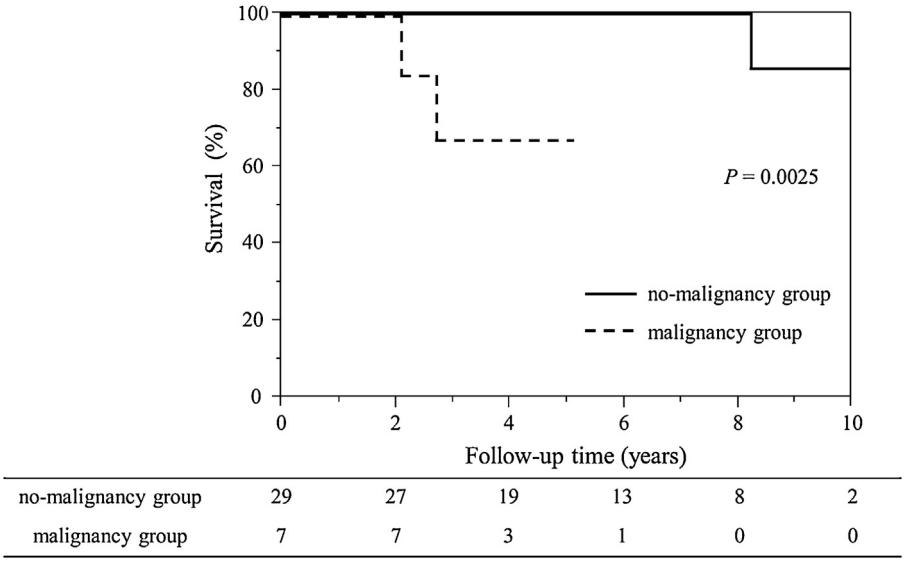
No.	Age at HTx (years)	Sex	Past history of malignancy	Induction therapy	Time[a] (years)	Maintenance therapy at diagnosis[b]	Type and stage of malignancy	Initial symptom	Examination	Treatment	Prognosis
1	60	M	–	OKT3	8.3	CYA MMF	*Burkitt's lymphoma* Ann Arbor stage IV	Back pain, femoral pain	• Ga scintigraphy revealed enhanced paravertebral tumor • EBV-DNA 3700	• Chemotherapy (R-THP-COP) • IT chemotherapy	CR
2	30	M	AML	–	8.6	TAC MMF	*DLBCL* Ann Arbor stage II	Epigastric pain, nausea	• EGD revealed gastric ulcers • FDG-PET enhanced LN • EBV-DNA 2.0	• Tac + MMF → EVL • Chemotherapy (R-CHOP)	CR
3	26	M	–	–	1.4	PSL CYA EVL	*DLBCL* Ann Arbor stage III	Fever, headache	• CT revealed epigastric tumor enhanced by Ga scintigraphy • EBV-DNA 7300000	• CYA discontinued, anti-EBV therapy • Chemoradiation (R-CHOP) • Autologous stem cell transplant	Death
4	25	M	–	–	17.7	TAC MMF	*Bowen's disease* Skin cancer	Erythema at anus	• Skin biopsy revealed in-situ squamous cancer	• Resection of anal canal • Permanent colostomy	CR
5	24	M	–	OKT3	7.3	TAC EVL	*Bladder cancer* cT1N0M0 stage I	Asymptomatic	• Urinary cytology revealed atypical cells • Cystoscope showed tumors	• Transurethral bladder tumor resection	PD
6	50	M	–	–	7.4	TAC EVL	*Sigmoid colon cancer* cT4aN1M0 stage IIIa	Hematochezia	• CA19-9 49.2 U/mL • CT revealed thickened colon • CF showed sigmoid colon tumor	• Laparoscopic colectomy, LN dissection • Postoperative adjuvant chemotherapy	Death
7	43	F	–	Basiliximab	6.7	TAC EVL	*Sigmoid colon cancer* cT3N0M0 stage II	Asymptomatic	• Positive fecal occult blood test • CT revealed thickened colon • CF showed sigmoid colon tumor	• Laparoscopic left colectomy	CR

No., patient number; M, male; F, female; AML, acute myeloid leukemia; OKT3, muromonab-CD3; CYA, cyclosporine; MMF, mycophenolate mofetil; TAC, tacrolimus; PSL, prednisolone; EVL, everolimus; DLBCL, diffuse large B cell lymphoma; Ga, gallium; EBV, Epstein-Bar virus; EGD, esophagogastroduodenoscopy; CT, computed tomography; CF, colon fiberscope; IT, intrathecal; R, rituximab; THP, pirarubicin; COP, cyclophosphamide, vincristine and prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; LN, lymph node; CR, complete response; PD, progressive disease.
TNM classification was used for solid malignancy and Ann Arbor staging was used for post-transplant lymphoproliferative disorders.
[a] Time from heart transplantation to diagnosis of malignancy.
[b] Maintenance therapy at diagnosis of malignancy.

Table 5
Risk factors of de novo malignancy after heart transplantation.

Factors	Univariate		Multivariate	
	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Age (per 1 year)	0.98 (0.92–1.04)	0.56		
Male sex	1.89 (0.30–36.66)	0.54		
Diabetes mellitus	2.55 (0.34–13.30)	0.32		
Previous history of malignancy	15.83 (0.58–435.85)	0.09	23.05 (0.99–534.53)	0.071
Family history of malignancy	n/a	0.25		
Smoking	1.87 (0.39–9.91)	0.43		
CMV mismatch	n/a	0.095		
Previous infection of EBV	0.62 (0.09–12.39)	0.69		
Follow-up time (per 1 year)	1.18 (1.02–1.39)	0.03	1.19 (1.00–1.42)	0.043
Induction therapy	1.14 (0.22–5.47)	0.86		
Basiliximab	0.33 (0.02–2.07)	0.26		
OKT3	7.28 (0.89–45.07)	0.062		
CYA as initial maintenance therapy	1.73 (0.31–9.66)	0.53		
ACR ≥ 1B	1.06 (0.05–6.96)	0.96		
AMR ≥ 1	9.2 (1.10–61.39)	0.042	10.7 (1.37–83.68)	0.038
Pulse steroids	4.23 (0.87–22.82)	0.072		

OR, odds ratio; CI, confidence interval; CMV, cytomegalovirus; EBV, Epstein-Barr virus; IQR, interquartile range; OKT3, muromonab-CD3; CYA, cyclosporine; ACR, acute cellular rejection; AMR, antibody mediated rejection; n/a, not available.



no-malignancy group	29	27	19	13	8	2
malignancy group	7	7	3	1	0	0

Fig. 1. Kaplan–Meier curve for survival in the no-malignancy and malignancy groups. Time zero for the malignancy group was defined as the time at malignancy diagnosis and that for the no-malignancy group was defined as the mean time of malignancy diagnosis in the former group (2971 days). The table shows the number of patients in the malignancy and no-malignancy groups at the time from time zero.

recipients. Therefore, early diagnosis and treatment are important to improving the prognosis after HTx and adequate screening examinations are needed. In the malignancy group, 2 patients were asymptomatic and were diagnosed by regular screening examinations. ISHLT guidelines recommend that screening protocols for breast, colon, and prostate cancer in the general population should also be followed in heart transplant recipients, and that they receive close skin cancer surveillance, including education on preventive measures and yearly dermatologic examinations [20]. However, differences in frequency of specific malignancies between countries should be considered, and appropriate screening examinations must be selected. In Japan, EBV-DNA, tumor markers, urinary cytology, and esophagogastroduodenoscopy could supplement the ISHLT recommendations considering age, sex, follow-up time, and other risk factors of de novo malignancy.

This study has several key limitations that should be discussed. Firstly, this study included patients who underwent HTx from 1999 to 2017, and the immunosuppression regimens used differed during that period. For example, OKT3 was used until 2010 and everolimus was available from 2007. These differences might affect the development of de novo malignancy or prognosis after HTx. Secondly, Japanese heart transplant recipients who underwent HTx in the USA and Germany were included. Finally, the sample size was relatively small and there were few patients with de novo malignancy. Therefore, this study might be prone to statistical errors, especially in multivariate analysis. Our institution is one of the high-volume centers for HTx in Japan. However, the number of HTx procedures is still small compared to other countries. Therefore, a registry of Japanese heart transplant recipients with de novo malignancy is needed for more precise investigation.

In conclusion, the overall incidence of de novo malignancy after HTx was 6.8% in Japan. The long follow-up time and previous AMR ≥ 1 were risk factors of de novo malignancy after HTx. Japanese heart transplant recipients with de novo malignancy have a worse prognosis. Therefore, appropriate screening examinations are important for early diagnosis and treatment of malignancy after HTx.

Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest.

Acknowledgments

All authors attributed to the conception, design, critical revision, and final approval of this manuscript. YK, KI, KK, and MY acquired data. YK and KI performed statistical analyses. YK interpreted the data and drafted the manuscript under supervision of senior authors MY and NF. The data partially have already been presented at a Japanese scientific meeting. We would like to express our gratitude to Eri Miyoshi, Nobuaki Konishi, Shiho Tsuboi, and Yumiko Hori for their contributions to patient care.

References

[1] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.
[2] Benden C, Edwards LB, Kucheryavaya AY, Christie JD, Dipchand AI, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Lung and Heart-Lung Transplantation Report – 2013; focus theme: age. J Heart Lung Transplant 2013;32:989–97.
[3] Fukushima N, Ono M, Saiki Y, Sawa Y, Nunoda S, Isobe M. Registry report on heart transplantation in Japan (June 2016). Circ J 2017;81:298–303.
[4] Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report – 2013; focus theme: age. J Heart Lung Transplant 2013;32:951–64.
[5] Youn JC, Stehlik J, Wilk AR, Cherikh W, Kim IC, Park GH, et al. Temporal trends of de novo malignancy development after heart transplantation. J Am Coll Cardiol 2018;71:40–9.
[6] Fröhlich GM, Rufibach K, Enseleit F, Wolfrum M, von Babo M, Frank M, et al. Statins and the risk of cancer after heart transplantation. Circulation 2012;126:440–7.
[7] Engels EA, Pfeiffer RM, Fraumeni Jr JF, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891–901.
[8] Miyazaki T, Sato S, Kondo T, Kusaka M, Gotoh M, Saiki Y, et al. National survey of de novo malignancy after solid organ transplantation in Japan. Surg Today 2018;48:618–24.
[9] Billingham ME, Cary NR, Hammond ME, Kemnitz J, Marboe C, McCallister HA, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Study Group. The International Society for Heart Transplantation. J Heart Transplant 1990;9:587–93.
[10] Higgins RS, Brown RN, Chang PP, Starling RC, Ewald GA, Tallaj JA, et al. A multi-institutional study of malignancies after heart transplantation and a comparison with the general United States population. J Heart Lung Transplant 2014;33:478–85.
[11] Kellerman L, Neugut A, Burke B, Mancini D. Comparison of the incidence of de novo solid malignancies after heart transplantation to that in the general population. Am J Cardiol 2009;103:562–6.
[12] Fukushima N. Posttransplant lymphoproliferative disorder after cardiac transplantation in children: life threatening complications associated with chemotherapy combined with rituximab. ISRN Transplant 2013. http://dx.doi.org/10.5402/2013/683420.
[13] Crespo-Leiro MG, Alonso-Pulpón L, Vázquez de Prada JA, Almenar L, Arizón JM, Brossa V, et al. Malignancy after heart transplantation: incidence, prognosis and risk factors. Am J Transplant 2008;8:1031–9.
[14] Van Keer J, Droogné W, Van Cleemput J, Vörös G, Rega F, Meyns B, et al. Cancer after heart transplantation: a 25-year single-center perspective. Transplant Proc 2016;48:2172–7.
[15] Caforio AL, Fortina AB, Piaserico S, Alaibac M, Tona F, Feltrin G, et al. Skin cancer in heart transplant recipients: risk factor analysis and relevance of immunosuppressive therapy. Circulation 2000;102:222–7.
[16] Nair N, Gongora E, Mehra MR. Long-term immunosuppression and malignancy in thoracic transplantation: where is the balance? J Heart Lung Transplant 2014;33:461–7.
[17] Yoosabai A, Mehta A, Kang W, Chaiwatcharayut W, Sampaio M, Huang E, et al. Pretransplant malignancy as a risk factor for posttransplant malignancy after heart transplantation. Transplantation 2015;99:345–50.
[18] Majewski M, Korecka M, Joergensen J, Fields L, Kossev P, Schuler W, et al. Immunosuppressive TOR kinase inhibitor everolimus (RAD) suppresses growth of cells derived from posttransplant lymphoproliferative disorder at allograft-protecting doses. Transplantation 2003;75:1710–7.
[19] Brewer JD, Colegio OR, Phillips PK, Roenigk RK, Jacobs MA, Van de Beek D, et al. Incidence of and risk factors for skin cancer after heart transplant. Arch Dermatol 2009;145:1391–6.
[20] Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914–56.