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Malignancy after Heart Transplantation: A Systematic Review of the Incidence and Risk Factors Compared with Other Solid Organ Transplants

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Abstract

The continuing improvements in heart transplant (HT) outcomes have increased the risk of developing complications, such as post-transplant malignancy (PTM). Our aims are to focus on the incidence and risk factors in PTM in heart transplant recipients and compare with other solid organ transplantations (SOT). In 20 publications analyzed, the incidence of PTM in individuals undergoing SOT ranges from 4.1% to 16.3%, representing a 2 to 4-fold overall increased risk of cancer over the general population. It seems that the incidence of cancer risk is probably higher in HT than SOT recipients. Cutaneous carcinomas, post-transplant lymphoproliferative disorders (PTLD), carcinomas of lung and liver represent the four most common malignancies in this specific post-transplant population. It is also evident that the risk factors in developing PTM in HT recipients include immunosuppressive therapy, viral infection, older age, tobacco smoking, and unprotected sun-exposure. Transplant physicians should probably increase the threshold of attention for cancer risk surveillance in addition to anti-rejection therapy for graft survivals.

Keywords: Heart transplantation; Solid organ transplantation; Malignancy post transplantation; Post transplantation lymphoproliferative disorders; Skin malignancy

Introduction

Solid organ transplantation (SOT) is a mostly unavoidable and extremely viable treatment modality for patients with end-stage organ disease, and outcomes of SOT have improved dramatically over the past few decades [1]. Since the first successful human heart transplant (HT) performed in 1967 [2], heart transplants have become the third most common organ transplant operation in many transplant centers [3,4].

The continuing improvements in HT outcomes have increased the number of patients receiving and living with HT who are at risk of long-term transplant complications. Post transplant malignancy (PTM), along with graft vasculopathy, are the two major long-term complications and causes of death following HT. Excess risk of cancer in HT is largely due to immunosuppression and infection with oncogenic viruses, with a spectrum of tumors similar to the range observed in human immunodeficiency virus (HIV) infection [5-7].

Previous population-based studies have not included skin cancers [3,4], which are important drivers of transplant recipient cancer risk [8]. To understand better the emerging epidemic of malignancies following HT, we reviewed scientific literature that focused on observational epidemiologic studies of incidence, and risk of malignancies following HT and compared with those in SOT.

Methods

The investigators independently identified eligible studies through searches of National Library of Medicine Medline/PubMed and reference lists of publications from relevant and review articles for additional studies.

The following criteria were included for selecting publications:

1. Search terms and keywords: solid organ transplantation, heart transplantation, malignancy post transplant, and post-transplantation lymphoproliferative disorders.
2. Inclusion criteria: data from 1980 on English language, adult and studies of >100 subjects or large centre or national studies. Organs (heart, lung, liver, kidney).
3. Exclusion criteria: transplants of stem cells, bone marrow, bones or intestine, clinical trials cohorts, and studies of cancer therapy

PTM tumors were classified into three groups: 1. Skin malignancy, including Kaposi's sarcoma (KS), 2. Hematolymphoid malignancy (HLM) including post transplantation lymphoproliferative disorders (PTLD), and 3. Other (non-cutaneous non-hematolymphoid malignancy, NCNL)

Results

Transplant recipients and cancer risk

In nine population-based studies including over 400,000 SOT (heart, liver, lung and kidney) recipients recorded, the incidence of posttransplant malignancy ranged from 4.1% to 16.3%, and a 2 to 4-fold overall increased risk of cancer over the general population was observed [3,8-10]. HT represented 10% of the solid organs transplanted, and the incidence of cancer risk was probably higher in HT than SOT allograft recipients. Almost all organ sites were reportedly associated with PTM as cancer of origin, however, cutaneous carcinomas, PTLD, and carcinoma of lung, liver and kidney represented the five most common malignancies in these transplant populations (Tables 1 and 2).

In 11 studies of HT, the incidence of post transplant malignancy

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in HT recipients ranged from 2.3%–27% and skin malignancies represented up to 50% of PTM (Table 2). Squamous cell carcinoma (SCC) predominated over basal cell carcinoma, reversing the proportion of skin malignancies seen in the general population [23]. Squamous carcinomas of PTM behaved more aggressively and more likely to have increased number of primary tumors, deep tissue spread, perineural and lymphatic invasion and recurrence [11,13]. An infectious etiology may contribute to the increased aggressiveness of nonmelanotic skin cancers. Significantly, higher levels of human papillomavirus (HPV) DNA have been discovered in SCC, and up to 80% of SCC in SOT contains HPV DNA [13].

The second most common cancer in HT recipients was PTLD (Tables 1 and 2). PTLD represent a heterogeneous spectrum of abnormal lymphoid tissue proliferations occurring in SOT recipients. Risk elevation was seen in both nodal and extranodal non-Hodgkin lymphomas, and risk was highest in the first year after transplant, then decreased, and increased again to a plateau beginning at 4-5 years after transplant [4]. The higher cancer risk in the first year post-transplantation likely resulted from more aggressive immunosuppression in the first year to avoid the severe consequences of graft failure due to rejection [25]. Epstein-Barr virus (EBV) is also considered a risk factor for the development of PTLD in HT recipients. EBV infects the B-cells and incorporates into B-cell DNA in latent infections [26]. PTLD occurs in the setting of cytotoxic T cells deficiency induced by anti-rejection immunosuppression therapy. The reason behind the augmented incidence of the lymphomas, mostly diffuse large B cell lymphomas, after transplantation as well as the wide range of the incidence rates is related to several factors including seropositivity to viral infections or seroconversion, and, a particular role is played by the potency of pharmacologic immunomodulation. The use of Rituximab has been an outstanding achievement in the treatment of these patients.

Posttransplant malignancy risk factors in ht recipients

Individual risk factors associated with a higher risk of developing a malignancy post HT included a higher age at transplantation, male gender, and an ischemic cardiomyopathy as pretransplant diagnosis and aggressive immunosuppressive therapy [27]. The following risk factors were identified for cutaneous PTM: skin type, unprotected sun exposure, tobacco smoking, and chronic alcoholism; for lung PTM: tobacco smoking and chronic alcoholism; and for PTLD: aggressive immunosuppressive therapy, and EBV serology.

Discussion

We reviewed and analyzed 20 publications regarding SOT and HT studies spanning the continents of America (US, Canada, Argentina), Europe (UK, Italy, Spain, Sweden) and Asia (Israel, Taiwan). There

Table 1: Incidence of de novo malignancy in SOT recipients.

						Type of PTM # of patients with tumors (% incidence)		
Reference	**Organ txpt**	**# pts**	**#HT**	**#PTM**	**Organ site H&N**	**Skin (incl. KS)**	**HLM incl. PTLD**	**NCNL tumor**
Sampaio [3]	SOT	193,905	-	7,897 (4.1%)	-	NR	1,645 (20.8%)	6,247(79.2%)
	HT	16,511	-	1,073 (6.5%)	-	NR	172 (16.0%)	901(84.0%)
Engels [4]	SOT	175,732	-	10,656 (6.1%)	-	NR	1,599 (15%)	9057(85%)
	HT	17,593	-	NR	-	NR	267(37%)	462(63%)
Serraino [6]	SOT	2,875	-	222(7.7%)	-	KS 39(17%)	42(19%)	141(64%)
	HT	682	-	95(14%)	-	KS 11(12%)	22(23%)	62(65%)
Krynitz [8]	SOT	10,476	557	1,610(15.3%)	-	668(41%)	173(11%)	769(48%)
Collett [9]	SOT	37,617	3609	5,706(15.1)	-	3,276(57%)	444(8%)	1986(35%)
Adami [10]	SOT	5,931	236	692 (11.6%)	-	292 (42%)	61(9%)	339(49%)
Rabinovics [11]	SOT	2,817	11	460 (16.3%)	175(6.1%)	163 (93%)	NR	12(7%)
Deeb [12]	SOT	3,639	NR	NR	95(2.6%)	78(82%)	NR	17(18%)
	HT	-	NR	NR	18	16(21%)	NR	2(12%)
Lott [13]	SOT	-	NR	-	-	193 (2.7%)	NR	NR
	HT	-	NR	59	-	59 (31%)	NR	NR

PTM, posttransplant malignancy, txpt transplanted, H&N head & neck, KS Kaposi's sarcoma, HLM hematolymphoid malignancy, NCNL, non-cutaneous non-lymphomatous, SOT, solid organ transplant, HT heart transplant, NR, not reported

Table 2: Incidence of malignancy in HT recipients including single organ site or tumor types.

	Transplant				Type of PTM # of patients with tumors (% incidence)		
Reference	**Organ**	**# pts**	**# Patients PTM**	**Tumor site**	**Skin (includes KS)**	**HLM incl PTLD**	**NCNL tumor**
Kellerman [14]	H	851	73(8.6%)	-	6(8%)	-	67(92%)
Favaloro [15]	H	309	11(3.5%)	-	-	11(100%)	-
Alam [16]	H	6,271	440(7%)	Skin	440(100%)	-	-
Caforio [17]	H	488	51(10%)	-	NR	17(30%)	34(70%)
Crespo-Leiro [18]	H	4,357	102(2.3%)	Lu		-	102(100%)
Hamour [19]	H	399	108(27%)	-	52(48%)	40(37%)	16(15%)
Crespo-Leiro [20]	H	3,393	639(19%)	-	324(51%)	62(10%)	253(39%)
Jiang [21]	H	1,703	160(9.4%)	-	NR	59(37%)	101(63%)
Hsu [22]	H	291	17(5.8%)	-	3(18%)	7(41%)	7(41%)
Molina [23]	H	3,393	324(9.5%)	Skin	324(100%)	-	-
Sanchez-Lazaro [24]	H	597	109(18.3%)	-	62(57%)	9(8%)	38(35%)

PTM, posttransplant malignancy, KS Kaposi's sarcoma, HLM hematolymphoid malignancy, NCNL, non-cutaneous non-lymphomatous, H heart transplant, NR, not reported, Lu Lung

was a 2 to 4-fold increase in risk developing PTM, infection-related or unrelated compared with the general population. The types of PTM were remarkably similar, but there were distinct variations in risk of skin, hematolymphoid and NCNL malignancies in HT and SOT recipients.

Higher risk of cancer overall in HT compared with kidney recipients was well recognized and had been attributed to the often considerably higher doses of immunosuppressive agents required to avoid graft rejection. The risk of cutaneous SCC outranked all other cancer risks, and highest estimates observed among HT recipients. The risk of lymphomas (especially PTLD), of lung, and liver cancers were substantially increased among HT and SOT recipients. The risk of malignancy types occurring most frequently in the general population was only moderately elevated or not elevated, as seen in colorectal, breast, and prostate cancers [8,9].

There were several limitations in the present study. Many of the larger studies excluded reporting nonmelanoma skin cancers due to underreporting of these cancers in Tumor Registries. Reporting of skin cancers may not be complete because some lesions would have been removed or ablated without histological confirmation and some of the cancer registries did not collect data on basal cell carcinomas. The incidence may not have been accurately accounted for in several of the large population-based studies, as duplication of reported cases might have occurred in studies from several European countries (Italy, Sweden, UK, Spain) [6,8-10,17-20,27], and that the combined heart and lung transplants were not included in the analyses. The number of follow-up years was not uniformly reported in the studies resulting in under-reporting or low numbers due to early follow-up years. Cumulative incidence estimates properly account for the competing risks of death and diagnoses for other cancers. At 15 years posttransplantation, the cumulative incidence for all cancers was estimated to be 17%, indicating that 17% of a cohort of heart transplant recipients would be expected to be diagnosed with cancer within 15 years [21]. Furthermore, the major risk factors of PTM not reported in most of the studies included pretransplant diagnosis, history of tobacco smoking and anti-rejection immunosuppressive therapies.

In conclusion, despite tremendous improvements in graft survival and transplant recipients quality of life in the last few decades, many SOT and in particular HT recipients continue to suffer from the development of PTM. Post-transplant malignancies appear in many organ sites; thus, in particular, transplant physicians need to be well aware of the risk factors of PTM, and continue to closely monitor these parameters in addition to anti-rejection therapy for transplant graft survivals. Researches in laboratory medicine and pathology and other disciplines should be aimed to identify new parameters or biomarkers that can be relevant for prevention, early detection and prognosis of cancer.

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