

RESEARCH COMMUNICATION

Special Malignancy Pattern in Chinese Renal Transplantation Recipients: A Single Center Experience and Literature Review

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Abstract

Malignancy is one of the main complications after renal transplantation but the situation in Chinese renal allograft recipients remains an enigma. We therefore reviewed 1,000 (8,531 person-years follow-up) renal allograft recipients from Jinling Hospital, Nanjing University, revealing an incidence rate of 2.4% of post-transplant malignancies, with a standardized incidence ratio (SIR) of 17.8 (95% C.I.: 16.7-18.8); the standardized rate is 1.67%, compared with 0.29% in the general population. However, our group demonstrated an extremely low incidence of skin cancer, which dominates in western countries. To confirm the findings, we reviewed the literature on post-transplant malignancies in Chinese renal allograft recipients, covering 296 malignancies in 18,548 renal transplant recipients in 21 reports. The top three most common sites of malignancies were the digestive tract, bladder and liver. The incidence of skin cancer was very low in most centers. These data show that Chinese renal allograft recipients have a unique spectrum of post-transplant malignancies, with an extremely very low incidence of skin cancer as compared to populations from western countries.

Keywords: Kidney transplantation - malignancy - tumour spectrum - outcome - China

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Introduction

Renal transplantation now represents the treatment of choice for patients developing end stage renal failure. With the improvement of the tissue typing techniques and the use of new immunosuppressants, the long term graft survival has been significantly improved, Malignancy is becoming one of the main complications after renal transplantation nowadays (Penn, 2000; Adami et al., 2003; Kasiske et al., 2004; Morath et al., 2004; Villeneuve et al., 2007). In US, the most common carcinoma is skin cancer, with a calculative incidence of 7.43% three years after transplantation. The calculative incidence of non-skin malignancies is 7.5% after 36 months' follow-up. Obviously malignancy is turning to be another important threaten for the recipient's survival (Arend et al., 1997; Briggs, 2001).

China has the largest amount of patients with end stage renal failure. In the recent fifteen years, a large number of renal transplantation has been performed. Now China has taken the 2nd place in the quantity of renal transplantation. However, the situation of malignancy in China remains an enigma to the world. Fortunately, malignancy after transplantation has been recognized as an important issue in many Chinese centers, and some of these centers had published their data (see Table 2). These publications give

us an opportunity to know the status of malignancy post renal transplantation in this population. Also we reviewed renal allograft recipients in Jinling Hospital, Nanjing University School of Medicine; the data of recipients developed malignancy were collected. These data revealed a specific spectrum of malignancy post transplantation in Chinese renal allograft recipients.

Materials and Methods

Data from Jinling Hospital

The local data in Jinling Hospital were derived from the renal allograft recipients transplanted during 1994-2004. All patients were followed for at least three years. Patients with de novo malignancies were retrospectively reviewed. Altogether 1000 recipients were enrolled in this study, all of the transplantations were ABO blood type-compatible, and all of the grafts were from cadaveric donors. The warm/cold ischemia time was limited to within 10 min/24 hrs separately. The recipients' ages ranged from 12 to 70 years old, and the ages of the donors ranged from 18 to 50 years old. The recipients were patients who had developed end-stage renal failure caused by various renal diseases. Those with active infection were excluded from the waiting list. The immunosuppressants included azathioprine (Aza), MMF, cyclosporine (CsA),

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FK506, Tripterygium wilfordii (TW, a multiglycoside extracted from Tripterygium Wilfordii Hook F, which is a kind of Chinese herb), and Rapamycin. The diagnosis of cancer was based on the clinical manifestations as well as pathology. The research meets the ethical guidelines of China. Written informed consent was obtained from all patients who underwent the study procedures, and the Human Subjects Committee of Jinling Hospital, Nanjing University School of Medicine approved all study protocols.

Literature screening and review

Data derived from published literatures were added to the data derived from Jinling Hospital, Nanjing University School of Medicine. We searched the database of China National Knowledge Infrastructure (CNKI, www.cnki.net), which is a key national project of China, including 8,419 Chinese journals. Time period is from 1994.3 to 2006.1. With the key words “renal transplantation” (“Shen Yi Zhi” in Chinese Pinyin) and “carcinoma” (“Zhong Liu” in Chinese Pinyin), we got 120 articles. With the key words “renal transplantation” (“Shen Yi Zhi” in Chinese Pinyin) and “cancer” (“Ai” in Chinese Pinyin), we got 25 articles. These articles were screened with the following criteria: (1) case serials (more than one patient), with the total amount of recipients available, can calculate the prevalence of malignancies; (2) the studied population of recipients is over 100. Studies will be excluded if (1) the study is a case report; (2) the amount of the studies population is not available, or (3) the report was based on a population less than 100. If the same center had multiple reports, the latest updated data will be analyzed. According to these criteria, 4 reports had been excluded; finally data from 21 studies (see Tables 2-4) have been selected for pooled analysis. The data derived from the literatures were sorted into a standard style as study period, follow-up time, patients’ number, malignancy incidence. The type of malignancies were sorted as hepatocellular carcinoma, digestive tract cancer, pancreatic carcinoma, non-Hodgkin lymphoma, leukemia, skin cancer, renal carcinoma, bladder carcinoma, urinary tract malignancies, lung cancer, breast cancer (in female), Kaposi sarcoma, brain cancer, and others.

Statistical analysis

Standardized incidence rates were generated according to patients’ age. Standardized incidence rate in general population was based on the population of Shanghai 2005, which is very close to Nanjing. The overall standardized incidence ratio (SIR) in Nanjing post-transplant population was based on data from Chinese malignancy registry agency (Zhang et al., 2008). 95% confidence intervals (CI) were calculated using SPSS 11.0 (SPSS Inc., Chicago, IL).

Results

Data from Jinling Hospital, Nanjing University

Among the 1000 renal transplant recipients, 733 were males and 267 were females, all were well followed-up except for 37 recipients. A total of 8,531 person-years of observation were accumulated. The mean age is 38 ±

Table 1. Standardized Incidence Rate for Patients Undergoing Renal Transplantation Between 1994 and 2004, Jinling Hospital, Nanjing University School of Medicine

Cancer site	ICD-9	Observed	Incidence Rate (%)	Standardized incidence rate*	Standardized incidence rate in General Population#
All cancers	-	24	2.4	1.67	0.29
Liver	155	1	0.1	0.05	0.03
Digestive tract	150-154	8	0.8	0.59	0.11
Non-Hodgkin’s	200,202	1	0.1	0.04	0.01
Kidney	189	2	0.2	0.08	0.01
Bladder	188	3	0.3	0.11	0.01
Lung	162	2	0.2	0.07	0.06
Breast	174	3	0.3	0.44	0.04
Tongue/Lip	140	1	0.1	0.04	0.001
Others	161,180,201	3	0.3	0.26	0.02

*Standardized incidence rate for patients undergoing renal transplantation between 1994 and 2004, Jinling Hospital, Nanjing University; #Standardized incidence rate for the general population in Shanghai, 2005

9.8 yrs at transplant. Only three cases received a second renal transplantation; for the other 997 cases, this was the first renal allograft. As for the donor sources, all were cadaveric donors. Till Dec 2007, 24 recipients developed malignancies, all were proved by pathology. The overall incidence of malignancy is 2.4%, and the standardized incidence rate is 1.67%. According to Chinese malignancy registry agency (Zhang et al., 2008), we can get a standardized incidence ratio (SIR) of 17.76 (95% CI: 16.69 - 18.83).

As to the 24 patients who developed post-transplant malignancies, 15 were males and 9 were females, with an average age of 48.4 ± 10.3 (ranged from 30 to 68) at diagnosis. One third of the malignancies were digestive tract cancer (n = 8) (see Figure 1), including 2 located in esophagus, 2 in stomach, 3 in colon, 1 in rectum. Urinary system is the second place to develop malignancies post

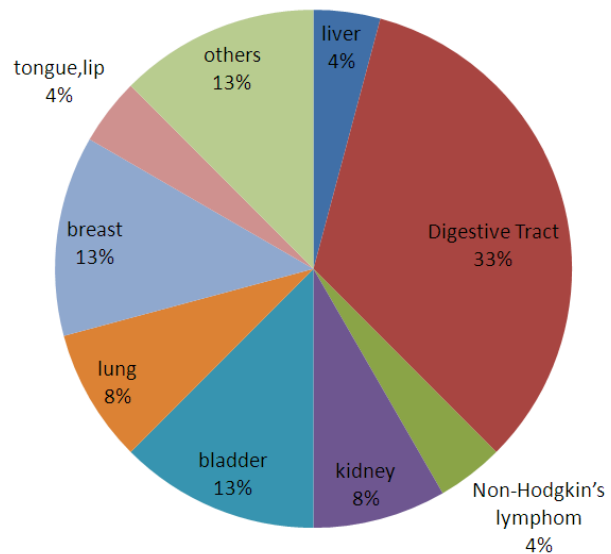


Figure 1. Ratios of Different Malignancies in Renal Allograft Recipients (derived from the data from Jinling Hospital)

Table 2. Malignancy Spectrum in Chinese Renal Transplant Recipients

Study (ref.)	Digestive						Urinary								
	Hepatocellular carcinoma	Tract cancer	Pancreatic carcinoma	non-Hodgkin lymphoma	Leukemia	Skin cancer	Renal carcinoma	Bladder carcinoma	Tract carcinoma	Lung cancer	Breast cancer	Tongue/lip cancer	Kaposi sarcoma	Brain cancer	Others
Study (ref.)	8	1	1	3	1	3	1	2	0	2	2	1	1	0	7
Wang et al.(2005)	3	5	0	1	0	8	6	2	2	0	2	1	0	0	0
Dong et al.(2004)	4	11	2	5	2	1	3	5	1	2	1	4	1	2	3
Fan et al.(2003)	4	2	1	1	0	0	0	1	0	2	3	1	2	0	2
Qu et al.(2004)	6	0	1	0	1	0	0	0	0	2	0	0	4	0	1
Lin et al.(2003)	2	2	0	1	0	0		11*		2	1	0	0	0	0
Dong et al.(2001)	0	3	0	1	0	0	2	5	1	2	0	0	0	0	0
Zhao et al.(2004)	2	0	0	1	0	0	3	3	1	4	0	0	0	3	0
Yang et al.(2003)	0	4	0	0	0	0	0	0	0	0	0	0	2	0	0
Chen et al.(2003)	2	2	0	1	0	0	0	1	0	2	0	1	0	1	0
Yang et al.(2001)	1	1	1	1	0	0	3	0	2	1	0	0	0	1	1
Meng et al.(2002)	1	1	0	3	0	0	2	2	0	1	0	0	0	0	0
Wang et al.(2005)	1	1	1	0	0	0	1	4	2	0	0	0	0	1	0
Wang et al.(2000)	1	0	0	0	0	0	1	3	1	0	0	0	0	0	0
Tian et al.(2005)	1	2	0	0	0	0	2	6	1	2	0	0	1	0	0
Tian et al.(1998)	2	1	0	1	0	1	1	2	0	0	0	0	0	0	0
Cai et al.(1998)	0	0	0	1	1	0	0	4	0	0	0	0	0	0	0
Lin et al.(2004)	1	1	0	0	0	1	1	2	0	0	0	0	0	0	0
Xu et al.(2004)	0	2	0	1	0	0	1	0	0	0	0	0	0	0	0
Xu et al.(2002)	0	1	0	1	0	0	0	2	0	1	0	0	0	0	0
Zhang et al.(1997)	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Ma et al.(2003)	1	8	0	1	0	0	2	3	0	2	3	1	0	0	3
Local Data	42	49	7	7	5	14		98#		25	12	6	11	8	17

*not specified, altogether 11 cases developed malignancies in urinary system; #altogether 98 cases developed malignancies in urinary system, including 29 located in renal, 47 in bladder, and 11 in urinary tract, and 11 unspecified

Table 3. Cumulative Incidences of Main Types of Malignancies Between Countries

	China	Korea (Kim et al., 2003)	United States (Kasiske et al., 2004)	AU & New Zealand (Chapman et al., 2004)	Canadian (Villeneuve et al., 2007)	Sweden (Adami et al., 2003)
Hepatocellular carcinoma	0.22%	0.13%	0.22%	0.10%	0.04%	0.07%
Digestive tract cancer	0.22%	0.37%	0.72%	0.14%	0.64%	0.96%
Pancreatic carcinoma	0.04%	0.01%	0.10%	0.09%	0.06%	0.07%
Non-Hodgkin lymphoma	0.03%	-	1.02%	0.15%	1.12%	0.76%
Leukemia	0.03%	-	0.25%	0.24%	0.15%	0.13%
Skin cancer	0.08%	0.22%	7.43%	1.10%#	0.18%#	4.92%
Breast cancer	0.06%	0.09%	1.05%	1.33%	0.47% (overall)	0.40%(overall)
	(overall)	(overall)	(female)	(female)	1.27%(female)	1.02%(female)
Renal carcinoma	≥0.15%	0.10%	1.01%	0.80%	0.64%	0.47%
Bladder carcinoma	≥0.24%	0.08%	0.32%	0.41%	0.22%	0.33%
Urine tract	≥0.06%	N/A	N/A	0.08%	N/A	N/A
Lung cancer	0.12%	0.08%	0.69%	1.00%*	0.97%	0.40%
Tongue/lip cancer	0.03%	0.02%	0.32%	3.19%	0.73%	0.86%
Kaposi sarcoma	0.06%	0.21%	0.14	0.14%	N/A	N/A
Brain cancer	0.04%	0.02%	0.29%	0.04%	0.07%**	0.12%
Overall	1.64%	1.92%	14.88%	12.14%	6.97%	11.67%

*including trachea, bronchus; #non-melanoma skin cancers not included; **including all malignancies located in nervous system

transplantation in this cohort; 3 recipients developed bladder cancer and 2 developed native kidney cancer. Among nine females who developed post transplant malignancies, three were diagnosed as breast cancer. Other malignancies including lung cancer (n=2), tongue cancer (n = 1), cervical carcinoma (n=1), thyroid cancer (n=1), malignant lymphoma (n=2), and 1 liver cancer (n=1). Standardized incidence rates were generated according to patients age (Table 1).

Literature review

From the literature we got 21 reports regarding the

incidence of malignancies in Chinese renal allograft recipients (see Table 2). These reports reported 296 malignancies in 18,548 renal transplant recipients. The detailed information of the 21 reports was listed in table 2. The individual reports were published from 1997 to 2005, all in Chinese, and most (n=18) of them were published after 2000. The patients were transplanted during 1977 to 2004, with a follow-up period ranged from 1 to 25 years. The reported malignancy incidences were variable, ranged from 0.6% to 4.2%. The majority centers had an incidence of 1.0-2.0%. The earliest malignancy happened in the 2nd month post transplantation, the diagnosis time

ranged from 2-180 months. The range of mean diagnosis time was from 21 to 84 months post transplantation. The mean age of the patients diagnosed as malignancies was ranged from 42 to 61. The youngest patient was only 17 years old at the diagnosis of malignancy.

The spectrum of malignancies was listed in table 4. In the majority centers, the most common malignancies were located in the urinary system and digestive system. Digestive system malignancies took the first place in 10 centers, and urinary system malignancies were most common in 11 centers. Skin cancer was rare in most centers except one. Regardless the follow-up time, we pooled the data together, and found that urinary system (n=98) and digestive system (n=98) were also top places to develop malignancies, which covered 61.3% of all the post transplant malignancies. Although one center had not clarified the sub-type of urinary system cancer, we still can say that the top three most common malignancies were digestive tract cancer (n=49), bladder carcinoma (over 47), hepatocellular carcinoma (n=42). On the contrary, only 4.7% (n=14) of the malignancies were skin cancer.

Discussion

Malignancy has been becoming one of the most important complications after renal transplantation (Penn, 2000; Adami et al., 2003; Kasiske et al., 2004; Morath et al., 2004; Villeneuve et al., 2007). The original objective of this study is to observe the status of malignancies in the 1000 recipients in Jinling Hospital. However, the local data revealed a low incidence and unique spectrum of malignancies in this cohort. The most obvious feature is the very low incidence of skin cancer. In order to prove this finding, a pooled analysis was performed and similar results were achieved.

In this pooled analysis, we revealed a special epidemic features of malignancy in Chinese renal transplantation recipients. This report was based on a population of 19,548 renal allograft recipients from 22 of the largest transplant centers in China. This population covered one third of the total renal transplantation performed before 2005 in China. The shortcoming of these reports is nearly all of them didn't use standardized incidence ratio/rate, which will be helpful to get a more precise incidence. However, this pooled analysis can reflect the spectrum of the malignancies in Chinese renal allograft recipients.

The incidence of malignancies post renal transplantation is variable, ranged from 7.97% to 14.88% in countries beside Asia (Adami et al., 2003; Kasiske et al., 2004). This study revealed a lower incidence (1.64%) of malignancies after renal transplantation in Chinese population. The standardized incidence rate for patients after renal transplantation between 1994 and 2004 in Jinling Hospital, Nanjing University is 1.67% (the incidence ratio is 2.4%). This incidence is much lower than reported from the United States, Canada, Australia and New Zealand area (Adami et al., 2003; Chapman et al., 2004; Kasiske et al., 2004; Villeneuve et al., 2007), but is similar to reports from two other Asian countries, Korea and Japan, with an incidence of 1.9% and 2.6% separately (Hoshida et al., 1997; Kim et al., 2002). This is consisted with the

study performed in the US by Kasiske et al (Kasiske et al., 2004), in which they found the incidence of malignancy was lower in Asians than other ethnic groups.

This study unexpectedly revealed a special malignancy spectrum compared with the population from western countries. The most significant difference on the spectrum of malignancies between Chinese renal transplant recipients and other non-Asian recipients is the extremely low incidence of skin cancer (Table 5). In American, Europe, Australia and New Zealand, the most common cancer is skin cancer. In these areas, about half of all the post transplant malignancies are skin cancer, with a reported incidence as high as 4.92-7.43% (Adami et al., 2003; Kasiske et al., 2004). However, in Chinese recipients, the incidence of skin cancer is only 0.08%. This incidence is only 1/90 of the incidence in the US, and 1/60 of the incidence in Sweden. Anyway, this incidence is similar to reports from Korean and Japanese (Hoshida et al., 1997; Kim et al., 2002). The low incidence of skin cancer may account partially to the lower incidence malignancies in Asian. Multiple risk factors have been recognized to be associated with skin cancer after renal transplantation; this pooled analysis suggests that the color of the skin might be the most important risk factor for skin cancer.

Besides skin cancer, the incidences of several other malignancies, such as breast cancer, non-Hodgkin lymphoma, tongue/lip cancers, are also significantly lower than western countries, and similar with Korean, another Asian country (Kim et al., 2002). Those findings also account for the overall lower incidence of malignancies in Asia.

The most common malignancy in Chinese renal allograft recipients are urinary system malignancies and digestive system malignancies. The top three malignancies are bladder carcinoma, hepatocellular carcinoma and digestive tract cancer. It is very interesting because they are not the most common malignancies in Chinese general population. In renal allograft recipients, lung cancer takes the fifth place after bladder carcinoma, hepatocellular carcinoma, digestive tract cancer and renal cancer. This result is consistent with some single center reports from Taiwan (Chiang et al., 2004; Feng et al., 2007). Actually the incidences of the top four malignancies are very close, so it is not strange that in some centers, different leading malignancies had been reported.

The high incidence of hepatocellular carcinoma is consisted with a high incidence of HBV and/or HCV infection in Chinese renal allograft recipients (Qi et al., 2003). With the waiting list for renal transplantation getting longer and longer, the incidences of HBV and HCV infection are also getting higher and higher. The high incidence of persistence of hepatitis virus infection might account for the high incidence of post transplant malignancies.

Here we revealed a low incidence of malignancies in Chinese renal transplantation recipients, however, this incidence can be expected to go higher in the near future, because most of the selected data have a relatively shorter observing period. Although in most centers, the study periods were over 10 years, the majority transplantations

were performed in the last 5 years. Also, in China, there lack of a national transplantation registration system before 2006, some of the patients who developed malignancies might have lost of follow-up. Now China is establishing a nationwide transplantation registration system, patients are expected to get well follow-up between centers with a sole ID. With the follow-up time getting longer and longer, the estimated incidence of malignancies will be getting higher.

In conclusion, Chinese renal allograft recipients have a unique spectrum of post-transplant malignancies. Recipients under long term immunosuppressants should be paid more attention to urinary and digestive system malignancies.

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