Incidence, Site and Risk Factor of Post-Transplant Malignancies – Analysis of 771 Renal Transplant Recipients for 40 Years in Japanese Single Center

Masahiko Okamoto*, Kazuki Sakai2, Shuji Nobori2, Masahide Matsuyama1, Hitotaka Ushigome2, Hideaki Okajima2 and Norio Yoshimura1,2

1Department of Organ Interaction Research Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
2Department of Transplantation and Regenerative Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Abstract

Backgrounds: A number of studies have observed increased cancer incidence rates among renal transplant recipients. However, the interval from transplant and the site of malignancies quite vary by era and region.

Methods: We retrospectively reviewed the records of 771 renal transplant recipients in Kyoto Prefectural University of Medicine between 1970 and 2010. 172 were done in conventional era (1970.4-1982.3), and 599 were done in calcineurin inhibitor (CNI) era (1982.4-). Overall incidence, site and risk factor of malignancies were analyzed.

Results: A total of 63 (8.2%) kidney recipients developed 66 malignancies. Graft-loss censored cumulative incidence in CNI era at 5, 10 and 20 years were 3.6%, 6.8% and 13.9%, while those in conventional era were 1.8%, 4.9% and 19.5%. Sites of malignancies occurring within three years following transplantation were breast, stomach, uterus, liver, leukemia, adult T cell lymphoma (ATL), Kaposi Sarcoma and post transplant lymphoproliferative disorder (PTLD). Univariate analysis showed age at the time of transplantation (≧50 y.o., OR=7.011, p<0.01), diabetic nephropathy (OR=6.785, p<0.01) and use of mycophenolate mofetil (OR=4.510, p<0.01) were significant risk factors to develop malignancies within 5 years. Among them, age at the time of transplantation (OR=4.645, p<0.05) and diabetic nephropathy (OR=4.311, p<0.05) were independent risk factors by multivariate analysis.

Conclusions: Thus, recent potent immunosuppressive regimen shortened the interval between malignancy and transplantation, increasing viral-related malignancies. In the long-term follow-up, it is crucial to pay special attention to those who have risk factors to develop them.

Keywords: Complication; Immunosuppression; Kidney transplantation; Malignancy

Introduction

Because newly developed immunosuppressive strategies have steadily reduced the frequency of acute rejection, kidney transplant recipients tend to survive longer than ever with continuous immunosuppression. Therefore, post-transplant malignancy has become an important issue which causes considerable morbidity and mortality [1-2]. The etiology of post-transplant malignancy is believed to be multifactorial and might involve impaired immunosurveillance and depressed antiviral immune activity of kidney recipients. Although conventional immunosuppressive drug has been linked with posttransplant malignancy, newer agents have not and indeed may have antitumor properties [3-6].

Although a number of studies have demonstrated increased cancer incidence rates, the interval from transplant and the site of malignancies were quite different by the era and the region [7-10]. Then, these studies have been limited by relatively small sample sizes, short follow-up intervals or focused on fewer cancer sites. As we have conducted kidney transplantation since 1970, retrospective study of these recipients has been performed to elucidate the incidence, site and risk factor of malignancies after renal transplantation in Japanese population, in which clinical characteristics are different from western countries.

Materials and Methods

We retrospectively reviewed the records of 771 renal transplant recipients who received the first renal allograft (excluding re-transplant) at Kyoto Prefectural University of Medicine between 1970 and 2010 and recorded the incidence and types of de novo malignancies that developed in these patients. The mean age at transplant of all recipients was 35 ± 13 (4-70) years old. 356 (46.5%) were male and 235 (30.5%) were female. 695 (90.1%) were living donor transplant and 76 (9.9%) were deceased donor transplant. They were divided into two groups according to the immunosuppressive era; conventional era (1970.4-1982.3: n=172), when CNI had not been introduced yet, and CNI era (1982.4-: n=599), when CsA or Tac were used in combination with or without antimetabolite and antibody induction.

Cumulative incidence studies were performed with the Kaplan-Meier method. Graft-loss censored cumulative incidence was defined as the incidence among graft survivors under continuing immunosuppression. Therefore, when graft-loss censored cumulative incidence was calculated, the date of graft loss without malignancies was identified as the endpoint of malignancy-free survival and malignancies after induction of dialysis was not counted.

To determine risk factors for malignancy, univariate analysis

*Corresponding author: Masahiko Okamoto, M.D, Ph.D, Department of Organ Interaction Research Medicine, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566 Japan, Tel. +81-75-251-5532; Fax: +81-75-223-6189; E-mail: amoto@koto.kpu-m.ac.jp

Received December 07, 2011; Accepted February 13, 2012; Published February 18, 2012

Citation: Okamoto M, Sakai K, Nobori S, Matsuyama M, Ushigome H, et al. (2012) Incidence, Site and Risk Factor of Post-Transplant Malignancies–Analysis of 771 Renal Transplant Recipients for 40 Years in Japanese Single Center. J Transplant Technol Res S1:006. doi:10.4172/2161-0991.S1-006

Copyright: © 2012 Okamoto M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
of demographic characteristics, including gender, age at the time of transplantation, pre-transplant chronic renal failure duration, original disease, donor source, blood-type incompatibility, experience of acute rejection and type of immunosuppression used, was first performed with a Cox proportional-hazards model. After examining the relations of individual demographic factors, a Cox proportional-hazards model taking into account interactions among demographic factors was again used to identify risk factors for malignancy using SPSS software. The statistical significance of the difference in non-parametric data was analyzed using Student's t test. Statistical significance was set at \( P < 0.05 \).

Results

Site, interval, therapy and prognosis of malignancies

A total of 63 (8.2%) kidney recipients out of 771 developed 66 malignancies. Twenty-seven were included in conventional era and 36 were in calcineurin inhibitor (CNI) era. The mean age at diagnosis of malignancy was 47 ± 11 (12-66) years old. Forty-two (66.7%) were male and 21 (33.3%) were female. Fifty-five (83.3%) were living-donor transplant and eight (16.7%) were deceased-donor transplant. The average interval between transplantation and development of malignancy was 133 ± 89 (7-340) months. The tumors included 13 skin cancers, 12 gastro-intestinal tract cancers, 9 liver cancers, 6 breast cancers, 6 renal cell carcinomas, 5 leukemia, 5 lymphoma and 10 others (Figure 1). Nineteen cases died of cancer, and 5 died of other disease. Nine were living after re-induction into dialysis, and 30 were living with functioning graft. Mortality was high in liver cancer (89%) and leukemia (100%). Of 61 solid tumors, 45 (74%) were treated with surgical resection with or without radiation and/or chemotherapy, while remaining 16 (26%) tumors were not resected because other therapy was suitable or lesion was too advanced to be resected.

Cumulative incidence of malignancies by era

Cumulative incidence of malignancies of all 771 kidney recipients at 5, 10, 20, 30 years were 2.2%, 4.5%, 10.5% and 13.8%, respectively (Table 2). Among them, age at the time of transplantation (OR=4.645, \( p<0.05 \)) and diabetic nephropathy (OR=4.311, \( p<0.05 \)) were found to be independent risk factors by multivariate analysis (Table 3).

Univariate analysis showed conventional immunosuppression (OR=2.912, \( p<0.01 \)) was significant risk factors to develop malignancies during total period after transplant, while use of CsA (OR=0.494, \( p<0.01 \)) and basiliximab (OR=0.092, \( p<0.01 \)) were significant negative risk factors. However, as this analysis included bias influenced by observation period, we next looked at the risk factor to develop malignancies within 5 years after transplant. Univariate analysis showed age at the time of transplantation (≥ 50 years old, OR=7.011, \( p<0.01 \)), diabetic nephropathy as an original disease (OR=6.657, \( p<0.01 \)), ABO-incompatible transplant (OR=5.785, \( p<0.01 \)) and use of mycophenolate mofetil (MMF) (OR=4.510, \( p<0.01 \)) were shown to be significant risk factors to develop malignancies within 5 years (Table 2). Among them, age at the time of transplantation (OR=4.645, \( p<0.05 \)) and diabetic nephropathy (OR=4.311, \( p<0.05 \)) were found to be independent risk factors by multivariate analysis (Table 3).

Discussion

Recent progress in immunosuppressive strategy have decreased the rate of acute rejection and substantially improved graft survival in renal transplantation. In spite of these encouraging trends, long-term cumulative incidence in CNI era at 5, 10 and 20 years were 3.6%, 6.8% and 13.9%, while those in conventional era were 1.8%, 4.9% and 19.5%, showing early higher incidence in CNI era outstripped by conventional era by 12 years (Figure 2b). Site of malignancies in CNI era occurring within 3 years following transplantation, which was never observed in conventional era, were breast, stomach, uterus, liver, leukemia, adult T cell lymphoma (ATL), Kaposi Sarcoma and post transplant lymphoproliferative disorder (PTLD) (Table 1).

Risk factor of post-transplant malignancies

Citation: Okamoto M, Sakai K, Nobori S, Matsuyama M, Ushigome H, et al. (2012) Incidence, Site and Risk Factor of Post-Transplant Malignancies—Analysis of 771 Renal Transplant Recipients for 40 Years in Japanese Single Center. J Transplant Technol Res S1:006. doi:10.4172/2161-0991.S1-006

Cumulative incidence of malignancies of all 771 kidney recipients (Figure 1a). Cumulative and Graft-loss censored cumulative incidence of post-transplant malignancy (b) Graft-loss censored cumulative incidence of post-transplant malignancy in conventional and CNI era.
out of 11 malignancies were known to be associated with oncogenic virus such as human papilloma virus, hepatitis C virus, human T-cell leukemia virus, human herpes virus-8 and Epstein-Barr virus. These results suggested that depressed antiviral immune activity caused by recent immunosuppressive regimen facilitated the occurrence of viral-related malignancy in relatively early period following transplantation in our population.

Multivariate analysis in the present study showed that age at the time of transplantation was independent risk factors to develop malignancies within 5 years. Consistent with our results, 'age at the time of transplantation' has been reported to be a risk factor for malignancy in western countries [11,18-20] and in other Japanese institutes [15,16]. We also found that diabetic nephropathy as the cause of end stage renal disease is clearly a risk factor for malignancy. Although Webster et al. [14] reported otherwise, the risk of malignancies in general population is reported to be increased from earlier stages of glucose metabolism abnormalities, with a linear relationship between cancer risk and plasma insulin levels [21,22], indicating justification of our results.

A correlation between the use of immunosuppressant and the development of malignancy has been reported by many authors. In our results, use of tacrolimus (Tac) was a relatively high risk factor of malignancy in 5 years (OR=2.659, p=0.053), while use of cyclosporine (CsA) was relatively low risk factor (OR=0.692, p=0.465). In experimental model, CsA [23,24] and Tac [25,26] exerted both progressive and suppressive effect for tumor growth. As for clinical data, according to a US multicenter study of renal transplantation [27], the incidence of malignancy was not significantly different in CsA and Tac group. A meta-analysis of 30 recent studies also showed no significant difference between two groups [28]. However, one study showed that the incidence of lymphoma 2 years after transplantation was about double in the Tac group than in the CsA group [29]. It is also reported that the use of Tac is associated with a high risk of PTLD [30]. In contrast, Kauffman et al. [31] found no difference in the incidence of PTLD between CsA and Tac regimen and even found significantly less incidence in the rates of any cancer, nonskin, nonlymphoid solid cancer, and nonmelanoma skin cancer in Tac regimen. Thus, which CNI becomes more oncogenic after transplantation is still controversial.

Although conventional immunosuppressive drug have been linked with posttransplant malignancies, newer agents such as MMF [3,4] and sirolimus [5,6] have not and indeed may have antitumor properties. Actually, Leckel et al. [4] showed that MMF prevented receptor-dependent tumor dissemination in vitro. However, in our patients, use of MMF was significant risk factors to develop malignancies within 5 years by univariate analysis, although multivariate analysis did not find it as an independent risk factor. It is possible that depressed antiviral immune activity by MMF might facilitate the occurrence of viral-related malignancy which was seen relatively early period following transplantation. However, another interpretation of these results was that the cumulative dose of immunosuppression was a risk for malignancies, therefore ABO-incompatibility and MMF itself might not be the point, but the higher dose of cumulative immunosuppression used in these patients.

The limitation of present study is that the number of the population is quite small, so the conclusions about risk factors to develop malignancies should be evaluated cautiously. However, this study is relevant because most of these kinds of studies are from western countries.

In conclusion, our results demonstrated that recent potent immunosuppressive regimen shortened the interval between survival following transplantation has remained largely unchanged with considerable number of death with functioning graft. High mortality among renal-transplant recipient is attributed mainly to increased risks of cardiovascular disease and malignancy while infectious disease becomes less lethal. In North America [11,12], Europe [13] and Australia/New Zealand [14], the incidence of malignancy among renal transplant recipients ranges from 7% to 14.9%.

In our present follow-up study, the incidence of malignancy was 8.2% in renal transplant recipients. This incidence is slightly higher than the incidence of 6.8% reported in 1998 by Kishikawa et al. [15] and 6% in 2007 by Imao et al. [16] from other Japanese institutes, conceivably reflecting the longer follow-up period as long as up to 40 years in the present study. Thus, a post-transplant period was reported to be a risk factor for the development of malignancy [17]. Therefore, care must be taken to the risk of malignancy in long-term survivors after renal transplantation.

The site of malignancy occurring in our series was quite similar with those reported from other Japanese institutes where gastrointestinal and renal cancers were frequent. The difference was that our most common site was skin while fewer patients had skin cancer in other Japanese institutes. They suggested that the low incidence of skin cancer is a characteristic of Asian patients [16], referring to the Chinese results reported by Tang et al. [18]. The reason why skin cancer was most common in our series as seen in western countries was not obvious, but possible reason was that our previous patients frequently came from south part of Japan where there were much sun exposures.

On the other hand, malignancy occurring in the early period after transplantation had special characteristics. As shown in Table 2, 8 survival following transplantation has remained largely unchanged with considerable number of death with functioning graft. High mortality among renal-transplant recipient is attributed mainly to increased risks of cardiovascular disease and malignancy while infectious disease becomes less lethal. In North America [11,12], Europe [13] and Australia/New Zealand [14], the incidence of malignancy among renal transplant recipients ranges from 7% to 14.9%.

In our present follow-up study, the incidence of malignancy was 8.2% in renal transplant recipients. This incidence is slightly higher than the incidence of 6.8% reported in 1998 by Kishikawa et al. [15] and 6% in 2007 by Imao et al. [16] from other Japanese institutes, conceivably reflecting the longer follow-up period as long as up to 40 years in the present study. Thus, a post-transplant period was reported to be a risk factor for the development of malignancy [17]. Therefore, care must be taken to the risk of malignancy in long-term survivors after renal transplantation.

The site of malignancy occurring in our series was quite similar with those reported from other Japanese institutes where gastrointestinal and renal cancers were frequent. The difference was that our most common site was skin while fewer patients had skin cancer in other Japanese institutes. They suggested that the low incidence of skin cancer is a characteristic of Asian patients [16], referring to the Chinese results reported by Tang et al. [18]. The reason why skin cancer was most common in our series as seen in western countries was not obvious, but possible reason was that our previous patients frequently came from south part of Japan where there were much sun exposures.

On the other hand, malignancy occurring in the early period after transplantation had special characteristics. As shown in Table 2, 8 survival following transplantation has remained largely unchanged with considerable number of death with functioning graft. High mortality among renal-transplant recipient is attributed mainly to increased risks of cardiovascular disease and malignancy while infectious disease becomes less lethal. In North America [11,12], Europe [13] and Australia/New Zealand [14], the incidence of malignancy among renal transplant recipients ranges from 7% to 14.9%.

In our present follow-up study, the incidence of malignancy was 8.2% in renal transplant recipients. This incidence is slightly higher than the incidence of 6.8% reported in 1998 by Kishikawa et al. [15] and 6% in 2007 by Imao et al. [16] from other Japanese institutes, conceivably reflecting the longer follow-up period as long as up to 40 years in the present study. Thus, a post-transplant period was reported to be a risk factor for the development of malignancy [17]. Therefore, care must be taken to the risk of malignancy in long-term survivors after renal transplantation.

The site of malignancy occurring in our series was quite similar with those reported from other Japanese institutes where gastrointestinal and renal cancers were frequent. The difference was that our most common site was skin while fewer patients had skin cancer in other Japanese institutes. They suggested that the low incidence of skin cancer is a characteristic of Asian patients [16], referring to the Chinese results reported by Tang et al. [18]. The reason why skin cancer was most common in our series as seen in western countries was not obvious, but possible reason was that our previous patients frequently came from south part of Japan where there were much sun exposures.

On the other hand, malignancy occurring in the early period after transplantation had special characteristics. As shown in Table 2, 8
transplantation and increased viral-related malignancies. In the long-term follow-up, it is crucial to pay special attention to the groups that have risk factors to develop malignancies. More importantly, screening for malignancy should be performed periodically after renal transplantation to detect malignancy at an early stage [32-35].

References

1. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, et al. (2006) Cancer incidence before and after kidney transplantation. JAMA 296: 2823-2831.
2. van Leeuwen MT, Webster AC, McCredie MR, Stewart JH, McDonald SP, et al. (2010) Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. BMJ 340: c570.
3. Carter SB, Franklin TJ, Jones DF, Leonard BJ, Mills SD, et al. (1969) Mycophenolic acid: an anti-cancer compound with unusual properties. Nature 223: 848-850.
4. Leckel K, Beecken WD, Jonas D, Oppermann E, Coman MC, et al. (2003) The influence of immunosuppressive drugs on the growth and invasion of human liver cancer cells. Clin Exp Immunol 134: 238-245.
5. Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, et al. (2005) Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 352: 1317-1323.
6. Campistol JM, Schena FP (2007) Kaposi's sarcoma in renal transplant recipients—the impact of proliferation signal inhibitors. Nephrol Dial Transplant 22: 117-122.
7. Yildirim Y, Ozyilkiran O, Emiroglu O, Karakayali H, et al. (2006) Early diagnosis of cancer in renal transplant patients: a single center experience. Asian Pac J Cancer Prev 7: 336-339.
8. Stratta P, Morello V, Musetti C, Turello E, Palmieri D, et al. (2008) Malignancy after kidney transplantation: results of 400 patients from a single center. Clin Transplant 22: 424-427.
9. Andrés A (2005) Cancer incidence after immunosuppressive treatment following kidney transplantation. Crit Rev Oncol Hematol 56: 71-85.
10. Popov Z, Ivanovski O, Kolevski P, Stankov O, Petrovski D, et al. (2007) De novo malignancies after renal transplantation—a single-center experience in the Balkans. Transplant Proc 39: 2589-2591.
11. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C (2004) Cancer after kidney transplantation and increased viral-related malignancies. In the long-term follow-up, it is crucial to pay special attention to the groups that have risk factors to develop malignancies. More importantly, screening for malignancy should be performed periodically after renal transplantation to detect malignancy at an early stage [32-35].

Prevalence of co-morbidity in different European RRT populations and its effect on access to renal transplantation. Nephrol Dial Transplant 20: 2803–2811.
20. Marcen R, Pascau J, Tato AM, Teruel JL, Villafuerra JJ, et al. (2003) Influence of immunosuppression on the prevalence of cancer after kidney transplantation. Transplant Proc 35: 1714–1716.
21. Nicolucci A (2010) Epidemiological aspects of neoplasms in diabetes. Acta Diabetol 47: 67-66.
22. Giovannucci E, Michaud D (2007) The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 132: 2208-2225.
23. Hojo M, Morimoto T, Maluccio M, Asano T, Morimoto K, et al. (1989) Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 397: 530-534.
24. Morisaki T, Matsunaga H, Beppu K, Ibara E, Hirano K, et al. (2000) A combination of cyclosporin-A (CsA) and interferon-gamma (INF-gamma) induces apoptosis in human gastric carcinoma cells. Anticancer Res 20: 3363-3373.
25. Mistriková J, Mrmusová M, Durmanová V, Rajcán J (1999) Increased neoplasms development due to immunosuppressive treatment with FK-506 in BALB/c mice persistently infected with the mouse herpesvirus (MHV-72). Viral Immunol 12: 237-247.
26. Sakai M, Miyake H, Tashiro S, Okumura Y, Kido H (2004) Inhibitory effect of FK506 and cyclosporine A on the growth and invasion of human liver cancer cells. J Med Invest 51: 63-69.
27. Jensik SC (1998) Tacrolimus (FK 506) in kidney transplantation: three-year survival results of the US multicenter, randomized, comparative trial.FK 506 Kidney Transplant Study Group. Transplant Proc 30: 1216–1218.
28. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC (2005) Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients meta-analysis and meta-regression of randomized trial data. BMJ 331: 810.
29. Opelz G, Kohler B (2004) Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 4: 222–230.
30. Cavall D, Dharnidharka V, Agodoa L, Boen H, Abbott K (2005) Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 80: 1233–1243.
31. Kaufmann HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW (2006) Post-transplant de novo malignancies in renal transplant recipients: the past and present. Transpl Int 19: 607-620.
32. Haritharan S (2006) Recommendations for outpatient monitoring of kidney transplant recipients. Am J Kidney Dis 47: S22-S36.
33. Wong G, Chapman JR, Craig JC (2008) Cancer screening in renal transplant recipients: what is the evidence? Clin J Am Soc Nephrol 3: S87-S100.
34. Kibler BA, Keough-Ryan T, Clase CM (2003) Screening for prostate, breast and colorectal cancer in renal transplant recipients. Am J Transplant 3: 619-625.
35. Wong G, Howard K, Craig JC, Chapman JR (2008) Cost-effectiveness of colorectal cancer screening in renal transplant recipients. Transplantation 85: 532-541.