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Gastrointestinal and Liver Malignancies after Renal Transplantation: A Multicenter Study

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Abstract

Background: Immunosuppression increases the incidence of cancer and promotes the growth of neoplasm in kidney transplant recipients. There have been few reports on the incidence of gastrointestinal (GI) and liver cancers from transplant registries.

Methods: In the current study, we collected data from 8 kidney transplant centers in Iran between 1984 and 2008, to detect the incidence, type, and outcome of GI and liver cancers after kidney transplantation. Only histologically confirmed tumors that occurred after renal transplantation were included in the analysis. We also compared their data with 3028 kidney recipients of two transplant centers.

Results: Of the 9355 patients who underwent kidney transplantation, GI tumors were detected in 14 (0.15%), 12 males and 2 females. Male gender was predominant between patients with GI and liver tumors (P=0.02). Colorectal carcinoma (CRC) was the most common GI cancer (n=7) followed by gastric adenocarcinoma (n=3) and hepatocellular carcinoma (n=3). Mean age of patients was 48.0 ± 10.6 (27 – 61) years and mean time of diagnosis since transplantation was 72 (5-284) months. Significant risk factors for the development of a *de novo* malignancy were male gender, older age (>50 years of age) and the total time on immunosuppression. Patient and graft survival rates from the time of GI and liver cancers onset were poor.

Conclusions: CRC was the most common GI tumor following kidney transplantation and was predominant in male. GI and liver malignancies have poor prognosis and early diagnosis and prompt treatment of the post-transplant malignancies is essential.

Keywords: Kidney Transplantation, Gastrointestinal Neoplasm, Liver, Colorectal Carcinoma

Introduction

Kidney transplantation is the best treatment of choice for the end stage renal disease (ESRD) patients requiring renal replacement therapy. The incidence of

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malignancies in renal recipients has steadily increased following a dramatic rise in the number of kidney transplantations, use of potent immunosuppressive agents and longer survival for transplant recipients. Consequently, neoplastic disorders are an important cause of the late morbidity and mortality in renal transplants(1). Although tendency to develop skin cancer and lymphoproliferative disorders is clearly increased after renal transplantation, the association between this setting and gastrointestinal (GI) cancer is not clearly known (1). The association of colorectal carcinoma (CRC) and renal transplantation has been reported. A significant overall increase of colon cancer with a risk ratio of 2.6 was reported after renal grafts in Australia, New Zealand and the Nordic countries (2, 3). Further studies support the idea of an increased risk of colon cancer however, not of rectal cancer after renal transplantation (4-6). In a series of 498 cases of *de novo* malignancy following renal transplantation, risk ratios for CRC and liver cancer were 1.28 and 3.96, respectively (7). However, Kasiske et al. (2004) reported that relative risk (RR) for any GI tumors within first 3 years after transplantation was 0.83 and RR for cancers of colon, esophagus, stomach and hepatobiliary were 0.74, 2.76, 0.89 and 0.77, respectively (8).

Although, Iran has the largest reported experience of kidney transplantation among the Middle East countries(9), there have been no reports on the incidence of malignancy from transplant registry in Iran. It is difficult to precisely determine the incidence of most tumors, and to compare their rates of occurrence with those in the general population, using data from single-center studies (10, 11). Therefore, we made a plan in a larger and multicenter study with adequate sample size to detect the incidence and to determine the impact of demographic factors, immunosuppression, treatment options and outcome of GI cancer after kidney transplantation. In the current study, we collected data from 8 kidney transplant centers, accounting for up to 37% of all kidney transplantation in Iran between 1984 and 2008.

Materials and Methods

A retrospective study was designed to identify all the renal transplant recipients with GI and liver malignancies from eight centers in Iran. A total of 9355 patients, receiving a kidney between Oct 1984 and Oct 2008, were reviewed for the development of GI and liver cancers. We also compared their data with 3028 kidney recipients of two transplant centers. The time between renal transplantation and onset of GI and liver neoplasms was defined as the period between the graft and the first signs of tumors. All GI and liver cancer specimens were confirmed by histologic examination.

The variables studied were patient age, gender, immunosuppressive regimen before and after diagnosis of GI and liver cancers, post-transplant latency period, simultaneous infectious problems, treatment received, progression of tumors in individual patients, serum creatinine level at the time of diagnosis and follow-up visits, rejection episodes, the clinical presentation of GI and liver malignancies, follow-up and outcome.

All recipients had no evidence of CMV infection. Pre-transplantation hepatitis C serologic status was documented in all the patients. All the tested patients were seronegative at transplantation. HBSAg was positive in three patients with hepatocellular carcinoma.

Immunosuppression consisted of various combinations of prednisone, cyclosporine, azathioprine/mycophenolate mofetil (MMF), and anti thymocyte/lymphocyte globulin (ATG/ALG). None of the patients received OKT3. Of the 14 recipients who developed GI cancer, 2 received ATG/ALG. All patients that had taken ATG/ALG had also received prophylactic antiviral therapy (ganciclovir) for a minimum of 1 month after transplantation.

Besides, surgical treatment and decrease or withdrawals of immunosuppressive agents, chemotherapy was given palliatively to 6 patients. Outcome was

Table 1: Characteristics of transplant patients with GI and liver cancers

Characteristic	Value
Recipient age at the time of diagnosis, yr - Mean ± SD (Range) , Median	48.0 ± 10.6 (27 – 61), 51.5
Recipient gender (male/female), n	12 / 2
Time from transplantation to diagnosis, mo-Mean ± SD (Range), Median	72±78 (5-284), 38
Mean follow up after diagnosis, mo - Mean ± SD (Range), Median	5.2±1.4 (3-7), 6
Episodes of acute rejection	3
Treatment modalities, n Withdrawal of IS/Reduction of IS/ Surgical Therapy/Chemotherapy/ Died before treatment	6 / 6 / 8 / 6 / 1
Patient outcome, n (%) 6 months mortality / Overall mortality	12 (85.7%) / 2 (14.3%)
GI cancer-free survival, Kaplan Maier (%) Patient and graft survival (6 mo)	48.6/66
Location of Cancer, n (%) Colon/Stomach/Rectum/ampulla of water/Liver	5 (2.8%)/3 (1.65%)/2 (1.1%)/1 (0.5%)/3 (1.65%)
Local/Metastasis/Unknown	2/9/3

SD: Standard Deviation; **yr:** years; **n:** number; **mo:** months

assessed by response to therapy, remission duration, and survival.

Statistics:

Data were analyzed using SPSS version 15.0 for windows. Categorical data and continuous variables were reviewed using relative frequency and mean values ± standard deviation, respectively. Continuous data of the two groups, with or with no GI cancer, were compared by Student's t-test and non-parametric data by Mann-Whitney U test. Kruskal-Wallis test carried out for comparison between more than two groups. Categorical data were analyzed using the chi-square or Fisher's exact test. Patient and graft survival rates were defined as the time from the diagnosis of the GI and liver cancers to death and graft loss, respectively. Overall survival was calculated using the Kaplan-Meier method. Statistical significance was defined as a probability value less than 0.05.

Results

Fourteen (0.15%) recipients who developed GI and liver cancers following renal transplantation were retrospectively appraised with a median follow-up of 43 (12-290) months, representing 7.7% of all post-transplant malignancies (14 out of 181 cases).

Table 1 summarizes the demographic characteristics of the recipients who had GI and liver tumors. CRC was the most common GI cancer, accounting for up to 50% of all cases. Male recipients had more tumors than female recipients; male to female ratio in the affected patients was 6:1. Although this difference was not statistically significant between GI and liver cancer and non- cancer groups (P=0.08), but male gender was predominant between patients with GI and liver tumors (P=0.02) (Table 2).

The higher occurrence of GI and liver malignancies in renal transplant patients reached statistical significance considering the age at transplantation,

Table 2: Comparison of age, gender and time of diagnosis since transplantation between recipients with cancer according to organ involvement

	Location of cancer			
Variable	Colorectal	Stomach	Liver	P Value
Age at the Tx, yr - Mean ± SD	50.6±10.8	43.3±13.3	42.3±3.8	0.3 [a]
Gender, n – male/female	7/0	2/1	3/0	0.02 [b]
Time from transplantation to diagnosis, mo	85±105	37±12	50±31	0.9 [a]

Tx: Transplantation; **yr:** years; **SD:** Standard Deviation; **n:** number; **mo:** months
[a] Kruskal-Wallis Test
[b] Pearson Chi-Square Test

i.e. GI and liver cancers occurred more frequently among recipients with older age when compared to cases without GI and liver tumors (43.7±9.3 versus 36.4±15.5 years, P= 0.01). The clinical presentation of these neoplasms was demonstrated less frequently in the first 3 years after transplantation (35.7%); this means that the time interval between transplantation and onset of GI and liver cancers was relatively late as compared to other tumors, with a median period of 38 (5-284) months.

The main cause of mortality was sepsis. Patient and graft survival rates from the time of GI and liver cancers onset were poor. (Table 1)

Discussion

Post-transplant cancer is a major complication of renal transplantation that causes considerable short and long-term mortality. GI and liver malignancies were relatively less prevalent in our study, in comparison with other reports (1, 8, 12). Moreover, these cancers were less common when compared to other tumors; the most frequent tumors in Tremblay et al. study were skin and lip (42.3%), followed by genitourinary (15.3%) and GI neoplasms (12.6%) (12).

The relative frequency of CRC among the neoplasms that involved our kidney transplant recipients (3.86%) was low. In a series of 93 cases with a post-transplantation diagnosis of cancer, CRC accounted for 5.4% of all malignant cases (12). The common carcinomas found in Korean recipients were cervix uteri cancer, Kaposi's sarcoma and stomach cancers (13). In addition, stomach and cervix uteri cancers are common malignancies in the general population of Korea (13). Furthermore, gastric cancer was found most prevalent (13%) in Japan (14).

Hepatocellular carcinoma is a common malignancy in Taiwan, not only in the general population but also in renal allograft recipients (15).

The ANZ (Australia/New Zealand) registry suggests that colon cancer (but not rectal and anal) has a higher that expected incidence in renal transplant patients (16) . For most common GI tumors, e.g. colon, stomach, esophagus, pancreas, cancer rates were roughly two fold higher in the first 3 years after kidney transplantation compared with the general population (8). Incidence rate of colon carcinoma was 2- to 4-fold as high as that of the general population in transplantation registries of EDTA-ERA (European Dialysis and Transplantation Association- European Renal Association), ANZ, SCR (Swedish Cancer Registry) and USRDS (United States renal Data System) (8). Cancer rate of gastric cancer was similar to the rate of colon carcinoma in ANZ, SCR and USRDS and incidence rate of hepatobiliary neoplasm was at least five fold higher compared with the general population in ANZ and USRDS registries (8).

In the current study, GI and liver malignancies was common in males. These cancers tend to occur in older patients and are less strongly correlated with the onset of the disease than with the duration of

immunosuppression. However, the age of our patients with GI and liver cancers was higher than those had no disease. Significant independent risk factors for the development of a *de novo* malignancy were male gender, older age (>50 years of age) and the total time on immunosuppression (7). GI and liver neoplasms usually appear late (a median interval of 38 months from transplantation); and the mean age at the time of diagnosis was 44 years in our patients, which is less than that among the patients with GI and liver malignancies in general population. Other work has shown a younger age at the cancer diagnosis in renal recipients compared to the general population (17).

This study highlights outcome of patients who had a renal transplant and later developed GI and liver carcinoma. The clinical course of these cancers was more aggressive and tumor stage at presentation was advanced. Majority of patients died within 6 months of diagnosis and 64% of the cases presented with metastatic disease. The course of malignancies developing in post-transplant recipients is more aggressive than that expected in non-transplant patients.

Because of this, it is important to intensively follow long-term survivors in order to detect malignant tumors as early as possible (16). Another possible cause for the poor outcome in the patients with a renal transplant could be delay in diagnosis (16).

In our study, reduction or cessation of immunosuppressive agents following the diagnosis of GI and liver malignancies resulted in graft loss in 3 (21%) cases of withdrawal/ reduction of immunosuppressive agents and it seemed to be relatively safe for kidney allograft function.

Surgery in patients after renal transplantation and on immunosuppressive drugs may carry greater than usual risk (16). Once a patient with a renal transplant and on immunosuppressive therapy is diagnosed with GI carcinoma, surgical resection where indicated is appropriate. The results from this study indicate that the operative therapies seem safe to perform. In these patients if there is advanced disease (local or metastatic) the prognosis is very poor and any therapy should only be undertaken to palliate symptoms(16).

Patients with CRF, dialysis or renal transplantation should be screened for CRC.

Transplant recipients should be followed very closely because they are likely to develop a malignancy, especially of the skin. The importance of gynecological and gastrointestinal assessment cannot be overemphasized (13). The current study suggests that measures to decrease the risk of these malignancies, e.g. screening for colon, stomach and liver cancer is essential. No guideline can be proposed at present for cancer screening in renal transplant populations.

However, regular medical examination, a minimum of annual fecal occult blood testing, appropriate investigation of anemia and/or 5-yearly flexible sigmoidoscopy in recipients older than 50 for CRC and α-fetoprotein and ultrasonography performed 6-monthly in high-risk individuals for HCC may improve the diagnosis and hence prognosis of these patients (18).

Conclusions

Although, the incidence of GI and liver malignancies in this large population studied was lower as compared to that reported in other transplant patient groups, however, GI and liver malignancies have poor prognosis and early diagnosis and prompt treatment of post-transplant malignancies is an important emerging challenge in transplantation medicine. Therefore, we recommend a follow up at suitable intervals so that any signs of cancer are detected earlier.

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