COMMENTARY

Early Diagnosis of Cancer in Renal Transplant Patients: A Single Center Experience

Yesim Yildirim[1]*, Ozgur Ozyilkan[1], Remzi Emiroglu[2],Beyhan Demirhan[3], Hamdi Karakayali[2], Mehmet Haberal[2]

Abstract

Renal transplantation confers increased survival with improvement of immune suppressive drugs, but certain types of neoplasm can arise as secondary complications. It is thus well known that recipients have significantly increased risk of developing de novo malignancy when compared with the age-matched general population. Cancer is the 4th most common cause of death in transplant patients after cardiovascular disease, infections and liver failure. Our transplantation team has performed 1,582 kidney transplantations since 1975. Fifty-nine of the patients developed malignancies in the posttransplantation period. The most common was Kaposi's sarcoma (19 patients, 32.2 %), followed by lymphomas (16 patients, 27.1 %) and skin carcinomas (13 patients, 22.0 %). Many factors can contribute to high susceptibility in these patients; age at transplantation, certain types of viral infections like Epstein-Barr virus, human herpes virus-8, human papilloma virus or chronic usage of immune suppressive agents, type of immune suppressive drugs, and ethnic characteristics . Transplant recipients generally have advanced stage cancers at the time of diagnosis with a poor prognosis. Since some neoplasms are common early detection of cancer is important to decrease cancer related mortality and morbidity. This article considers risk factors and recommendations for early diagnosis of cancer in renal transplant patients.

Key Words: Renal transplants - immune suppression - secondary malignancy - risk factors

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Early Diagnosis of Cancer in Renal Transplant Patients

Malignancy is an important cause of mortality and morbidity after solid organ transplantations. In a recent study it was estimated that more than 1 in 5 renal transplant recipients will develop malignancy within 15 years, and this incidence will further increase after 20 years (London et al., (1995). In renal transplant recipients the most prevalent neoplasms are not the cancers of the colon, breast, or lung that are commonly observed in general population. Rather, uncommon tumors like Kaposi's sarcoma, vulvar/anal carcinomas, lip and hepatocellular carcinoma, in situ cervix carcinomas are frequently observed (Penn, 1998). We have observed a large number of malignancies in our renal transplant patients over 30 years experience(Table 1). Advanced stage of malignancy, multiple site involvement or early relapse after treatments are the main discouraging factors that contribute to decreased survival of persons with grafts. The aim of this article is to highlight the increased risk of neoplasm and to suggest guidelines for early detection of cancer in renal transplant recipients.

Table 1. Number of Cancer Patients in our Center after Renal Transplantation between 1975-2004

Tumor type	No	Percentage
Kaposi's Sarcoma	19	32.2
Malignant Lymphoma	16	27.1
Skin		
Basal Cell Carcinoma	7	11.8
Squamous Cell Carcinoma	6	10.2
Urinary Bladder Carcinoma	2	3.4
Breast Carcinoma	2	3.4
Gastric Carcinoma	2	3.4
Renal Cell Carcinoma	2	3.4
Cervix Carcinoma	1	1.7
Acute Myeloid Leukemia	1	1.7
Acute Lymphoid Leukemia	1	1.7
Total	59	100

Skin Cancer

Skin cancers are the most common neoplasm after renal transplantation (Fuente et al., 2003). In renal transplant recipients, risk of developing a squamous cell carcinoma (SCC) or a basal cell carcinoma (BCC) was found to be

*Baskent University Faculty of Medicine [1]Department of Medical Oncology, [2]General Surgery , [3]Pathology Fevzi Cakmak Cad. 12. Sokak 7/5†Bahcelievler TR 06490 Ankara, Turkey *For Correspondence Fax: +90(312)2127572 e-mail: dryesimyildirim@yahoo.com*

increased 253 and 10 times, respectively, in the Netherlands (Hartevelt et al., 1990). Cumulative incidence of skin cancer varies between 10 to 48% 10 years after the transplantation (Fuente et al., 2003; Hartevelt et al., 1990). The mean time to diagnosis of skin cancer after transplantation varies between 36 and 67.7 months in different studies (Bahador et al., 2003; Zavos et al., 2003). In some transplant centers SCCs are more common than BCCs, but in our institution the incidence of BCC was higher (Haberal et al., 2002) (see Table 1). The risk factors for skin cancer are multifactorial. Intensity of sun exposure is the main factor contributing to skin cancers. In addition, old age at transplantation and male sex and duration of immune suppression are the independent risk factors (Marcen et al., 2003). Type of immune suppressive agent also could be an etiologic factor. In a recent study, cessation of azathioprine resulted in regression of skin lesions in renal transplant patients (Veroux et al., 2004). Human papilloma viruses (HPV), potentially oncogenic viruses, may be found in premalignant skin lesions like warts and actinic keratosis, as well as in both BCC and SCC (Dreno, 2003). Incidences of warts and actinic keratosis increase with the duration of immune suppression. In transplant patients skin cancers tend to be more aggressive and multiple at the time of initial diagnosis, with SCC and BCC often found together (London et al., 1995). Zavos et al found that skin cancer related mortality was 4.5% in their transplant center (Zavos et al., 2003). Therefore, all renal transplant patients should be aware of increased risk of skin cancer and any skin change should be considered important. For surveillance of patients, strict protective measures from sun exposure with hats, clothes are advisable. Also regular use of sunscreens may decrease incidence skin cancers.

Kaposi's Sarcoma

Kaposi's sarcoma (KS) with the 500-fold increased incidence than that of general population, is another common malignancy seen in recipients (Ziegler et al., 1984). One of the risk factors includes Mediterranean, Jewish, Black or Arabian ancestry (El-Agroudy et al., 2003). Patients received cyclosporin were at higher incidence of developing KS in our center (Haberal et al., 2002). Penn et al. suggested similar reports that explained increased incidence of KS with the use of cyclosporin Penn, 1991). Presence of anti-human herpes virus type-8 serology is another contributory factor (Cathomas et al., 1997). The average time between transplantation to diagnosis of KS was 15 to 24 months. and the mean age of patients was 41 to 45 years. Patients mostly represented with cutaneous involvement. Spontaneous regression was observed after cessation of immune suppressive drugs in most cases. However visceral involvement can be associated with mortality. Whereas Duman et al (2002) reported no deaths, Farge et al (1993) found a 21% mortality rate in their patients. For surveillance of transplant patients, anti-HHV-8 serology should be checked, especially in patients of Mediterranean, Jewish, Black or Arabian origin. Today the most effective way to decrease risk of KS is to decrease the immune suppressive dosage; also if possible cyclosporin doses could be tapered off in these patients.

Post-transplantation Lymphoproliferative Diseases

Post-transplant lymphoproliferative diseases (PTLD) associated with EBV infection are the second most common malignancy after solid organ transplantation (Penn, 1999). There are two peaks of incidence: the first year and late after transplantation, and the incidence of PTLD in renal transplant patients is 20 times higher than in general population (Opelz et al., 1993). The risk factors for developing PTLD are EBV seronegativity of the recipient, use of polyclonal antibodies (ATG and ALG) or monoclonal antibodies (OKT3), and donor positive recipient negative cytomegalovirus (CMV) serology (Danpanich and Kasiske, 1999; Alamartine et asl., 1996; Lauzurica et al., 2003). Most lymphomas originating from B cells have EBV markers. PTLD occurs following primary infection or reactivation of latent virus. Besides EBV serology, immune suppressive drugs like cyclosporin are also associated with early appearance of PTLD (Penn, 1991). CMV infection may activate EBV replication. In our center, the mean time to diagnosis was 87.5 months and most patients were in an advanced stage (Akcali et al., 2003). The mortality rate in PLTD is approximately 50% (Arican et al., 2001;Akcali et al., 2003; Zavos et al., 2003). For surveillance, recipients and donors should be checked for EBV seropositivity before transplantation. EBV and CMV serology should be followed up. In case of seroconversion early empirical antiviral treatment can be beneficial. Since decrease in immune competence following transplantation is the main step initiating PTLD, reduction of immune suppression whenever possible is crucial in renal transplant recipients.

Anogenital and Solid Organ Tumors

Anogenital cancers, another HPV associated carcinomas, are also increased frequency in transplant patients. As in the skin cancers, premalignant lesions like warts and condyloma accuminata should be treated before transplantation. The incidence of native kidney malignancies also increases in renal transplant recipients approximately 8 fold. In a recent study, it was suggested that early stage renal malignancies of recipients have comparable prognosis that of non-transplant patients (Grochowiecki et al., 2002). Recently a higher incidence of prostate cancer than expected was also reported (Agraharkar et al., 2004). Colorectal tumors an the important cause of cancer related mortality in general population. In renal transplant patients there is no increased risk, but those tumors that occur tend to be more aggressive (Saidi et al., 2003). Like colon cancer, breast cancer does not occur at increased incidence in renal transplant recipients but an increased incidence of benign breast disease especially in patients using cyclosporin has been described (Sangthawan et al., 2002).

The average age at the time of cancer development is approximately 50 years, most malignancies being observed at the 40th- 50th months after transplantation. Chronic

Table 2. Risk Factors for Neoplasia in Recipients

Older age at transplantation Male gender
Ancestry: Mediterranean, Jewish, Black or Arabian
Viral seropositivity: EBV,CMV,HHV-8
Premalignant lesions:
Warts, actinic keratosis, condyloma accuminata
Immune suppressive agents:
Azothioprine for skin cancers,
Cyclosporin for KS
ATG/ALG or OKT3 for lymphoma

immune suppression is again the main factor.

Recommendations for Screening

Risk factors for development of neoplasia after renal trransplantation are summarized at Table 2. These should clearly be taken into account in any screening program for renal transplant recipients. Table 3 summaries the screening recommendations of renal transplant recipients. Since skin cancer is the most common tumor associated with transplantation, it is advisable that visual examination of sun-exposed skin should be a part of regular follow-up. Dermatological examination is recommended every 6 months. Anogenital tumors are also frequent in renal transplant patients so we recommend annual pelvic examination. Population studies have demonstrated efficacy of Papanicolaou test in reducing cervical cancer mortalityand this should be a part of screening program for all women. Native kidney tumor has somewhat more common in recipients and annual abdominal ultrasound examinations are effective for detection of renal tumors. Since the risk of prostrate cancer increases steeply with age, we recommend annual digital rectal examination together with prostate determination of specific antigen (PSA) levels.

Conclusion

Malignancy is an important cause of mortality and morbidity after renal transplantation. Individuals with renal transplantation are at risk for developing malignancies. When malignancy presents with clinical symptoms the patients may have few therapeutic options. Thus, screening and surveillance for cancer would appear to be appropriate. In light of our experience over 30 years we would like to recommend screening guidelines in order to increase graft recipient survival.

Table 3. Cancer Screening Recommendations for Renal Transplant Recipients

Dermatological examination
Pelvic examination*
Papanicolaou test for woman**
PSA for men*
Abdominal ultrasound
Digital rectal examination*
Fecal occult blood test*
Self breast examination††
Mammography *

*: After 50 years of age**: After 40 years of age

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