Original Article The Eurasian Journal of Medicine Eurasian J Med 2016; 48: 33-6

Are We Late in the Diagnosis of Malignities Occurring in Solid Organ Transplant Patients? 11 Years' Experience

Solid Organ Transplatasyonlu Hastalarda Gelişen Malignitelerin Tanısında Geç mi Kalıyoruz? 11 Yıllık Deneyim

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Abstract

Objective: Our aim is to evaluate the frequency and characteristics of cancer in the population of patients with solid organ transplant who are under immunosuppressive medication. In this study we aimed to emphasize the importance of early diagnosis of cancer in solid organ transplant recipients. An aging population began to receive solid organ transplantation and survival times prolonged. But this had a cost and new problems came forward. Especially de novo cancers because of immunosuppressive therapy took notice. Risk of malignancy increases after organ transplantation and cancer incidence was about 2.3-3.1% in these patients including skin cancer, lung cancer, malign lymphoma, cervix cancer, kaposi sarcoma, and hepatobiliary cancer.

Materials and Methods: The files of 328 organ transplant recipients followed from January 2004 to April 2015 at Atatürk University Medical Faculty were retrospectively reviewed.

Results: Eight patients developed cancer (2.4%). There were six males and two females. Age at cancer diagnosis ranged from 42 to 79 years old with average of 55 years. The interval from solid organ transplantation to cancer diagnosis ranged from 6 months to 30 years. Among the patients, five were renal transplant recipients and two were liver transplant recipients. Four patients had stage IV disease, one patient stage IIIB, and three patients had stage I disease. For none of the patients a diagnosis with screening methods was used for cancer before any complaints of tumor emerged.

Conclusion: To diagnose cancer at early stages in solid organ transplant recipients, earlier and detailed cancer screening is very important. The association between diagnosis of cancer at early stages and prolonged overall survival time is well known. Detailed and careful evaluation for occult malignancies in pre-transplantation period is also important.

Keywords: Cancer, immunosuppression, screening, transplantation

Öz

Amaç: Amacımız solid organ transplantı olan, immunsupresif tedavi altındaki hastalarda gelişen kanser sıklığını ve özelliklerini değerlendirmektir. Bu çalışmada, solid organ transplant alıcılarında gelişen kanserlerin erken tanısının önemini vurgulamayı amaçladık. Yaşlanan nüfusla birlikte artan solid organ transplantı ile hayatta kalma süreleri uzamıştır. Fakat bu durum yeni maliyetler getirmiş ve yeni sorunlara neden olmuştur. Özellikle immunsupresif tedavilerin sonucunda de novo kanserler görülmeye başlamıştır. Organ nakli sonrası kanser riski artar ve en sık cilt kanseri, akciğer kanseri, malign lenfoma, serviks kanseri, kaposi sarkomu ve hepatobilier kanseri içeren bu grupta insidans %2,3-3,1'dir.

Gereç ve Yöntem: Atatürk Üniversitesi Tıp Fakültesi'nde Ocak 2004 ile Nisan 2015 tarihleri arasında takip edilen 328 organ transplant alıcısı dosyaları retrospektif olarak incelendi.

Bulgular: Hastaların sekizinde kanser gelişti (%2,4). Bunların altısı erkek ve ikisi kadındı. Kanser tanı yaşı 42 ile 79 arasında değişiyordu, ortalama yaş 55 idi. Kanser gelişimi ile solid organ nakli arasındaki süre 6 ay 30 yıl arasında değişmekteydi. Hastalar arasında beş böbrek transplant alıcısı ve iki karaciğer transplant alıcısı vardı. Hastaların dördünde Evre IV, bir hastada evre IIIB ve üç hastada evre I kanser tanısı vardı. Tümör kaynaklı herhangi bir şikâyetin ortaya çıkmasından önce hiçbir hasta için tarama yöntemleri ile kanser tanısı konmamıştı.

Sonuç: Solid organ transplant alıcılarında erken evrede kanser tanısı için ayrıntılı ve erken kanser taraması çok önemlidir. Erken tanı ve tedavi ile uzun süreli genel sağkalım arasındaki ilişki iyi bilinmektedir. Nakil öncesi dönemde okült maligniteler için detaylı ve dikkatli bir değerlendirme de önemlidir.

Anahtar Kelimeler: Kanser, immusupresyon, tarama, transplantasyon

This study was presented at 21st National Cancer Congress as a poster presentation, Antalya, Turkey, 2015.

Received: December 18, 2015 / **Accepted:** December 24, 2015

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DOI: 10.5152/eurasianjmed.2015.0087

Introduction

In recent years with the use of new technologies important advances achieved in solid organ transplantation. Thus, an aging population received transplantation and survival times of patients improved and prolonged. However, this prolongation brought new problems for both patients and physicians. Especially the long-term complications of immunosuppressive therapy draw attention. Providing a convenient environment for malignant cell proliferation, infection or reactivation of oncogenic viruses, and increasing cytokine levels by chronic antigenic stimulation may lead to impaired immune surveillance [1-3]. Some immunosuppressive drugs may also affect the intrinsic oncogenic properties of malignant cells [4]. Alcohol and tobacco use and acute rejection episodes are also risk factors [4]. Older age was significantly associated with increased risk of de novo malignancy in solid organ transplant recipients [5].

After organ transplantation, risk of malignancy increases about three to four fold compared to general population [6, 7]. An incidence rate about 2.3-3.1% has been reported for organ-transplant related malignancies [8, 9]. The most common malignancy observed in solid organ transplant recipients is non-melanoma skin cancer (NMSC) [10-12] and particularly in squamous cell carcinoma (relative risk 14-82) [13, 14]. Many etiologic factors such as ultraviolet radiation, human papillomavirus infection, genetics and immunosuppressive therapy play an important role in the occurrence of post-transplant NMSC [15, 16]. The International Society of Heart and Lung Transplantation (ISHLT) recently reported that among solid tumours, lung carcinoma is the second most common malignancy after skin carcinoma [17]. The incidence of malign lymphoma, cervix cancer, kaposi sarcoma and hepatobiliary cancer also increases in solid organ transplant recipients.

Our aim is to evaluate the frequency and characteristics of cancer among patients with solid organ transplant who are under immunosuppressive medication.

Patients and Methods

The files of 328 (8 cancers) organ transplant recipients followed from January 2004 to April 2015 at Ataturk University Medical Faculty were retrospectively reviewed. Eight patients developed cancer in the follow up period (2.4%). There were six males and two females. Age in the cancer diagnosis ranged from 42 to 79 years old with the median age of 55 years. The interval from solid organ transplantation to cancer diagnosis ranged from 6 months to 30 years. Among the patients, five were renal transplant recipients and two were liver transplant recipients. We could not obtain the complete medical historical data of one patient. Clinical symptoms included fever, vomiting, chest-abdomen pain, skin lesions, abdominal pain, haematuria, dyspnoea, and dysphagia. Four patients had stage IV disease, one patient stage IIIB, and three patients had stage I disease. While four patients died because of cancer, four patients are still alive and on follow-up program. None of the patients had a diagnosis with screening methods used in establishing cancer at early stages before any complaints of tumour emerged.

First patient was a 59-year-old male, who was diagnosed with stage IV non-small cell lung cancer at the 29th year of his immunosuppressive treatment for renal transplantation. Only palliative radiotherapy could be applied, and he died two months after the diagnosis without receiving any chemotherapy. Second patient was a 52-year-old male, who was diagnosed with large cell neuroendocrine carcinoma metastasis to liver at the first year of his renal transplantation, and he died just after cancer diagnosis before receiving any oncological treatment. Third patient was a 61-year-old male, who was diagnosed with squamous cell carcinoma of skin by an excisional biopsy performed from a lesion localized on his head-neck at the 18th month of his immunosuppressive treatment for renal transplantation. The patient is still on follow up after surgical excision for stage I disease. Fourth patient was a 52-year-old female, who was diagnosed with stage IIIB colon cancer at the 6th year of her liver transplantation. She has undergone right hemicolectomy due to acute abdomen and still at adjuvant chemotherapy program. Fifth patient was a 51-year-old male, who was diagnosed with low-grade papillary urothelial carcinoma of bladder at the 6th year of his renal transplantation. Bladder transurethral resection (TUR) was performed because of haematuria. The patient, whose local treatment was adequate, is still in 6th month of his follow up period. Sixth patient was a 70 year-old male, who was diagnosed with non-small cell lung cancer at the second year of his liver transplantation, and died five months after diagnosis only receiving one cycle of chemotherapy. Seventh patient was a 42-year-old male who was diagnosed with kaposi sarcoma on his follow-up period for renal transplantation. We could not reach his other medical history records. Eighth patient was a 66-year-old female who was diagnosed with local advanced oesophagus squamous cell carcinoma at the 9th month of her liver transplantation, and chemo radiotherapy was planned for her treatment. Three patients, who diagnosed at early stages, were examined for tumour related complaints. One patient had undergone surgery for acute abdomen and diagnosed with stage IIIB colon cancer. Patients who did not have tumour related complaints were diagnosed at advanced stages and died before receiving any curative oncological treatments. Overall survival times ranged from 0 to 8 months in patients who were diagnosed

Table 1. Clinical profiles of organ transplant recipients with solid malignancies

Patient No	Sex	Age	Time Interval	Complaint At Diagnosis	Stage	Survival Time	Outcome	Diagnosis
1	Male	59	367 months	Fever, vomiting	4	1 month	Died	Lung cancer
2	Male	52	6 months	Chest-abdomen pain	4	0 month	Died	NEC
3	Male	61	21 months	Skin lesion	1	4 months	Alive	Skin cancer
4	Female	52	67 months	Abdomen pain	3	8 months	Alive	Colon cancer
5	Male	51	56 months	Bleeding with urine	1	7 months	Alive	Bladder cancer
6	Male	70	33 months	Dyspnea	4	5 months	Died	Lung cancer
7	Male	42	Unavailable	Skin lesion	1	240 months	Died	Kaposi sarcoma
8	Female	66	9 months	Dysphagia	3	Not calculated	Alive	Esophagus cancer

NEC: neuroendocrine carcinoma

at advanced stages (stage III-IV). The patients who were diagnosed at early stages (stage I) are still alive and the time passed from diagnosis is 4 months for one patient and 7 months for the other one. The other stage I patient whose clinical records could not be reached completely, had a survival time of 240 months (Table 1).

Discussion

Our results show that our transplant patients need a comprehensive and detailed cancer-screening program in our region. De novo cancer risk increases with immunosuppressive treatment for solid organ transplantations. These patients are normally under routine control as a part of organ transplant follow up. However, for the diagnosis of cancer at early stages, earlier and detailed cancer screening with a multidisciplinary approach is required.

For early diagnosis of skin cancers, these patients should undergo periodic skin examinations and various clinical and environmental factors should be assessed as part of their follow-up [18]. When a suspicious lesion is observed, biopsy threshold may be lower compared to normal population and the importance of sun avoidance and protection should be emphasized.

In a study, it was suggested that cancer screening should be a part of the yearly evaluation of solid organ recipients and should include chest x-ray, oral and dermatologic examination, screening colonoscopy, mammography and Papanicolaou test for women, and prostate specific antigen (PSA) level measurements for men over the age of 40 years. These are important especially in patients with prior history of nicotine abuse and malignancy, and older age [19]. For aerodigestive malignities, surveillance strategies did not give result with earlier diagnosis, but in cases with higher risk rates physicians should be more suspicious [20].

The time interval between the solid organ transplantation and cancer diagnosis was reported to be longer than 5.08 years [21]. This time interval was 8 years after transplantation if skin cancer was excluded [22, 23]. In our patients, this time interval ranged from 6 months to 30 years, in accordance with the literature.

The association between the diagnosis of cancer at early stages and prolonged overall survival time is well known. This is also acceptable for cancers in solid organ recipients. In our study, we observed that overall survival times were really shorter in patients who were diagnosed at advanced stages compared to early diagnosis. These patients could not live enough to get any oncological treatments for their diseases. Contrary, the patients who were diagnosed at early stage of cancers got adequate treatment and two of them are still on follow-up.

In conclusion, de novo cancer risk increases with immunosuppressive treatment for solid organ transplantations. These patients are normally under routine control as a part of organ transplant follow up. Early diagnosis of malignities will contribute to survival thanks to screening programs. Another important point is the detailed and careful evaluation of these patients for occult malignancies in pre-transplantation period. Studies are needed to determine the factors to decrease the cancer occurrence in solid organ transplant recipients, and to constitute consensus on screening programs under immunosuppressive medications.

Ethics Committee Approval: Ethics committee approval was not obtained due to the retrospective nature of the study.

Informed Consent: Because of the retrospective design of the study we did not obtain written informed consent from patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.T.; Design - M.B.; Supervision - S.B.T.; Resources - E.C.; Materials N.Y.; Data Collection and/or

Processing - S.A.; Analysis and/or Interpretation - M.N.A.; Literature Search - E.K.; Writing Manuscript - M.S.; Critical Review - B.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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