Post-transplant malignancies in pediatric liver transplant recipients: Experience of two centers in Turkey

Miray Karakoyun[1], Şebnem Önen[2], Maşallah Baran[3], Murat Çakır[4], Çiğdem Ömür Ecevit[5], Murat Kılıç[6], Mehmet Kantar[7], Serap Aksoylar[7], Funda Özgenç[8], Sema Aydoğdu[8]

[1]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Tepecik Training and Research Hospital, İzmir, Turkey
[2]Department of Pediatrics, Ege University School of Medicine, İzmir, Turkey
[3]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Katip Celebi University School of Medicine, İzmir, Turkey
[4]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Karadeniz Technical University School of Medicine, Trabzon Turkey
[5]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Prof. Dr. Behçet Uz Children's Hospital, İzmir, Turkey
[6]Department of Transplantation and General Surgery, Kent Hospital, İzmir, Turkey
[7]Department of Pediatric Oncology, Ege University School of Medicine, İzmir, Turkey
[8]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ege University School of Medicine, İzmir, Turkey

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ABSTRACT

Background/Aims: *A liver transplant is the preferred treatment for patients with end-stage liver disease, as it usually results in long-term survival. However, due to the use of chronic immunosuppressive therapy, which is necessary to prevent rejection, de novo cancer is a major risk after transplantation. The aim of this study was to assess the incidence of post-transplant malignancies in children after liver transplantations.*

Materials and Methods: *The study group consisted of 206 liver transplant recipients, with no history of cancer, including hepatocellular carcinoma, in two liver transplantation centers in Turkey between 1997 and 2015. Data were obtained from patient's data chart.*

Results: *In the study group, de novo cancer was diagnosed in 13 of the 206 patients. Post-transplant lymphoproliferative disease (PTLD) occurred in seven (53.8%) patients and other malignancies in six of the 13 patients. The types of PTLD were as follows: B-cell origin (n=2), Epstein-Barr virus (EBV)-related (n=2), T-cell origin (n=1), and Hodgkin's lymphoma (n=2). EBV DNA was isolated from seven patients, three of whom developed PTLD. The others developed Kaposi's sarcomas, Burkitt's lymphomas, cutaneous large-cell lymphomas, Hodgkin's lymphomas, and liver sarcomas.*

Conclusion: *After transplantation, immunosuppressive treatment is unavoidable, increasing the risk of malignancies. However, a close follow-up and periodic screening can reduce cancer-related mortality and morbidity.*

Keywords: *Immunosuppression, malignancy, liver transplantation*

INTRODUCTION

Orthotopic liver transplantation is the preferred treatment option in end-stage renal diseases. However, persistent immunosuppression and a high risk of malignancies are complications of liver transplantation (1-6). Children are one of the highest risk groups for post-transplant cancer. The risk of cancer in pediatric transplant patients is about two to three times greater than that in the general population (7). The incidence of malignancy among pediatric transplant recipients is 10 times higher than that of non-transplant patients in the same age group (8).

Immunosuppression is associated with an increased risk of malignancies due to impaired immunosurveillance and direct damage of host DNA (2,9). Reduced immunological surveillance is thought to allow atypical cells to survive and proliferate. In addition, the direct carcinogenic effects of some agents, together with immunosuppression, enable oncogenic viruses, such as the Epstein-Barr virus (EBV), to proliferate. Immunosuppressive agents, such as azathioprine and cyclosporine, are strongly associated with cutaneous malignancies, and tacrolimus is associated with the risk of solid organ tumors (6,9,10). The mechanisms underlying the association of different tumor types with specific immunosuppressive agents are unclear. Post-transplant malignancies are the main cause of death in 5%-16% of liver transplantation patients. The estimated incidence of de novo malignancy is 20% after 10 years and almost 30% after 20 years of chronic immunosuppression. Death is due to various diseases, such as lymphoma/post-transplant lymphoproliferative disease (PTLD), skin cancers, and various solid organ tumor types (1,11-16).

Address for Correspondence: **Miray Karakoyun** *E-mail:* **miraykarakoyun@hotmail.com**
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The aim of this study was to evaluate the prognosis and prevalence of de novo malignancy in a pediatric population after pediatric solid organ transplantation.

MATERIALS AND METHODS

The study group consisted of 206 pediatric liver transplant patients, with no history of cancer, including hepatocellular carcinoma, who underwent a liver transplantation at two centers in Turkey between 1997 and 2015. Data were obtained from patient's data chart. The immunosuppressive regimen consisted of calcineurin inhibitors (sirolimus, rapamune, Phizer, Belgium) in combination with steroids, with or without azathioprine, mycophenolate, or cyclosporine (Sandimmun, Novartis Farma SA, France). Cyclosporine was the first-line drug until 2004. Thereafter, it was replaced with tacrolimus (prograf, Astellas Pharma, France) in accordance with the immunosuppressive protocol at our center.

Liver function tests and routine blood tests were performed, and the level of immunosuppression was determined weekly for the first 3 months and then once every 3 months for the first year. In symptomatic patients, further tests, such as tumor markers, sedimentation, computed tomography, biopsy, and viral serology were conducted. The diagnosis of malignancy was established by histological examination of a biopsy or a surgical procedure. Data were collected on the type of malignancy, histopathological features, immunosuppressive regimen, and patient survival.

The study was approved by the local scientific ethics committee of our medical faculty. Informed consent forms were signed by all the patients in the study.

Statistical analysis

Descriptive statistics were used to describe continuous variables (mean, median, and standard deviation). The X^2 test was used for categorical variables. Statistical significance was accepted at 0.05. All the statistical analyses were performed using MedCalcx Software (Ostend, Belgium, https: medcalc.org; 2013) version 12.7.7.

RESULTS

Six patients were excluded from the study due to malignancies diagnosed before transplantation. Among the 206 cases included in the study, 105 were boys and 101 were girls. The mean age was 5.4±5.1 years at the time of transplantation. Re-transplantation was performed in two of the 206 patients due to cirrhosis secondary to bile duct complications. Forty-eight patients were treated with cyclosporine, 140 with tacrolimus, and 18 with sirolimus.

De novo cancers were diagnosed in 13 (6.3%) of the 206 liver transplant patients (male/female [M/F], 7/6). The mean time to a cancer diagnosis was 35.6±26.5 months after transplantation. Four of these patients were cadaveric transplant recipients, and the other nine were living relative donor recipients. The primary diagnoses were biliary atresia, progressive familial intrahepatic cholestasis (PFIC), tyrosinemia, autoimmune hepatitis, fulminant hepatic failure, and congenital hepatic fibrosis (Table 1,2). All the patients received cyclosporine as the first-line treatment until 2004. Regarding the incidence of malignancy before and after 2004, malignancies were detected in 2.08% of patients who received cyclosporine and in 8.5% of patients who received tacrolimus. No cases of malignancy were found among the patients treated with sirolimus. Throughout the study period, 7.6% of the patients who developed malignancies had been treated with cyclosporine and 92.3% had been treated with tacrolimus.

Seven (53.8%) patients developed PTLD (M/F, 2/5). In all cases, PTLD originated in the small intestine. The types of PTLD were as follows: B-cell origin (n=2), EBV related (n=2), T-cell origin (n=1), and Hodgkin's lymphoma (n=2). All the PTLD patients had received tacrolimus. Among the PTLD patients, 42.8% of cases were associated with primary EBV infection or EBV reactivation (n=2). Two patients with positive EBV DNA also had positive cytomegalovirus (CMV) DNA. In the study, 42.8% of the children with PTLD had been treated with reduced immunosuppression and rituximab, and 15.3% had received chemotherapy. One of these patients died. Two (15.3%) patients who were diagnosed with Kaposi's sarcoma associated with human herpes virus-8 (HHV-8) infection survived after radiotherapy and reduced immunosuppression. One patient with positive EBV DNA developed a liver sarcoma. The patient who was treated with tacrolimus received chemotherapy. In all the patients, the immunosuppressive treatment protocol was changed to sirolimus. One of the patients died 1 month after the diagnosis, and one patient died 2 years after the diagnosis. No recurrence was noted in any of the other patients.

The average follow-up period after the diagnosis of a malignancy was 2.8 years. The characteristics of the patients who developed post-transplant malignancies are provided

Table 1. Features of the patients who developed PTLD

Age at Tx, years	Primary diagnosis	Sex	Oncologic diagnosis	Diagnosis time, months	Rejection	EBV	Immunosuppression	Prognosis	Pre-transplant EBV serology
6	Congenital hepatic fibrosis	M	PTLD	60	No	Positive	Tacrolimus	Alive	Positive
1	Biliary atresia	F	PTLD	36	No	Negative	Tacrolimus	Alive	Negative
11	Autoimmune hepatitis	F	PTLD	96	No	Positive	Cyclosporine	Alive	Positive
9	Fulminan Hepatitis A	F	PTLD	7	N	Negative	Tacrolimus	Alive	Positive
1	Bile acid synthesis defect	F	PTLD	24	Yes	Negative	Tacrolimus	Alive	Negative
3	PFIC	M	PTLD	12	No	Negative	Tacrolimus	Died	Negative
4	Biliary atresia	F	PTLD	7	No	Negative	Tacrolimus	Alive	Negative

PFIC: progressive familial intrahepatic cholestasis; PTLD: post-transplant lymphoproliferative disease; EBV: Epstein-Barr virus; M: male; F: female; Tx: transplantation

Table 2. Features of the patients who developed post-transplant solid organ malignancies

Age at Tx, years	Primary diagnosis	Sex	Oncologic diagnosis	Diagnosis time	Immunosuppression	Malignancy treatment	Prognosis
1	Tyrosinemia	F	Kaposi	36	Tacrolimus	Radiotherapy	Alive
1	BA	F	Burkitt's lymphoma	60	Tacrolimus	Died before starting treatment	Died
1	BA	F	Liver sarcoma	24	Tacrolimus	Imatinib mesilat	Alive
1	BA	M	Hodgkin's lymphoma	60	Tacrolimus	Cyclophosphamide, vincristine, prednisolone, procarbazine	Alive
7	BA	F	Cutaneous lymphoma	60	Tacrolimus	Cyclophosphamide, vincristine, prednisolone, procarbazine	Alive
2	BA	E	Kaposi	30	Tacrolimus	Radiotherapy	Alive

BA: biliary atresia; F: female; M: male

in Table 1, 2. The development of malignancies was not significantly associated with age or sex. However, it was significantly associated with tacrolimus treatment and other immunosuppressive regimens (sirolimus and cyclosporine).

DISCUSSION

Pediatric solid organ transplant recipients have a high risk of transplant-associated malignancies due to the destruction of the immune system, carcinogenic exposure, and viral stimulation due to long–term immunosuppressive treatment, which is capable of initiating carcinogenesis. Reduction in immunosuppressive drugs' level, viral prophylaxis, elimination of environmental risk factors, and early detection can reduce malignancy-related mortality and morbidity (16). Transplant recipients have a 28 to 49 times higher risk of developing secondary malignancies compared with the general population (17). The primary immunosuppressive regimen used in our center is a combination of a calcineurin inhibitor and prednisone, with or without mycophenolate mofetil. Previously, cyc-

losporine was used as a calcineurin inhibitor, but this has now been replaced with tacrolimus.

Post-transplant lymphoproliferative disease is one of the most frequent post-transplant neoplastic diseases (18). EBV infection and immunosuppression therapy are the most important risk factors for PTLD. The incidence of PTLD depends on several factors: the age of the transplant recipient, duration of post-transplant immunosuppression or types of immunosuppressants used, and EBV infection (18,19). Reduction or cessation of immunosuppression is the most common initial approach for the development of PTLD. The cessation of immunosuppression as an approach was first reported by Starzl et al. (20) in 1984, and it has been practiced widely ever since (21,22). The hypothesis underlying this strategy is that the recovery of the host's immune system will lead to the induction of cytotoxic T lymphocytes against EBV, with subsequent control of EBV-driven B-cell proliferation. Another approach is the use of mammalian target of rapamycin (mTOR) inhibitors, such as rapamycin (sirolimus). The mTOR inhibitors were shown to exert potent antiproliferative effects on in vitro PTLD-derived cell lines (23,24). They also inhibited the growth of solid tumors in a PTLD mouse model, without significantly compromising graft rejection (23,24). In literature, PTLD has been reported to occur months or years after transplantation. The experiences of multicenter clinical studies in the European transplant centers support the use of mTOR inhibitors in the management of PTLD following renal transplantation, with a reported PTLD incidence of 1%-10% in adults and 9.7% in children (19,25,26). In our study, 13 (6.3 %) of the 206 pediatric patients developed de novo malignancies post-transplantation, and the mean time to the occurrence of PTLD was 37.7±26.6 months. In our series, the incidence of PTLD was 3.4%. Among the patients in whom malignancies occurred, 7.6% had received cyclosporine and 92.3% had received tacrolimus. We changed the treatment in all these patient cases to sirolimus.

Recent studies have reported that PTLD developed with all immunosuppression regimens, with the exception of high-dose steroids and tacrolimus (27,28). According to a study by Farge et al. (29), four patients who developed Kaposi's sarcoma had visceral involvement. These patients failed to show at least partial regression of the neoplasia, except one patient in whom Kaposi's sarcoma was diagnosed in the autopsy. In all the patients with Kaposi's sarcoma, a polymerase chain reaction (PCR) assay detected HHV-8 DNA in histological sections (29). In our study, two patients were diagnosed with Kaposi's sarcoma and both were HHV-8 positive. One of the most important adverse effects of immunosuppression in all solid organ transplant recipients is an increased risk of solid organ malignancy (30,31). We detected solid organ tumors in 46.2% of our patients with malignancy.

In conclusion, liver transplantation is a life-saving treatment in children, but long-term immunosuppressive treatment, which is necessary post-transplantation, can result in the development of malignancies. The incidence of malignancy is markedly higher in transplant patients than in the normal population, with EBV infections posing a significant problem in the children population. However, a close follow-up and periodic screening can reduce cancer-related mortality and morbidity in this patient population. The smallest possible dose of immunosuppressive drugs capable of preventing organ rejection should be administered, with the aim of combating future malignancies.

Ethics Committee Approval: Ethics committee approval was received for this study from Ethics Committee of Tepecik Training and Research Hospital (Decision No: 27).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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