original article

De novo malignancies after liver transplantation: a single-center experience

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BACKGROUND AND OBJECTIVES: The recipients of liver transplantation (LT) are subjected to lifelong immunosuppression with its many drawbacks. De novo and recurrent malignancy in transplant recipients are attributed to attenuation of immunosurveillance. In the present study, we present our experience with de novo malignancies encountered after both deceased and living donor liver transplantations.

DESIGN AND SETTING: Retrospective study of patients referred to LT center between April 2001 and January 2010

PATIENTS AND METHODS: Various data were collected including type of malignancy and histopathologic features, immunosuppression regimen, and patient survival.

RESULTS: Of 248 LT procedures performed in 238 patients (10 retransplants), 8 patients (3.4%) developed de novo post-LT malignancies. De novo malignancies included post-LT lymphoproliferative disorders (PTLD) in 5 patients who were all Epstein-Barr virus (EBV) positive, and who were treated successfully with anti-CD20 monoclonal antibody therapy, reduction of immunosuppression, and control of EBV activity; urinary bladder cancer in 1 patient who was treated with radical surgical resection and chemotherapy but died of bone and lung metastasis within 1 year of diagnosis; endometrial carcinoma in 1 patient who was treated with radical surgical resection; and Kaposi sarcoma in 1 patient who was successfully treated with surgical excision and reduction of immunosuppression.

CONCLUSION: EBV-associated PTLD is the most frequently encountered de novo malignancy after LT and is easily treatable by chemotherapy and reduction of immunosuppression.

Liver transplantation (LT) is a well-established procedure for patients with acute and chronic liver failure. Many centers achieve patient and graft survival rates exceeding 90% in 1 year. However, the recipients of LT are subjected to lifelong immunosuppression with its many drawbacks.[1] De novo and recurrent malignancy in transplant recipients are attributed to attenuation of immunosurveillance.[2]

In recent years, de novo malignancy following LT has been increasingly reported,[3-7] and is suggested as a major cause of mortality in this population.[8,9] In 1968, Starzl was the first to predict an increased incidence of de novo malignancies in immunosuppressed organ transplant recipients and confirmed it shortly thereafter.[10] Single-center reports[11,12] have shown increased incidences of certain types of post-transplantation de novo malignancies, principally those linked to a viral cause. Estimates of developing de novo malignancies range from 4.1% to 16%, depending on the type and demographics of the transplant population, length of follow-up, and the era in which transplantations were performed.[13]

PATIENTS AND METHODS

A total of 238 patients underwent 248 LTs (169 deceased donor liver transplantation [DDLT] and 79 living donor liver transplantation [LDLT]) procedures (10 retransplants) during a 9-year period between April 2001 and January 2010. Collected data were reviewed for age at the time of diagnosis of malignancy, cause of liver disease, interval from LT to diagnosis of malignancy, type of malignancy and histopathologic

Table 1. Timing of presentation of malignancies after orthotopic liver transplantation.

Case number	Type of malignancy	Timing of presentation after transplantation (months)
1	De novo PTLD	19
2	De novo PTLD	64
3	De novo bladder cancer	63
4	De novo endometrial cancer	16
5	De novo Kaposi sarcoma	8
6	De novo PTLD	2
7	De novo PTLD	2
8	De novo PTLD	20

PTLD: Post-transplant lymphoproliferative disorder.

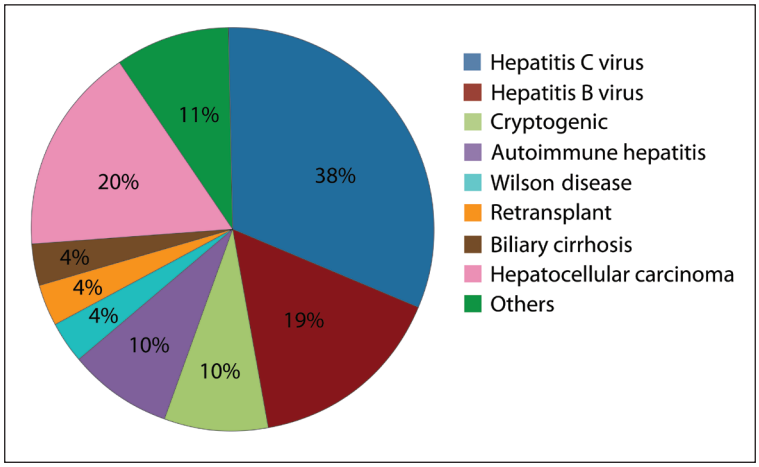

Figure 1. Indications for liver transplantation.

features, immunosuppression regimen, and patient survival. The primary immunosuppressive regimen was not significantly different among the cases and included a triple regimen of tacrolimus in combination with mycophenolate mofetil and prednisolone. The target blood level of tacrolimus was 8 to 10 μg/L immediately after surgery and aimed at 6 to 8 μg/L 6 months from transplantation. The dose of prednisolone was tapered to 5 mg daily 6 weeks post-transplant, and the withdrawal was achieved after 3 months. The diagnosis of de novo malignancy was confirmed by histology in all the cases. All the patients had undergone routine pre-transplant tumor surveillance with chest radiography, mammography, and computed tomography within 1 year of transplant.

RESULTS

The overall male/female ratio was 152/96, the adult/pediatric ratio was 229/19, and the median age was 48 years (range 1.5-70). Over a 9-year period, 8 patients (3.4%) developed de novo post-LT malignancies at a median interval of 3.6 years from the time of LT and were identified through a search of a computerized hospital database. Among the study population were 5 men and 3 women. **Table 1** shows the type of de novo malignancy developed and its timing in relation to the LT. The episodes of rejection were not higher in patients who developed de novo malignancies. Immunosuppression was decreased in all the patients who were diagnosed with post-transplant lymphoproliferative disorders (PTLDs). Among the cases in the study population, chronic hepatitis C and hepatitis B were the leading causes of liver disease. Indications for LT are shown in **Figure 1**.

In the DDLT group, the median operating time was 7 hours (range 4-19), the median blood transfusion was 6 U (range 0-55), and the median hospital stay was 16 days (range 6-206). After a mean follow-up period of 2.7 years (range 1-9), the overall patient and graft survival rates were 81.5% and 79.7%, respectively.

In the LDLT group, the median operating time was 11 hours (range 7-17), the median blood transfusion was 6 U (range 0-65), and the median hospital stay was 16 days (range 7-266). After a mean follow-up period of 3.6 years (range 1-9), the overall patient and graft survival rates were 78.5% and 73.5%, respectively. Biliary complications were significantly higher in the LDLT group compared with the DDLT group at 34.2% vs 5.9%, respectively ($P<.05$). Vascular complications were significantly higher in LDLT group compared with the DDLT group at 13.9% vs 6.5%, respectively ($P<.05$).

De novo malignancies included PTLD in five patients who were all Epstein-Barr virus (EBV) positive; two pediatric patients presented with nasopharyngeal masses; and two adults presented with abdominal masses. One patient presented with upper gastrointestinal tract bleeding; the upper endoscopy showed a duodenal mass and the histopathology showed diffuse large B-cell lymphoma. All the five patients had B-cell type PTLD, and all of them were successfully treated with anti-CD20 monoclonal antibody therapy (rituximab), reduction of immunosuppression, and control of EBV activity. Urinary bladder cancer was diagnosed in 1 patient who was treated by radical surgical resection and chemotherapy, but unfortunately the patient died of bone and lung metastasis within 1 year of diagnosis. One patient developed endometrial carcinoma and was treated with radical surgical resection, but unfor-

tunately died of aggressive tumor recurrence 1 year from the time of diagnosis. Kaposi sarcoma was diagnosed in one patient who was successfully treated with surgical excision and reduction of immunosuppression (**Figure 2**). A myeloproliferative disorder (MPD) was diagnosed in one patient who had LT for Budd-Chiari-related liver cirrhosis. This patient was being closely monitored for the possibility of developing acute leukemia post-transplant.

DISCUSSION

The reported incidence of de novo malignancies after LT has ranged from 4% to 16%, depending on the length of the follow-up, age distribution of the patients, and nature of the immunosuppressive regimen.[10] In this study involving 238 recipients of LT over a 9-year period, de novo malignancy was diagnosed in 8 patients (3.4%) at a median interval of 3.6 years from the time of LT. Herrero et al in 2005 reported after a median follow-up of 65 months the highest incidence of post-transplant malignancies at a rate of 26% (49 patients) in a cohort of 187 LT recipients.[14] Finkenstedt et al from Austria reported an incidence of 12.3% of de novo malignancies in a series of 779 consecutive LT recipients.[15] Moreover, Jain et al reported that in their large cohort of 1127 LT patients over a 10-year period, 6% developed de novo malignancies.[16] Only Saigal et al reported a lower incidence rate of 2.6%, but they did not include lymphoid tumors.[17] A plausible explanation for the discrepancies in the reported incidence rates includes the differences in the size of the population studies and the length of follow-up. The real incidence and factors increasing the risk are not completely defined. However, immunosuppression appears to be a major risk factor associated with the development of this serious complication.[3] Exogenous immunosuppression believed to be related to suppression of host defences (primarily T cells, which normally provide surveillance and protection from outgrowth of viral-infected cells).[10] This supports the finding that reduction or withdrawal of immunosuppression leads to regression of PTLD in many cases.[18] LT for alcohol-related liver disease was associated with a high probability of developing de novo cancers.[19] Interestingly, in our series, we had no LT for alcoholic liver disease because of the tradition of the study population. The lower incidence of post-transplant malignancies in the present study is not related to the length of the follow-up period as the median follow-up is 3.6 years, which is comparable to other studies.

In our series, PTLD was the most common type of post-transplant malignancy and all the patients were EBV positive, a finding that is consistent with the University of Pittsburgh experience.[10] These findings are in accordance with previous studies, which have shown that PTLD usually presents within the first or second year after LT.[20] We reported two pediatric patients in our series with PTLD. The Pittsburgh series included pediatric recipients, in whom the frequency of PTLD has been reported to be higher than adults.[21]

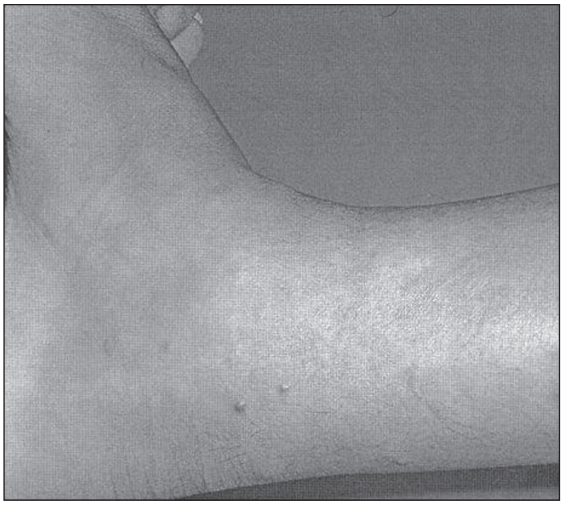

Figure 2. Kaposi sarcoma in the right leg which was successfully treated by surgical excision and reduction of immunosuppression.

The largest nonlymphoid class of de novo malignancies is skin cancer. The pathophysiological cause of skin cancer development is multifactorial, with sun exposure, race, age, and viral causes implicated.[10] Kaposi sarcoma is a viral-associated skin cancer, which is significantly higher in the transplantation population than in the general population.[22] The reported incidence of Kaposi sarcoma in the transplant population ranges from 0.18% to 6%. Marqués et al reported an incidence of 4% of Kaposi sarcoma in their large cohort of 528 patients undergoing LT with a mean follow-up of 2400 days.[23] In our study we had one patient diagnosed with Kaposi sarcoma who was successfully treated by surgical excision and reduction of immunosuppression.

Primary MPDs are a leading cause of Budd-Chiari syndrome, which frequently results in liver failure requiring LT. Acute leukemia occurred in 10% of patients with MPD.[24] There was a concern that immunosuppression after LT increased this risk.[25] The King's College group reported that of six patients with MPD, one patient developed acute leukemia after LT.[26] Dousset et al reported two patients with MPD and Budd-Chiari syndrome who had LT and developed leukemia (29 and 31 months) after LT.[27] In our series, we had one patient with MPD and Budd-Chiari syndrome; he had LT re-

cently and has not developed acute leukemia in the short period of follow-up (8 months).

In conclusion, PTLD remains the most common de novo malignancy in post-LT patients. The increased incidence of de novo malignancies in LT recipients in comparison to the general population is because of known preexistent risk factors for cancer, greater rate of chronic viral infection, and long-term exogenous immunosuppression. This mandates careful long-term screening programs to help in early diagnosis of the disease.

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