Posttransplantation De Novo Tumors in Liver Allograft Recipients

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De novo cancers occurred after transplantation in 8,008 organ allograft recipients, who developed 8,531 different types of malignancy. Three hundred twenty-four liver recipients developed 329 cancers. There were striking differences in the patterns of neoplasms observed when these were compared with 7,200 tumors that occurred in renal allograft recipients. Lymphomas were much more common in liver allograft recipients (57% v 12% of all tumors), whereas skin cancers (39% v 15%), carcinomas of the cervix (4% v 1%), renal tumors (4% v 1%), and vulvar carcinomas (3% v 0.6%) were more common in renal allograft recipients. The high incidence of lymphomas is related partly to the more intense immunosuppressive therapy administered to hepatic allograft recipients and partly to the large percentage of pediatric patients among them. The intense immunosuppression also accounts for the much shorter induction times of lymphomas (mean, 15 v 46 months; \( P < .001 \)) and nonlymphomatous tumors (mean, 27 v 72; \( P < .001 \)) in liver compared with kidney recipients. The longer follow-up of renal recipients probably accounts for the higher incidence of the other tumors that tend to appear relatively late after transplantation. A remarkable feature was the high incidence of allograft involvement by lymphoma (44%). Complete remissions after treatment occurred in 11 of 28 patients in whom the lymphoma was confined to the allograft. A few tumors in liver recipients were related to the underlying disease for which transplantation was performed: hepatomas in patients who underwent transplantation for hepatitis B cirrhosis and colon carcinomas or cholangiocarcinomas in patients who underwent transplantation for chronic ulcerative colitis with sclerosing cholangitis. A surprising finding was the development of four leiomyosarcomas, three occurring in the allograft itself, in pediatric liver recipients.

Materials and Methods

Data collected by the Cincinnati Transplant Tumor Registry (CTTR) from the fall of 1968 through December 1994, were analyzed. Statistical analyses included the paired student's \( t \)-test. A two-tailed \( P < .05 \) was considered significant.

Results

Overall, 8,531 types of cancer occurred de novo after transplantation in 8,008 organ transplant recipients. The patients included 6,707 who received kidney allografts and 729 heart, 324 liver, 145 bone marrow, 44 pancreas, 28 combined heart and lung transplantsations, 26 lung, 4 upper-abdominal organ “clusters,” and 1 small bowel allograft. The most common neoplasms in the overall series were cancers of the skin and lips (3,121 cases), lymphomas (1,444 cases), carcinomas of the lung (476 cases), Kaposi's sarcoma (345 cases), carcinomas of the uterus (338 cases), colon and rectum (301 cases), kidney (296 cases), breast (267 cases), head and neck (241 cases), vulva and perineum (217 cases), urinary bladder (190 cases), unknown primary site (186 cases), leukemias (164 cases), hepatobiliary carcinomas (146 cases), carcinomas of the prostate (136 cases), thyroid gland (106 cases), and sarcomas.
(other than Kaposi’s sarcoma) (100 cases). The malignancies that occurred in hepatic allograft recipients are listed in Table 1. Table 2 shows a very different pattern of neoplasms in hepatic compared with renal allograft recipients. Of note is the very high incidence of lymphomas in the former group (37% vs 12%) and the low incidences of carcinomas of the cervix, vulva and perineum, and renal tumors.

**Lymphomas**

Lymphomas by far comprised the largest group (57%). The tumors occurred in 94 males and 94 females, and in one instance the gender of the patient was not stated. The patients’ ages were not stated in 17 instances. In the other 172, they ranged from 5 months to 70 years (average 27, median 24 years) at the time of transplantation. Seventy-four patients (43%) were in the pediatric age group (18 years and younger). Of 169 patients with adequate data, 118 (70%) received triple therapy (cyclosporine, azathioprine and prednisone), 44 (26%) received double therapy (cyclosporine and prednisone), 5 (3%) received FK506-based regimens, and 2 (1%) received azathioprine and prednisone. The corresponding figures in renal transplant recipients were very different—31%, 9%, <1%, and 51%, respectively. A total of 20 patients in the various subgroups received FK506. Antilymphocytic agents-ALG (21), Om3 (53), or both (24) were used in a total of 98 patients (58%). This compares with 46% usage of antilymphocyte preparations in renal recipients with lymphomas in the CTTR. Lymphomas appeared from 3 weeks to 159.5 months after transplantation (average, 15; median, 6 months). This compared with a period of 1 week to 305.5 months (average 46, median 26 months) in renal transplant recipients. These differences are statistically significant ($P < .001$).

Morphologically and immunologically the lymphomas were a heterogeneous group, reflecting the diverse classification systems in use since the CTTR started to function. They are listed in Table 3. The organs affected by lymphoma were listed in 185 cases. Of these, 88 (48%) involved a single organ or site. The most common locations are listed in Table 4.

Extranodal disease occurred in 113 patients (61%). Of note in the 185 patients was the frequent involvement of the allograft that was affected in 82 instances (44%). In 35 patients (19%) the intestines, most often the small bowel, were affected. In some patients the presenting feature was generalized periton-
Table 3. Types of Lymphoma

<table>
<thead>
<tr>
<th>Type of Lymphoma</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTLD</td>
<td>77</td>
</tr>
<tr>
<td>B-cell lymphoma</td>
<td>58</td>
</tr>
<tr>
<td>Lymphoma (type not specified)</td>
<td>21</td>
</tr>
<tr>
<td>Large cell lymphoma</td>
<td>15</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>B-cell hyperplasia</td>
<td>4</td>
</tr>
<tr>
<td>Plasmacytomas</td>
<td>3</td>
</tr>
<tr>
<td>T-cell lymphomas</td>
<td>3</td>
</tr>
<tr>
<td>Small cell lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: PTLD, posttransplantation lymphoproliferative disease.

Tissues caused by perforation of an intestinal lymphoma. The tonsils and/or adenoids were involved in 20 patients (11%), mostly in the pediatric age group. The central nervous system was involved in only 18 patients (10%), mostly in patients with widespread disease.

Thirty-two patients received little or no treatment. In 19 instances, the patients died of the lymphoma and/or from other causes and the diagnosis was only made at autopsy examination. In another 13 patients no treatment was attempted, because their condition was terminal.

Table 4. Most Common Sites Affected by Lymphoma

<table>
<thead>
<tr>
<th>Organ/Site Affected</th>
<th>Localized (n = 88)</th>
<th>Widespread (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
</tr>
<tr>
<td>Allograft</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Bowel</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Tonsils/adenoids/pharynx</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Stomach</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Kidney</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Spleen</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Treatment of the lymphomas involved one or more of the following measures: reduction or cessation of immunosuppressive therapy, excision including retransplantation, localized radiation therapy, acyclovir or ganciclovir administration, chemotherapy, immunotherapy with agents including interferon-alpha, immune globulin and monoclonal anti-B-cell antibodies. The type of treatment administered was not recorded in 20 patients.

Reduction or cessation of immunosuppressive therapy carried a price. Graft failure from acute or chronic rejection occurred in seven patients, five of whom had complete remissions of their lymphomas. One of the seven died of liver failure and sepsis after 5 months. The other six required retransplantation, of whom one died intraoperatively, and a second died of fulminant hepatic failure of the new graft 5 days postoperatively. Of the four remaining patients, one died of failure of the second transplant 6 months after reoperation, and three are alive at 6.5, 11, and 26 months, respectively, after reoperation.

Of particular interest are 28 cases in which the allograft was the only site of disease. In two cases, there was also a mass in the porta hepatitis, whereas in two other cases disease was confined to the porta hepatitis rather than in the allograft. In two patients the disease was found at autopsy, one patient having died of lymphoma and the other from multiple organ failure. Of the 26 treated patients, 6 died of lymphoma, 2 died of other causes, 1 died of hemorrhage during attempted retransplantation, 6 are still being treated, and complete remissions were accomplished in 11 patients. Two of these are following single modality therapy (chemotherapy in one and retransplantation in another). The other 9 patients received multimodality therapy including reduction or cessation of immunosuppression (8 patients), administration of acyclovir or ganciclovir (5), chemotherapy (3), local excision of the liver lesion (2), immune globulin administration (2), retransplantation (1), radiotherapy (1), and monoclonal anti-B-cell antibody administration (1).

Overall eight patients underwent retransplantation as treatment of allograft lymphoma. One died of hemorrhage during reoperation, a second died shortly after surgery, and a third died of sepsis 2 months later. In two other patients the lymphoma recurred in the second allograft and both died of malignancy at 0.5 and 2 months, respectively, after operation. Three other patients are alive, of whom two are in complete remission from their lymphomas 9 and 56.5 months after reoperation.
Of all treated patients, 62 had complete remissions (8 of them died later from other causes). The types of treatment used in 61 of the 62 patients are listed in Table 5. Of the 62 complete remissions, 39 (63%) occurred in patients with disease localized to a single organ or site and 23 (37%) occurred in patients with widespread disease. In the former group 11 of 39 (28%) remissions occurred when the allograft was the only site of disease (see above). Overall postdiagnosis follow-up of treated patients ranged from days to 93 months (average, 15; median, 5 months). In 28 of the 62 patients with complete remissions, follow-up after treatment was brief, being less than 18 months, (range, 0.75 to 17.5; average, 8 months). However, in 14 patients the remissions were very durable, being more than 48 months (range, 49 to 93; average, 65 months). At present, 54 of the 189 patients are alive in complete remission, 32 are alive and receiving treatment, 64 died of lymphoma, and 39 died of other causes.

**Nonlymphomas**

There were 78 males (including one already mentioned with a lymphoma) and 58 females. Their ages ranged from 1.5 to 67 years (average, 47; median, 49 years). Only 8 were in the pediatric age group. Of 133 patients with adequate data, 111 (83%) received triple therapy (cyclosporine, azathioprine, and prednisone), 13 (10%) received double therapy (cyclosporine and prednisone), and 6 (5%) received azathioprine and prednisone. The corresponding figures in renal transplant recipients were very different 27%, 8%, and 64%, respectively. FK506 was used in 8 patients either alone or in the various subgroups described. Antilymphocytic agents antilymphocyte globulin (24), OKT3 (27), or both (0) were used in a total of 51 patients (38%). This compared with 26% usage of antilymphocyte preparations in renal recipients with nonlymphomatous tumors in the CITR. When renal transplant recipients in the CITR with nonlymphomas were compared with hepatic allograft recipients the time of appearance of the tumors in the latter group was surprisingly short. In the former group the average and median times were 71 and 57 months, respectively, (range, 1 to 298.5 months) whereas in liver transplant recipients the average and median times were 26 and 21.5 months, respectively (range, 2.5 to 95.5 months). These differences are statistically significant (P < .001). Surprisingly, only 0.5% tumors in the liver transplant recipients appeared less than 4 months after transplantation compared with 2.7% in the non-liver transplant recipients. The age of patients at the time the cancer was diagnosed ranged from 2 to 69 years (average, 49; median, 52 years). Follow-up after diagnosis of the cancer ranged from 0 to 58 months (average, 12; median, 5 months).

Thirty-six patients died of their malignancies including 1 patient described above who died of lymphoma. The other 35 malignancies that caused death were carcinomas of the colon (6), lung (6), pancreas (4), liver (3), head and neck (3), stomach (2), cervix (2), leiomyosarcoma (2), and one each of breast, kidney, ovary, skin (squamous cell carcinoma), unknown primary, brain, and Kaposi's sarcoma. Another 3 patients died of recurrent preexisting cancers for which transplantation had been performed, including two cholangiocarcinomas and one angiosarcoma; the de novo malignancies in these 3 patients played no role in their deaths. Another 11 patients died of causes unrelated to their cancers. Of the 86 patients who are currently alive 31 are well, 5 are being treated for their cancers, and in 50 the malignancies are apparently under control.

The following several cancers deserve special comment:

**Carcinomas of the colon and rectum.** Of the 18 patients, 6 had a history of chronic ulcerative colitis and 4 required liver transplantation because of sclerosis cholangitis. Two other patients had sclerosing cholan-
gitis with no apparent history of ulcerative colitis. Another patient had a family history (a father and brother) with colonic cancers.

In 3 patients, no curative treatment was possible because of the advanced stage of the disease and in another 3 because the tumor was only discovered at autopsy examination.

**Hepatic neoplasms.** One patient underwent partial auxiliary liver transplantation for hepatitis B cirrhosis. Twenty-four months later he died of metastatic hepatocellular carcinoma, which had occurred in his own diseased liver. The second patient underwent transplantation for fulminant hepatic failure due to hepatitis. After transplantation she developed hepatitis B cirrhosis in the allograft, complicated by a hepatoma, 54.5 months after transplantation. She died one day after attempted retransplantation. The third patient underwent transplantation for sclerosing cholangitis complicating chronic ulcerative colitis. Nineteen and a half months later a cholangiocarcinoma was discovered involving the allograft and causing bone metastases. The patient died of the malignancy 5.5 months later.

**Sarcomas.** Sarcomas comprised four leiomyosarcomas, one mesothelioma, and one fibrosarcoma. All leiomyosarcomas and the fibrosarcoma occurred in children aged 1.5 to 7.5 years and appeared from 25.5 to 54.5 (average, 37) months after transplantation. Remarkably, four of the five tumors, including the fibrosarcoma, involved the allograft, whereas the remaining leiomyosarcoma involved the mesentery. There was no evidence that the donors, or any recipients of other organs from them, had leiomyosarcoma or fibrosarcoma. In fact HLA-DR13 genotyping indicated that the fibrosarcoma was of recipient origin. Two patients are alive 8 and 9.5 months, respectively, after excision of a leiomyosarcoma of the left lateral hepatic segment and mesentery, respectively, and the patient with the fibrosarcoma is alive with tumor 40 months after commencement of chemotherapy. Two patients died of metastatic leiomyosarcoma 2 months and 7.5 months respectively after diagnosis of their malignancies.

A 56-year-old woman underwent transplantation for a hepatoma. An unknown interval after transplantation she developed a peritoneal mesothelioma and was receiving chemotherapy 1.5 months after diagnosis.

**Skin cancers.** Twenty-two patients had squamous cell carcinomas (SCCs), 19 had basal cell carcinomas (BCCs), 3 had SCCs and BCCs, and 2 had malignant melanomas, of whom 1 also had squamous cell carcinomas. The lip alone was involved in two patients with SCCs and the lip and skin in one patient with SCCs and BCCs. Thirty-six patients had single lesions, whereas 12 had multiple carcinomas. One patient with malignant melanoma had regional lymph node metastases and is alive 6 months after radical axillary clearance. One patient with multiple SCCs died of spread from a preauricular lesion.

**Carcinomas of the uterine cervix.** Whereas 74% of carcinomas in the overall series were in situ lesions, three of four (75%) of neoplasms in the hepatic allograft recipients were invasive cancers, which caused the deaths of two of the recipients.

**Kaposi’s sarcoma.** Eight patients were male and two were female. Five patients had nonvisceral disease limited to the skin, and five had visceral disease involving the internal organs. Most patients were from the Eastern Mediterranean area in keeping with CTTR findings that most transplant recipients with KS are either Arab, black, Jewish, or Mediterranean. One patient died of widespread visceral disease and two died of other causes. The other seven are alive, with three of them in complete remission after treatments which included reduction of immunosuppression (3), excision (1), ganciclovir (1), and chemotherapy (1). The length of follow-up from diagnosis in 9 patients ranged from 0.5 to 32.5 (average, 8) months.

**Discussion**

The most common malignancies in the overall CTTR series are carcinomas of the skin and lips, lymphomas, Kaposi’s sarcoma, carcinomas of the uterine cervix, carcinomas of the kidney, carcinomas of the vulva and perineum, hepatobiliary carcinomas, and various sarcomas excluding Kaposi’s sarcoma. A very different pattern of posttransplantation neoplasia is observed when one compares cancers in hepatic allograft recipients with those observed in the largest single group of patients in the CTTR, namely renal recipients. The most striking finding was a disproportionately high incidence of lymphomas in hepatic versus renal patients. This observation is confirmed by a study of 131 lymphomas from the University of Pittsburgh that showed a 1% incidence in renal transplant recipients, compared with a 2.7% incidence in hepatic allograft recipients. In contrast, renal patients exceeded hepatic recipients in the incidence of skin cancers, carcinomas of the cervix, and carcinomas of the vulva and perineum. Several factors may account for these differences. In
hepatic recipients, intense immunosuppressive therapy is often needed to prevent death from rejection, whereas severe rejection of kidney allografts can be managed by discontinuing administration of immunosuppressive agents and returning the patients to dialysis therapy. A complication of intense immunosuppressive therapy is a disproportionate increase in the incidence of those malignancies that occur in the early months after transplantation, namely lymphomas. This is borne out by the much greater use of triple therapy in liver recipients with lymphomas compared with kidney recipients, and the greater use of antilymphocyte preparations in the former group compared with the latter. The intense immunosuppression in the hepatic recipients probably accounts for the short induction time in them as compared with renal allograft recipients.

The high incidence of lymphomas in children is striking. Children have more lymphoid tissue than adults which, in areas such as the Peyer’s patches of the small bowel and the tonsils and adenoids, may become the site of lymphomas, if among other things, the child becomes infected with Epstein-Barr virus (EBV). Primary EBV infection is more common in childhood than in adulthood and in immunosuppressed patients is likely to have more deleterious effects.

In keeping with previous reports from the CITR, the great majority of lymphomas in liver allograft recipients were non-Hodgkin’s lymphomas with occasional cases of plasmacytoma or Hodgkin’s disease. The high percentage of patients in the present study who died of lymphoma is in keeping with a 179-fold increased death rate from this cause among liver transplant recipients reported in one study. In contrast, a gratifying feature is that 33% of patients had complete remissions in response to treatment. The most successful treatment was reduction or cessation of immunosuppressive therapy. Although polyclonal lesions are more likely to respond to such treatment than clonal lesions, the distinction is not absolute, and a trial of reduced immunosuppression appears to be indicated regardless of clonal status. However, this carries the risk of acute or chronic rejection, but complete remission with retention of good allograft function can be achieved in many cases.

In the present study, liver allografts appear more prone than others to be the site of lymphomas. Allograft involvement by lymphoma should always be considered in the differential diagnosis of graft dysfunction. It is characterized on computed tomography scans by single or multiple low-density areas in the allograft or by a hypodense mass in the porta hepatitis or by multiple hypoechoic areas on sonograms. The diagnosis is confirmed by percutaneous needle biopsy results, but occasional biopsies are misleading, as necrotic tissue only may be removed, necrotic areas being a common feature of many posttransplant lymphomas.

The length of follow-up after transplantation is an important factor in the types of malignancies encountered. Many renal transplant recipients have been observed for a decade or even 2 decades or more, whereas most hepatic transplant recipients were treated in the last 10 to 12 years. Because malignancies such as skin cancers, carcinomas of the cervix, and carcinomas of the vulva and perineum occur late after transplantation, this may explain the discrepancy in the incidences of these tumors in renal and hepatic allograft recipients. The small number of liver allograft patients compared with the large number of renal transplant recipients may have also contributed to the marked differences in the incidence of the various cancers.

Hepatic allograft recipients with nonlymphomatous tumors more frequently received triple therapy and antilymphocyte preparations than renal recipients. The heavy immunosuppression administered to hepatic allograft recipients compared with renal recipients may also account for the shorter induction time of nonlymphomatous neoplasms. It may also account for the rather aggressive behavior of some tumors and is in keeping with a more than sevenfold death rate from all cancers in liver allograft recipients reported in one study.

The pattern of malignancies observed in hepatic allograft recipients closely resembles that observed in cardiac transplant recipients. When the types of neoplasms observed in heart or heart-lung recipients were compared with those observed in renal transplant recipients, lymphomas predominated in the former group (42% v 11% of all malignancies), whereas other tumors were common in the latter group—skin cancers (39% v 28%), carcinomas of the cervix (4% v 1%), and carcinomas of the vulva and perineum (3% v 0.4%). The reasons for these differences are similar to those discussed above regarding liver allograft recipients.

Leiomyosarcoma is distinctly rare in children. The development of four cases of leiomyosarcoma and one of fibrosarcoma in pediatric liver allograft recipients is remarkable, particularly because the allograft was involved in four of the five cases.
Recently, Epstein-Barr virus in a clonal form, has been isolated form several smooth muscle tumors in organ allograft recipients suggesting that the virus has a role in the development of these malignancies.\(^2\)\(^9\)\(^2\)\(^6\)\(^2\)\(^8\) Smooth muscle tumors have also been observed in acquired immunodeficiency syndrome patients, mainly children, with liver involvement in at least five cases.\(^2\)\(^7\)\(^2\)\(^8\) Epstein-Barr virus infection has been associated with several of these tumors.\(^2\)

Although most posttransplant cancers are etiologically related to immunosuppressive therapy, a small number are associated with the underlying disease requiring transplantation or its sequelae. Thus, in kidney transplant recipients, 10% of renal carcinomas may have resulted from the carcinogenic effects of analgesic abuse, and a substantial number of others may have been related to acquired cystic disease of the kidney.\(^3\)\(^0\) We have no explanation of why four liver allograft recipients developed carcinomas of the kidney. The altered anatomy after orthotopic liver transplantation may make removal of right-sided renal tumors difficult.\(^3\)\(^1\)

In one third of liver allograft recipients with carcinomas of the colon in the present study, transplantation was necessitated by sclerosing cholangitis or other complications of chronic ulcerative colitis, a disease in which colonic carcinoma is a well-recognized complication.\(^3\)\(^2\) In one study, there was a 6.5% incidence of colorectal cancers among 36 liver allograft recipients who had been treated for sclerosing cholangitis and chronic ulcerative colitis,\(^3\)\(^3\) and a second study reported an 11% incidence of colorectal neoplasms (2 cancers and 1 large villous adenoma with severe dysplasia) in 27 patients.\(^3\)\(^4\)

In the present study, three liver transplant patients developed malignancies in their allografts or native liver almost certainly related to the underlying liver disease. Two patients developed hepatomas related to hepatitis B infection, a well-recognized precursor of this malignancy.\(^3\)\(^5\) The third patient, who underwent transplantation for sclerosing cholangitis complicating chronic ulcerative colitis, developed a cholangiocarcinoma that presumably originated in the recipient’s residual bile duct and then involved the allograft. Cholangiocarcinoma is known to occur in ducts affected by sclerosing cholangitis.\(^3\)\(^6\)\(^3\)\(^8\)

Acknowledgment

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References

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