De novo malignancies are one of the current problems in patients with organ transplantation. The incidence has been considered to be higher as a result of increases of oncogenic viruses in immunosuppressed organ recipients. Published reports have shown increased incidence of de novo tumors such as malignant lymphomas and cutaneous neoplasms but decreased incidence of breast cancer. A variety of factors affect de novo breast cancer development in organ recipients, including immunosuppression, viruses, and underlying disease. The aims of this review are to evaluate the incidence and management of patients with de novo breast cancer by giving the University of Pittsburgh’s data, and to evaluate the incidence of de novo breast cancer in the previously published series. The University of Pittsburgh’s incidence rate of de novo breast cancer was determined in a fashion similar to that for the Surveillance, Epidemiology and End Results data, we found increased incidence rate of de novo breast cancer in the previously published series. The University of Pittsburgh’s incidence rate of de novo breast cancer was determined in a fashion similar to that for the Surveillance, Epidemiology and End Results data, we found increased incidence rate of de novo breast cancer in the previously published series. Eighty-three percent of all patients were diagnosed at early stages, and it appeared to take longer for de novo breast cancer to develop in patients treated with tacrolimus than in patients treated with cyclosporine. In conclusion, surgical treatment of breast cancer in liver recipients is the same as treatment of breast cancer in patients without transplantation. However, the effects of chemotherapy, radiotherapy, and/or tamoxifen remain unclear in transplanted patients and need to be evaluated in larger studies. (Liver Transpl 2004;10:1–6.)

De novo malignancies are considered one of the serious long-term complications of organ transplantation. McKhann first reported the increased incidence of de novo malignancies, an observation confirmed shortly thereafter by others.1–4 A variety of factors are considered responsible for the development of de novo malignancies, such as the intensity of the immunosuppressive therapy, the type of transplant, and the use of different immunosuppressive agents. The most frequent cancers among these tumors are malignant lymphomas and cutaneous neoplasms. The observed rate of incidence of de novo malignancies in patients with transplantation range from 4.1% to 16% in different series.5–8 Although decreased incidence of de novo breast cancers (BCs) has been reported in the transplant literature,9,10 there are contradictory data concerning the incidence of BC in those patients compared with the overall population. Some previous studies indicate that the incidence of commonly seen tumors such as carcinoma of the breast is not increased in the transplant population.10–12

MEDLINE Search

Our review of published data on the incidence of de novo cancers following transplantation was based on English-language articles in the MEDLINE database. For this purpose, all published reports between 1963–2003 were searched in PubMed-based MEDLINE by using the words de novo cancer, transplantation, and liver, and those that presented de novo breast cancer were included in the study. In addition, data from the University of Pittsburgh’s experience with such cancers was summarized. A 1998 report by Jain et al. has been omitted from the present summary to avoid duplicate presentation of the same BC cases.5 Patients with recurrence of previous BC, retransplantation, multiorgan transplantation, and transplant patients under the age of 18 years were excluded. Incidence rates of BCs following transplantation were compared with age-specific incidence rates in the general U.S. population using confidence intervals (CIs) based on the Poisson probability distribution.

Abbreviations: BC, breast cancer; CI, confidence interval; Tac, tacrolimus; CsA, cyclosporine; TGF-β, transforming growth factor β; EBV, Epstein-Barr virus; HPV, human papillomavirus; NK, natural killer.

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Incidence Rates in Published Literature

In the literature, we found 21 \textit{de novo} BCs among 5,330 liver transplant recipients (Tables 1 and 2). The mean age of nine \textit{de novo} BC patients was 54.5 years at diagnosis of cancer.\textsuperscript{10,11,13,14,16} The mean age of 13 BC patients was 48.6 years at transplantation.\textsuperscript{11,13,14,17} The interval between transplantation and diagnosis of \textit{de novo} BC was available for eight out of the 21 patients in the literature, and the mean interval was 58.9 months (range, 3 months–13 years). Two reports out of eight articles presented the number of female patients.\textsuperscript{13,14} Four \textit{de novo} BCs were reported among 297 female patients (1.34 %), and the mean age of these four patients was 52.2 years.

In previously published data, the authors compared the incidence of \textit{de novo} cancer with incidence rates of

<table>
<thead>
<tr>
<th>Reference, Year</th>
<th>Number of Liver Transplantations</th>
<th>Female</th>
<th>Mean Age at Transplantation</th>
<th>Number of \textit{De Novo} Breast Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al., 1998\textsuperscript{10}</td>
<td>888</td>
<td></td>
<td>51.5</td>
<td>2</td>
</tr>
<tr>
<td>Saigal et al., 2002\textsuperscript{11}</td>
<td>1,140</td>
<td></td>
<td>43</td>
<td>1</td>
</tr>
<tr>
<td>Haagsma et al., 2001\textsuperscript{13}</td>
<td>174</td>
<td>106</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Jonas et al., 1997\textsuperscript{14}</td>
<td>458</td>
<td>191</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Levy et al., 1993\textsuperscript{16}</td>
<td>556</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sanchez et al., 2002\textsuperscript{17}</td>
<td>1,421</td>
<td></td>
<td>49.7</td>
<td>7</td>
</tr>
<tr>
<td>Catena et al., 2001\textsuperscript{19}</td>
<td>353</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Bessa et al., 1997\textsuperscript{40}</td>
<td>340</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5,330</td>
<td>1,337</td>
<td>48.6</td>
<td>21</td>
</tr>
</tbody>
</table>

University of Pittsburgh’s experience

<table>
<thead>
<tr>
<th>Reference, Year</th>
<th>Stage</th>
<th>Age* (yr)</th>
<th>MI (mo)</th>
<th>Treatment</th>
<th>Ca survi (mo)</th>
<th>Tcr/CsA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al., 1998\textsuperscript{10}</td>
<td>1</td>
<td>71</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>46</td>
<td>M + C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saigal et al., 2002\textsuperscript{11}</td>
<td>59</td>
<td>78</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>124</td>
<td>M + C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haagsma et al., 2001\textsuperscript{13}</td>
<td>55</td>
<td>156</td>
<td>Died: 11 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonas et al., 1997\textsuperscript{14}</td>
<td>T2 N0</td>
<td>43</td>
<td>SM</td>
<td>8</td>
<td>CsA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 N1</td>
<td>64</td>
<td>SM</td>
<td>26</td>
<td>CsA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4 N0</td>
<td>47</td>
<td>M + R + H</td>
<td>Recurrence: 45 months</td>
<td>CsA</td>
<td></td>
</tr>
<tr>
<td>Levy et al., 1993\textsuperscript{16}</td>
<td>54</td>
<td>16</td>
<td>M</td>
<td>54</td>
<td>CsA</td>
<td></td>
</tr>
<tr>
<td>Sanchez et al., 2002\textsuperscript{17}</td>
<td>43.8</td>
<td></td>
<td></td>
<td>5-year survival: 83%</td>
<td>CsA</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>54.5</td>
<td>58.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

University of Pittsburgh’s experience

*Mean age at diagnosis of breast cancer.

Abbreviations: MI, mean interval between transplantation and diagnosis of breast cancer; Ca survi, survival of patient with \textit{de novo} breast cancer; Tcr, tacrolimus; CsA, cyclosporine; A, azithioprine; M, mastectomy; C, chemotherapy; SM, segmental mastectomy; R, radiotherapy; H, hormonotherapy; T, tamoxifen; Tis, carcinoma in situ; AD, axillary dissection; TM, total mastectomy.
BC in the overall population. However, we believe that it would be more appropriate to make this comparison with age taken into account. When we evaluated de novo BC incidence with respect to the age-specific incidence rate presented by the National Cancer Institute’s Surveillance, Epidemiology and End Results data, we found similar or increased incidence of de novo BC among transplant patients. In two studies, while the presented incidence was 4 (1.34%) out of 297 female patients whose mean age was 52.2, the expected incidence rate was 0.75 (0.25%) among patients 50–54 years of age, according to Surveillance, Epidemiology and End Results data (Table 1). To determine the incidence among transplant patients and compare it with the age-specific incidence rate in the United States between 1994 and 1998, we evaluated two patient groups separately (Table 3). Group 1 represents the University of Pittsburgh’s experience, and group 2 represents two different published studies that evaluated de novo BC in female patients with liver transplantation (Tables 1 and 2). In the University of Pittsburgh study, the rate was 0.52%, or 523.5 per 100,000, which is comparable to the rate for the general U.S. population between 55 and 59 years old. The incidence in group 2 seems to be increased with respect to the age-adjusted rates. The estimated 95% CI for group 2 is 546.6–3,928.3, which is higher than the age-specific incidence in the United States from 1994 to 1998 (277.8 whites and 253.8 blacks per 100,000/general population).

Authors’ Data, and University of Pittsburgh’s Experience

Seven patients (0.52%) were identified retrospectively with de novo BC among 1,337 female patients over 18 years of age who underwent orthotopic liver transplantation between August 1989 and December 2001. These figures yield an incidence rate of 523.6 BC per 100,000 patients (95% CI = 210.5 to 1,078.7 BC per 100,000 patients). Because the 95% CI includes the incidence rate of BC in the general population (327.2 in whites and 289 in blacks per 100,000), there is no statistically significant difference between the rates among the Pittsburgh patients and the general population.

The mean age of seven patients was 52.2 years at transplantation and 56.6 years at diagnosis of BC. The mean interval between transplantation and diagnosis of de novo BC was 53.6 months. Six of the seven BC cases were diagnosed in stage 1; the seventh was an in situ carcinoma. Five cancers were invasive ductal carcinoma, one was ductal carcinoma in situ, and one was invasive lobular carcinoma. All BC patients underwent surgery and were alive at last follow-up with a mean of 51.6 months. Five patients have survived to more than 5 years, and two were still alive 10 and 15 months after surgery.

Stage, Treatment and Survival

Among 12 BC patients, five whose stages were presented in the literature and seven from the University of Pittsburgh, seven were in stage I, two in stage IIA, two in stage III, and one in stage 0 (Table 2). One of the stage III patients had no lymph node or distant metastases (T4 N0 M0). Most (83%) patients were diagnosed at early stages, probably due to closer screening of patients with liver transplantation.

Thirteen BC patients, seven of them in the University of Pittsburgh’s experience and six whose therapy was reported in the literature, underwent surgical therapy. Segmental mastectomy was done in six of these patients. Three patients received chemotherapy, four patients received radiotherapy, and four received hormone therapy (Table 2). Breast-conserving surgery was achieved in half of the patients (six out of 13). Unfortunately, limited data are available in the organ transplantation literature concerning treatments with chemotherapy and/or radiotherapy and/or use of tamoxifen in BC patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>De Novo Breast Cancer/Total Number of Transplantations</th>
<th>Mean Age (yr)</th>
<th>Study’s 95% Confidence Interval</th>
<th>Age-Specific Incidence, 1994–1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Pittsburgh</td>
<td>7/1,337</td>
<td>56.6</td>
<td>210.5–1,078.7</td>
<td>327.2 (white)</td>
</tr>
<tr>
<td>Haagsma13</td>
<td>4/297</td>
<td>52.8</td>
<td>546.6–3,928.3</td>
<td>277.8 (white)</td>
</tr>
<tr>
<td>Jonas14</td>
<td></td>
<td></td>
<td></td>
<td>253.8 (black)</td>
</tr>
</tbody>
</table>

Liver Transplantation and De Novo Breast Cancer

Table 3. Breast Cancer Incidence: Comparing Three Different Transplantation Populations With General Population

References:
1. University of Pittsburgh
2. Haagsma
3. Jonas
4. Liver Transplantation and De Novo Breast Cancer
The mean interval between transplantation and diagnosis of de novo BC was longer for patients who used tacrolimus (Tcr) for immunosuppression than for those who used cyclosporine (CsA). In Pittsburgh's experience, all patients received Tcr and had 53.6 months mean interval for BC diagnosis, which seems longer than the mean interval for patients using CsA (33.7 months in four published reports).^{11,14,16,17}

**Discussion**

**De Novo BC and Immunosuppression**

The immunosuppressive agents most commonly used by the reviewed patients were CsA and Tcr. CsA was used until 1995. Since that year, Tcr has been used for immunosuppression as a first step. CsA and Tcr are produced by fungus species. Although their chemical structures are different, both have similar mechanisms for inhibiting the nuclear factor responsible for activation of IL2 transcription. Thus both inhibit IL-2 gene expression, and the production and generation of cytotoxic cells. It is believed that CsA enhances the risk for carcinogenesis in an autonomous fashion, which is mediated by transforming growth factor β (TGF-β). Although CsA and Tcr both increase TGF-β transcription rates, comparative studies show that the effect is stronger for CsA.^5,18^ Azathioprine, the first immunosuppressive agent used in organ transplantation, effectively prevents rejection by inhibiting DNA synthesis as a maintenance agent. However, it has no value as a rescue or induction agent.^19^ Mycophenolate mofetil blocks the proliferative response both T and B lymphocytes, inhibits antibody formation, and prevents the generation of cytotoxic T cells.^19^

The relationship between immunosuppressive therapy and the increase of oncogenic viruses have been reported in previous studies. Kelly et al. suggested that immunosuppression leads to increased risk of malignancy because of replication of oncogenic viruses such as Epstein-Barr virus (EBV), herpes simplex 1 and 2, human papillomaviruses (HPV), disturbances of immunity through depression of natural killer (NK) cell activity, chronic antigenic stimulation, impaired immunoregulation, and decreased production of interferon.^10^ In the 25th Annual San Antonio Breast Cancer Symposium, two studies showed the importance of mouse mammary-tumor virus-related agent on human mammary carcinogenesis. The authors reported that HPV16 DNA was detected in 26% of core-biopsy proven BC patients with no history of known HPV exposure.^20–22^

Grinstein et al. reported that they found EBV in tissue with typical, atypical ductal and lobular proliferations, and in situ carcinomas. They suggested that EBV may play an oncogenic role in the development of BC.^23^ Bonnet et al. showed a positive relationship between EBV infection and hormone-receptor negative tumors, which behave more aggressively than hormone-receptor positive tumor.^24^ Labreque et al. also demonstrated the presence of EBV in BC, but found no association between EBV and the histological type of tumor.^25^ Desphande et al. analyzed the expression of LMP2A, a membrane protein of EBV, in breast cells but failed to detect expression of any of the EBV viral gene products and suggested that surrogate markers for the identification of cellular- or cytokine-related immune response would be necessary for identifying EBV association with BC.^26^ Kleer et al. detected EBV latent membrane protein 1 (LMP1) by immunohistochemical staining and EBV DNA by polymerase chain reaction in 45% (9/20) of fibroadenomas in patients with previous organ transplantation, compared with 0% in the nonimmunocompromised control group. They suggested that EBV infection is specifically localized to epithelial cells. More recently, Murray et al. detected EBV DNA in 19 out of 92 breast tumors. They suggested that the EBV genome is strongly associated with estrogen-receptor (ER)-negative tumors. Among the seven BC patients in University of Pittsburgh’s experience, invasive ductal carcinoma was predominant as in the general population. This tendency may be related to the EBV found in the ductal tissue with ductal proliferation as presented in previous published data.^23^

Stewart et al. suggested that NK cells, a subpopulation of lymphocytes, might act against tumor cells.^29^ Jonas et al. showed increased NK cell activity in patients with de novo cancer.^{14}^ Pros et al. revealed that NK cell activity could be increased by viral stimulation.^{30}^ It has been shown that NK cell activity is suppressed by alcohol in murine models.^{31}^ Alcohol is also considered to be responsible for the development of de novo carcinogenesis. Saigal et al. suggested that a suppressive effect of alcohol on NK cells could promote tumorigenesis.^{11}^ Although NK cells have a role in immunosurveillance, the role of these cells in the development of de novo BC and the relationship between NK cells and oncogenic viruses and the immune response against oncogenic viruses remain unclear.

It is possible that de novo BC is in part a result of immunosuppression following transplantation, but immunosuppression is not the only factor influencing the development of de novo cancer. Chronic kidney failure,
underlying disease before transplantation, early menarche, family history, late menopause, parity, hormone replacement therapy, and long-term exposure to estrogen are also believed to contribute to the development of de novo BC. Previous reports have shown the increased estrogen levels in patients with chronic liver disease to be parallel to the expectation of elevated estrogen level as estrogen is metabolized in the liver.\(^3\)\(^2\)–\(^3\)\(^5\) Becker et al. and Josannin et al. reported elevated estrone and estradiol levels in cirrhotic postmenopausal women.\(^3\)\(^3\)–\(^3\)\(^4\) Glud et al. showed that the ratio of estrogen to testosterone increases with declining liver function.\(^3\)\(^5\) Shaaban et al. also reported increased estrogen levels in the patients with chronic liver disease.\(^3\)\(^6\) Long-term exposure to the high levels of estrogen seen in the patients with chronic liver disease may be linked to the increased risk of development of de novo breast cancer. The effect of estrogen on the development of de novo BC is one possible explanation. However, supporting evidence is difficult to find, perhaps because information about estrogen levels in these patients are not available. Clearly, the development of de novo BC needs to be studied in light of many factors.

Underlying disease such as alcoholic cirrhosis has also been responsible for development of de novo cancer. Some data suggest a synergistic effect between alcohol and estrogen on the risk of BC.\(^3\)\(^7\) Recently, Saigal et al. showed increased incidence of de novo malignancies in patients who underwent transplantation for alcoholic cirrhosis, but no report was found addressing this relationship on development of de novo BC.\(^1\) A possible association between primary biliary cirrhosis and BC was previously reported by Wolke et al.\(^3\) In the University of Pittsburgh’s experience, three (43%) patients with HCV and two (28%) patients with postnecrotic cirrhosis among de novo BC cases (N = 7) were found, and hepatitis accounted for 71% of underlying disease. In contrast to University of Pittsburgh’s experience, Kelly reported that de novo BC was seen less in HCV patients.\(^1\)\(^0\)

If immunosuppressive treatment enhances BC, it is interesting to ask whether the use of immunosuppressive drugs should be reduced. In addition, it would be useful to know whether de novo BC would be affected by the type of therapy. However, previous studies have shown no differences among immunosuppressive drugs. Jonas has emphasized that the development of de novo cancer is related to immunosuppressive protocols such as CsA- or Tcr-based treatment.\(^1\)\(^4\) It has been suggested that immunosuppression dosage be reduced in these patients to the lowest possible level after tumor diagnosis.\(^9\) Because longer exposure to immunosuppressive drugs and the intensity of immunosuppression have been shown to increase development of de novo carcinogenesis, this suggestion seems logical.

In conclusion, we found similar de novo BC incidence among patients who underwent previous organ transplantation and in the age-matched general population data from the National Cancer Institute’s Surveillance, Epidemiology and End Results. This finding contradicts previous reports emphasizing the decrease of BC in transplant patients. Ten out of 12 patients (83%) were diagnosed at early stages, it appeared to take longer for de novo breast cancer to develop in patients treated with Tcr than in those treated with CsA. Surgical treatment of BC in liver transplant patients was similar to treatment among patients without previous liver transplantation. Because the age-specific incidence (after 50 years old) is similar to that of the general population, it is worthwhile for patients to obtain a yearly mammography after age 40 to detect breast cancer in an early stage. To make a suggestion about the effects of chemotherapy, radiotherapy and/or tamoxifen in liver transplant patients with breast cancer, larger studies should be done.

References


