LIVER TRANSPLANTATION 14:1406-1411, 2008

EDITORIAL

Incidence of De Novo Cancer and Lymphoproliferative Disorders After Liver Transplantation in Relation to Age and Duration of Follow-Up

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Received June 10, 2008; accepted July 3, 2008.

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An increased incidence of de novo malignancies in immunocompromised patients was first predicted by Professor Thomas Starzl and coworkers in 1968 and was confirmed shortly afterwards by others.[1-4] The immunocompromised state provides a permissive environment for malignant cells to grow, for an oncogenic virus to infect or reactivate within the host, for chronic antigen stimulation leading to a cytokine-rich milieu, and for impaired immune surveillance imposed by chronic immunosuppression.[5-7] With the increasing success of liver transplantation (LTx) and fewer episodes of acute rejection with virtual freedom from chronic rejection, long-term survival rates have improved.[8-11] In addition, with an aging population, older recipients are also being considered for LTx.[12] Currently, long-term graft loss and death are not commonly related to rejection but are often due to age-related complications, such as cardiovascular disease and de novo cancers.[13,14]

The rate of de novo cancers after LTx has been reported to range from 3% to 26%,[15-18] and the variation is partly due to the length of follow-up, different ways of reporting, and geographic variations in de novo malignancies. Although registry data of de novo cancers provide a valuable source for accounting for the various types of malignancies; these registries do not include the denominator of the population at risk. The cumulative number of years of follow-up is also unknown, and this makes it difficult to calculate the actuarial risk.[2,6,19-21] In this respect, data from single centers with long-term follow-up have become an important source of information for the incidence and nature of de novo cancers, which can then be compared with surveillance epidemiological end results data. Furthermore, these data can be presented as a standard incident ratio (SIR). Also, the incidence of de novo cancers can be evaluated on the basis of the number of person years post-transplantation; the cumulative actual survival of patients after transplants is included until the last follow-up or time of death.

Within the published literature, there are significant inconsistencies in the reporting of de novo malignancies. For example, some authors prefer to include posttransplant lymphoproliferative disorders (PTLDs) along with de novo solid cancers,[22-30] whereas others prefer not to include them.[15,18,31,32] This has caused a major discrepancy in reported rates of de novo cancers. Nonmelanoma, non-Kaposi's skin cancers (squamous cell cancer and basal cell carcinoma) are the commonest types of de novo malignancies in the posttransplant population, with an up to 70 times higher incidence in comparison with nontransplant populations.[24,30,33-35] One way to report this is to separate lymphoid lesions from nonlymphoid cancers and then separate the nonlymphoid cancers. Even after stratification of lymphoid and nonlymphoid cancers in this manner, there appears to be a wide variation in the different types of de novo cancers.

Abbreviations: IBD, inflammatory bowel disease; LTx, liver transplantation; PSC, primary sclerosing cholangitis; PTLD, posttransplant lymphoproliferative disorder; SIR, standard incident ratio.

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DOI 10.1002/lt.21609
Published online in Wiley InterScience (www.interscience.wiley.com).

TABLE 1. Incidence of De Novo Cancers in Various Age Groups in Relation to Length of Follow-Up with Actual Person Years Post-LTx

Recipient Age at the Time of LTx (Years)	Post-LTx Follow-Up (Person Years)	De Novo Cancer	Duration Post-LTx (Years) ≤3	>3 to ≤5	>5	Total	Cases per 100 Person Years
≤40, n = 354	3316	Nonmelanoma, non-Kaposi's skin cancer	0	2	2	4	1.2
		Other cancers	2	1	0	3	0.9
		Total	2	3	2	7	2.11
>40 to ≤60, n = 442	3499	Nonmelanoma, non-Kaposi's skin cancer	5	10	3	18	5.15
		Other cancers	12	9	8	29	8.3
		Total	17	19	11	47	13.46
>60, n = 204	1384	Nonmelanoma, non-Kaposi's skin cancer	3	3	5	11	7.97
		Other cancers	12	4	6	22	15.94
		Total	15	7	11	33	23.91
Overall	8199	Nonmelanoma, non-Kaposi's skin cancer	8	15	10	33	4.03
		Other cancers	26	14	14	54	6.59
		Total	34	29	24	87	10.62

Abbreviation: LTx, liver transplantation.

RATE OF DE NOVO CANCERS WITH LENGTH OF FOLLOW-UP

In the report by Åberg and coworkers[36] in this issue of *Liver Transplantation*, squamous cell carcinoma, melanoma, and Kaposi's sarcoma are included, whereas basal cell carcinoma of the skin is mentioned but is omitted from the calculation of the incidence and SIR. Lymphoid malignancies are also included in the current report. They show that the cumulative incidence of de novo cancers increased at 1, 5, 10, and 20 years of follow-up to 3%, 5%, 13%, and 16%, respectively. This can be compared to Haagsma et al.'s report,[24] which showed a cumulative risk of de novo malignancies (lymphoid cancers included) of 6%, 20%, and 55% at 5, 10, and 15 years post-LTx, respectively. The study population of 1000 consecutive post-LTx patients using tacrolimus from the University of Pittsburgh was first examined in August 1999 for de novo cancers with a mean follow-up of 77.8 ± 11.1 months (4795.3 total person years).[32] There were 57 cases of de novo cancers in all (lymphoid lesions excluded), which included 22 nonmelanoma, non-Kaposi's skin cancers. This incidence increased when the longitudinal follow-up was extended to 8199 person years in December 2002.[14] At that time point, there were 87 cases of de novo nonlymphoid malignancies (10.62 cases per 100 person years of follow-up). They consisted of 33 nonmelanoma, non-Kaposi's skin cancers and 54 other malignancies (Table 1). The details of the various de novo cancers are shown in (Table 2).

RATE OF DE NOVO MALIGNANCIES IN RELATION TO THE RECIPIENT'S AGE

Of interest was the variation in the incidence and nature of de novo malignancies in different age populations in this group. Herrero et al.[16] reviewed 187 cases and found 63 malignancies (lymphoid lesions included). On a univariate analysis, for they found age to be a significant risk factor for de novo cancers (P = 0.01). Similarly, Haagsma et al.[24] found age > 40 years to be a significant risk factor for an increase in de novo cancer compared to age < 40 years (P = 0.006; lymphoid lesions included).[24] In the University of Pittsburgh population, the numbers of nonlymphoid de novo malignancies in the age groups of ≤40 years (n = 354), >40 to ≤60 years (n = 442), and >60 years (n = 204) were 7 (1.97%), 47 (10.63%), and 33 (16.17%), respectively (Table 2). When expressed in terms of incidence per 100 person years post-LTx, the rates were 2.11, 13.46, and 23.91 in the age groups of ≤40 years, >40 to ≤60 years, and >60 years, respectively. The distribution of the de novo nonmelanoma, non-Kaposi's skin cancers and other malignancies is also given in relation to 100 person years for different age groups in Table 1 and Fig. 1.

PTLD IN RELATION TO THE AGE AND LENGTH OF FOLLOW-UP

As pointed out by the University of Pittsburgh, there is an inverse relationship to the rate of PTLD with de novo cancers with respect to the age at transplant.[13] The rate of PTLD was examined in the same 1000-patient population for the same duration of follow-up used for de novo cancers: overall, 43 cases were identified. The rates of PTLD in the age groups of ≤18 years (n = 166), >18 to ≤40 years (n = 188), >40 to ≤ 60 years (n = 442), and >60 years (n = 204) were 10.8%, 2.7%, 3.2%, and 2.9% respectively (Table 3). In the previously reported study from the University of Pittsburgh of PTLD

TABLE 2. Type of De Novo Malignancies According to Various Age Groups

Type of De Novo Malignancy	Age (Years) ≤40, n = 354	>40 to ≤ 60, n = 442	>60, n = 204	Total (%)
Skin (nonmelanoma, non-Kaposi's)	4	18	11	33 (37.93)
Gastrointestinal	0	7	1	8 (9.19)
Genitourinary	0	4	7	11 (12.64)
Lung	0	5	4	9 (10.34)
Oropharyngeal	0	7	3	10 (11.49)
Miscellaneous	3	6	7	16 (18.39)
Breast	1	2	0	3
Leukemia	1	0	2	3
Unknown primary	0	1	0	1
Kaposi's	1	0	1	2
Thyroid	0	2	0	2
Brain	0	0	1	1
Melanoma	0	0	2	2
Eye	0	1	0	1
De novo liver	0	0	1	1
Total	7	47	33	87

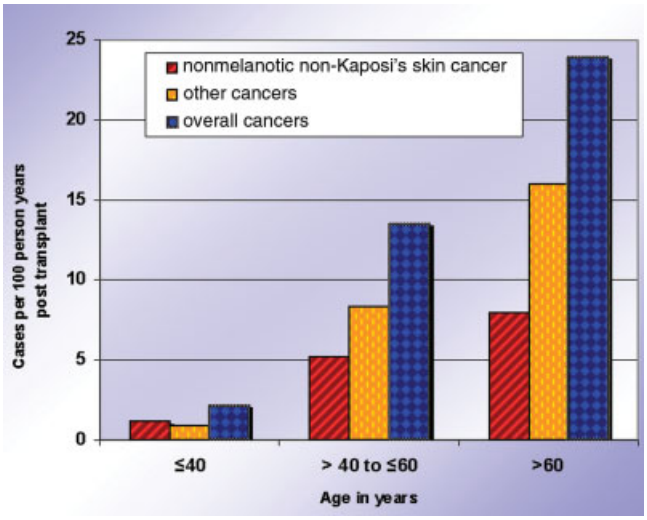

Figure 1. De novo cancers per 100 person years post–liver transplantation in various age groups.

in 4000 patients who were followed for nearly 20 years, the rate of PTLD decreased with time, and the children had a higher incidence than the adults.[37]

BRIEF DESCRIPTION OF THE DIFFERENCES IN THE INCIDENCE OF VARIOUS TYPES OF DE NOVO CANCERS REPORTED FROM SINGLE-CENTER STUDIES

Skin Cancers

Skin cancers are the most common types of de novo cancers in all the reported series, with an up to 70 times higher increase in the incidence in comparison with nontransplant populations.[29,30,33-35] The incidence is extremely high in the Australian reports and is lowest in the Japanese studies.[34] The overall incidence reported from various studies ranges from 30% to 70% for all tumors after LTx.[24,38,39]

Oropharyngeal and Lung Cancer

There is an increased incidence of oropharyngeal and lung cancers in tobacco users. In the United States, 20% to 25% of liver transplants are performed for patients with alcohol-related end-stage liver disease, a majority of whom are also tobacco users.[12,40] In 1 study, more than 50% of patients transplanted for alcohol-related diseases had a history of smoking.[41] DiMartini and coworkers[42] from the University of Pittsburgh reported a prospective study confirming the underreporting of smoking. An epidemiological study of 1.2 million US adults with alcohol consumption revealed a significantly higher risk for oral, esophageal, pharyngeal, laryngeal, and liver cancers in middle-aged and elderly populations.[43] In our study, the incidence of oropharyngeal cancers was 25.5 times higher and the incidence of lung cancer was 3.7 times higher for alcohol-related end-stage liver disease patients. A higher incidence of lung cancer post-LTx with poorer prognosis has been reported by Jiménez et al.[44] and others.[41,42,45] In contrast, Haagsma and others did not find any cases of oropharyngeal cancer in their series,[20,24,27,46-48] and only 1 case of oropharyngeal and lung cancer was observed in the present study by Åberg and coworkers,[36] which included 54 cases of alcoholic cirrhosis.

Gastrointestinal Cancer

Esophageal and Gastric Cancers

An increased incidence of de novo esophageal cancers has been reported in patients with Barrett's esophagitis.[49] Careful follow-up with gastrointestinal endoscopy may provide a survival benefit in such cases.[50]

Nagata and coworkers[51] reported a single case of

TABLE 3. Incidence of PTLD in Relation to Age and Length of Follow-Up Post–Liver Transplantation

Age	n	≤3 Years, n (%)	>3 to ≤5 Years, n (%)	>5 Years, n (%)	Cumulative, n (%)
≤18 years	166	16 (9.63)	1 (0.60)	1 (0.60)	18 (10.84)
>18 to ≤40 years	188	4 (2.12)	0 (0)	1 (0.53)	5 (2.65)
>40 to ≤60 years	442	8 (1.80)	2 (0.45)	4 (0.90)	14 (3.16)
>60 years	204	3 (1.47)	2 (0.98)	1 (0.49)	6 (2.94)
Total	1000	31 (3.1%)	5 (0.5)	7 (0.7)	43 (4.3)

gastric cancer post-LTx in which a *Helicobacter pylori* infection was noted. Adami et al.[33] reported a 2-fold increase in the risk for gastric cancer and a 3-fold increase in the risk for esophageal cancer.

Intestinal Cancer

Yao et al.[17] reported a high proportion of gastrointestinal tumors (46% of all nonskin, nonlymphoid cancers) in a case control study with a high incidence of small bowel malignancies. Vera and associates[52] (Birmingham, United Kingdom) found a 5.3% incidence of colonic cancers in patients with primary sclerosing cholangitis (PSC) versus 0.6% for non-PSC patients. However, although Loftus et al.[53] found a 4-fold increase in colon cancer in their posttransplant population, this rate was not significantly higher when it was compared to the rate in other patients with inflammatory bowel disease (IBD).

In a study comparing the risk of colon cancers in patients with LTx and a history of IBD, Bleday et al.[54] found early colorectal neoplasms in 11.1% of cases with surveillance colonoscopy

Genitourinary Cancers

The most common genitourinary malignancy is prostate cancer. However, the incidence does not appear to be higher in the post-LTx population.[17,18,22,23,26,32,33] Haagsma and coworkers[24] from the Netherlands reported a 30-fold increase in de novo cancers of the kidney. Also, in a large Swedish post–kidney and liver transplant population study of 5931 cases, SIR for kidney cancer was 4.9 times higher.[24,33]

Gynecological Cancers

Cancers of the Cervix

The Israel Penn registry of kidney transplant recipients[3] and Adami et al.[33] in a study of kidney and liver transplant recipients have reported an increased incidence of vulval and cervical cancers after transplantation. Jonas et al.[26] reported a high incidence of cervical intraepithelial neoplasia in patients post-LTx using quadruple therapy.

Breast Cancers

De novo breast cancers post-LTx were summarized by Oruc et al.[55] (University of Pittsburgh). Most of them were diagnosed in the early stages, and the overall survival was similar to that of nontransplant recipients.[29] A synergistic effect between alcohol use and estrogen on the risk of breast cancer has also been suggested.[56]

CONCLUSION

In conclusion, there is a wide variation in the incidence of post-LTx de novo cancers, which is partly related to the length of follow-up and partly related to the inclusion or exclusion of lymphoid lesions. There is also a wide variation in reported cancer types by geographic distribution. Oropharyngeal cancers are more commonly seen in those with alcoholic liver disease and particularly in those with a smoking history. The rate of renal cell cancers was much higher in the series of cases from the Netherlands. Colonic cancers are more common in patients with PSC and IBD. Barrett's esophagitis is a risk for carcinoma esophagus. The overall rate of de novo solid tumors increases with age at the time of transplant and the length of follow-up, whereas the rate of PTLD decreases with age at LTx, with a higher incidence in the first few years post-LTx.

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