Higher cancer rates found in liver transplant patients receiving cyclosporine for immunosuppression

June 24 2010

Researchers at Erasmus MC University Medical Centre in The Netherlands found that cyclosporine treatment is a significant risk factor for the development of de novo cancer in liver transplant patients. Full details appear in the July issue of *Liver Transplantation*, a journal published by Wiley-Blackwell on behalf of the American Association for the Study of Liver Diseases (AASLD).

The 1-year survival rate after liver transplantation has dramatically increased in the past three decades to more than 80%. In contrast, there has been little improvement in long-term outcomes. Malignancy is one of the major leading causes of late death after liver transplant and is reported to be directly related to the intensity and the cumulative dose of immunosuppression.

Calcineurin inhibitors (CNI) such as cyclosporine (CsA) or tacrolimus (TAC) are the cornerstone of immunosuppressive treatment after transplantation. Several studies have yielded conflicting results about the incidence of de novo cancer between CsA- based and TAC-based regimens. Elucidating the role of different CNI regimens in the occurrence of de novo cancer after liver transplant was the goal of this study.

The Dutch team performed retrospective analyses in 385 liver transplant patients who underwent surgery between 1986 and 2007. Analyzed data

included age of recipient at time of transplantation, gender of recipient, primary liver transplant indication, type of primary immunosuppressive therapy, de novo malignancy post transplantation, interval from liver transplant to diagnosis of malignancy, interval from liver transplant or diagnosis of cancer to death and interval from liver transplant to diagnosis of the first acute rejection. All patients were followed until December 2008. The primary endpoint was de novo malignancy, which was defined as the development of cancer other than recurrent primary liver cancer. Of the 385 study participants, 50 (13.0%) patients developed at least one de novo cancer.

The researchers observed that CsA in comparison to TAC treatment is the most important risk factor for de novo malignancy after liver transplant. This higher cancer risk was not, however, found in all CsA treated patients, but CsA specifically enhanced development of de novo cancer in patients transplanted in more recent years (2005-2007), and in younger patients (less than 50 years of age). In addition, CsA treatment particularly resulted in more aggressive types of cancer compared to TAC, with a 1-year survival rate less than 30%.

The reason for the increased cancer rates among CsA recipients is believed to be the fact that from January 2005, CsA dosing based on the conventional C0 level monitoring was replaced by dosing based on C2 level monitoring in all liver transplant patients. As this was the only major change in the CsA treatment in the recent study period, the team concludes that the C2 monitoring strategy was the reason for the increased early de novo cancer risk.

"Strikingly, CsA treated patients transplanted from 2005 on showed a 9.9-fold higher de novo cancer risk in the early phase after liver transplant compared to patients treated with TAC. These data indicate that only the specific CsA treatment used in recent years was associated with a higher risk for early development of de novo cancer," said

research team leader Herold Metselaar, M.D., Ph.D. "We also observed that, compared with TAC treated patients, CsA treated patients had a 2.5-times higher risk to develop more aggressive cancer types that do not belong to the non-melanoma skin cancer and post-transplant lymphoproliferative disorder (PTLD) categories, indicating that CsA is not only associated with a higher early de novo cancer risk, but also with cancer types having a worse prognosis."

In this month's editorial, Julie Thompson, M.D., suggests that further study is required, stating, "Metselaar and colleagues draw much-needed attention to concerns regarding overall immunosuppressant exposure and its relationship to long-term outcomes after liver transplantation. These data serve as a call to reassess the aggressiveness of current immunosuppressive regimens as a means of reducing risk from de novo malignancy."

More information: "Increased Incidence of Early de novo Cancer in Liver Graft Recipients Treated with Cyclosporine: An Association with C2 Monitoring and Recipient Age." Angela S.W. Tjon, Jerome Sint Nicolaas, Jaap Kwekkeboom, Robert A. de Man, Geert Kazemier, Hugo W. Tilanus, Bettina E. Hansen, Luc J.W. van der Laan, Thanyalak Tha-In, Herold J. Metselaar. Liver Transplantation; Published Online: March 8, 2010 (DOI: 10.1002/lt.22064); Print Issue Date: July 2010.

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