Research Highlights

Cynthia R. King, PhD, NP, MSN, RN, FAAN
Associate Editor

Study Compares Kaposi Sarcoma in Transplant Recipients and Patients With HIV

With increases in organ transplantation and the spread of AIDS, epidemiologists have noted a concurrent rise in the risk of virus-related cancers in transplant recipients and patients with HIV. Kaposi sarcoma (KS) is one of the most common of the virus-related cancers, the etiology of which is human herpes virus type 8.

Serraino et al. (2005) used already available demographic information from three longitudinal databases in France and Italy to compare the epidemiologic patterns of the development of KS in patients with AIDS with those of KS in transplant recipients. DMI-2 HIV is the national database of HIV-positive individuals with access to hospital care in France. The investigators looked at the information on 6,072 patients who were entered into the database from January 1988–June 2004 and were followed by Nice University Hospital for a median of 3.5 years. The database does not contain information on when patients seroconverted to HIV-positive status or how long they had been HIV positive prior to being entered into the database. As such, the usefulness of the data to the full study is limited.

The Italian HIV Seroconversion Study (ISS) is a multicenter study looking at the natural history of HIV infection. Patients in the database were followed an average of 8.1 years. Unlike patients in France's national database, patients in this study have documented seronegative tests and positively confirmed HIV tests. The maximum time accepted between the negative and positive tests is three years, and the midpoint between the two tests is taken as the estimated date of seroconversion. Thus, the Italian database includes an estimated length of HIV positivity. Excluded from the AIDS arm of the study were people diagnosed with KS within two months of enrollment in the study. A total of 2,002 patients who had seroconverted to HIV positive were included from Italy.

Information was collected on 2,705 organ recipients from 1970–2004 (1,844 renal, 702 cardiac, and 159 liver) in the organ transplantation databases of four Italian transplant centers. Patients were followed for a median of 5.5–7.9 years. Dates and times of follow-up varied slightly with each center. The risk of KS in patient years was calculated from the time of transplant until development of KS, death from another cause, or date of last visit, whichever came first. Patients who died within 10 days of transplant, who developed KS within 30 days of transplant (believed to be prevalent cases), or who had a pretransplant history of any cancer were excluded from the study.

The current study compared the risk of developing KS between the two groups using person years. In the HIV population, person years were calculated from the date of enrollment in the databases to the date of diagnosis of KS for those who developed it, or the date of death or date of last follow-up for those who had not developed KS by the end of the study. In organ transplant patients, patients were considered at risk for KS starting from transplant and ending at KS diagnosis, death, or date of last follow-up, whichever occurred first.

Among the 10,799 subjects who were followed for a total of 65,739 patient years, 356 cases of KS were diagnosed: 317 in patients with HIV and 39 in patients following transplants. Patients with HIV had a 451-fold higher risk for KS than the general population. In the HIV-positive population, homosexual men had a higher risk than women or IV drug users. CD4+ counts greater than 200 and use of highly active antiretroviral therapies (HAARTs) were associated with reduced incidence of KS.

In transplant recipients, risk was 128-fold higher than in the general population. Among transplant recipients, being younger than 50 years old and female resulted in reduced risk. KS risk was 2.7-fold higher in liver transplant recipients than in renal transplant recipients. Although cardiac transplant recipients have the most aggressive immunosuppressive regimen, their risk was no higher than those receiving renal transplants. No reason was provided. The risk for KS declined as the number of years following transplant increased.

When comparing patients with HIV to transplant recipients, researchers found that KS developed earlier in those receiving transplants. Four years post-transplant, KS developed in a pattern similar to patients with HIV who seroconverted following HAART (e.g., a decline of incidence in both). In looking at patients who became HIV positive before taking HAART, the development of KS is strongly associated with the duration of HIV infection, which is assumed to correlate with a decline in immunocompetency.

In conclusion, when comparing transplant recipients with patients with HIV, data show strong correlation between degree of immunosuppression in both groups and KS.

Serraino, D., Angeletti, C., Carrieri, M.P., Long, B., Piche, M., Piselli, P., et al. (2005). Kaposi's sarcoma in transplant and HIV-infected patients: An epidemiologic study in Italy and France. *Transplantation, 80,* 1695–1704.

Combined Therapies in Patients With AIDS-Related Lymphoma Are Safe and Improve Survival

Because of the introduction of highly active antiretroviral therapy (HAART), morbidity and mortality rates of AIDS-related lymphoma (ARL) have been greatly reduced. Because HAART improves survival and quality of life for patients with AIDS, assuming that it should not be withheld during chemotherapy treatment is logical. However, combining HAART with standard cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) therapy posed a potential risk for increased, possibly fatal, toxicities. Therefore, the German ARL Study Group decided to determine whether using HAART along with CHOP to treat ARL is efficacious and which patients can be treated safely with the modality.

One hundred fifty-seven patients with HIV and aggressive B-cell lymphomas registered to participate from 1997–2001. Registrants had their lymphomas staged according to Ann Arbor Classification, and standard HIV laboratory work was performed prior to acceptance into the study. Exclusionary factors included Ann Arbor IA lymphomas (not stage IE) or central nervous system lymphomas; treatment with chemotherapy or cytokines

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within four weeks of enrollment; active or opportunistic infection; serious cardiovascular, pulmonary, psychiatric, metabolic, renal, or hepatic disease; pregnancy; or a life expectancy of less than four weeks. Seventy-seven of the registrants were excluded and eight were lost to follow-up prior to starting chemotherapy, leaving 72 eligible participants to be divided into either a standard-risk (n = 48) or a high-risk (n = 24) group for developing lymphoma. High risk was defined as having two of three of the following: CD4 < 50, World Health Organization performance status ≥ 3, or previous AIDS-defining infection. Standard-risk patients had only one of the characteristics. Demographically and clinically, the groups did not differ with respect to age, lymphoma stage, presence of B symptoms, or lactate dehydrogenase or immunoglobulin G levels, and histologic subgroups were distributed evenly between the two risk groups.

Both groups were to receive six cycles of CHOP therapy, although at different doses, as well as standard HAART. Intrathecal methyltrexate also was administered prior to and during each cycle. All patients received pneumocystis carinii prophylaxis and had their anemia and granulocytopenia treated when necessary. The standard-risk group received 100% of the standard CHOP therapy on day 1 of each cycle, followed by prednisolone alone on days 2–5. The high-risk group received 75% of the standard CHOP dose during the first cycle, and if the neutrophil counts remained satisfactory and no opportunistic disease occurred, CHOP was increased gradually up to the 100% dosing (although not all patients were able to achieve it). Treatment cycles were repeated every 22 days. Patients were seen bimonthly following each cycle of CHOP, and treatment response was assessed after cycles 2, 4, and 6. Complete remission was defined as the disappearance of all lymphoma manifestations that lasted at least four weeks. Partial remission was defined as a reduction of more than 50% of all measurable lesions. All others were considered nonresponders.

In the standard-risk group, the complete response rate was 79% and the median survival was not reached after a median of 47 months of follow-up. This was comparable to the patients with aggressive lymphomas who were not HIV positive. Of note, despite immune-suppressing chemotherapy, CD4 counts did not change from baseline to four weeks post-therapy, and HIV viral loads actually decreased. In the high-risk group, the complete response rate was 29% and the median survival rate was 7.2 months. Toxicities were moderate (40% in the standard group and 69% in the high-risk group), and 38 patients died during the study (17 standard-risk patients and 21 high-risk patients). Sixty percent of patients in the standard-risk group were alive after three years, and 12.5% of the high-risk patients survived longer than three years. Based on the results, researchers believe that concurrent CHOP plus HAART can be administered safely in the outpatient setting for patients whether they are in a standard- or high-risk category.

Weiss, R., Mitrou, P., Arasteh, K., Schuermann, D., Hentrich, M., Duehrsen, U., et al. (2006). Acquired immunodeficiency syndrome-related lymphoma. *Cancer, 106,* 1560–1566

Patricia Herrera, RN, ACRN
Staff Nurse
Wake Forest University
Baptist Medical Center
Winston-Salem, NC

Bilateral Salpingo-Oophorectomy May Reduce Mortality in *BRCA1* and *BRCA2* Mutation Carriers

Women who are carriers of the *BRCA1* or *BRCA2* gene mutations often elect to have prophylactic bilateral salpingo-oophorectomies (PBSOs) to reduce the risk of ovarian and breast cancer. No studies thus far have addressed overall mortality reduction in *BRCA1* and *BRCA2* mutation carriers. The purpose of this study was to assess whether PBSO improves survival of women carrying *BRCA1* or *BRCA2* mutations.

The prospective cohort study involved participants from 13 centers in the United States and Europe. Participants generally were referred by other clinicians or loved ones because they were at a high hereditary risk for breast or ovarian cancer. Researchers identified a cohort of 666 women who met the criteria of having a *BRCA 1* or *BRCA2* gene mutation and never being diagnosed with cancer. For the primary analysis, a comparison was made between a group of 155 women who had undergone PBSO and 271 women who were matched for age within five years and who had not undergone PBSO. A secondary analysis was performed in which 188 women who had had PBSO were compared to 478 women who had not had the procedure. Overall mortality and cancer-specific mortality were examined in both analyses. All analyses were adjusted to center (multisite), mutation (*BRCA1* versus *BRCA2*), and birth year.

Follow-up of the women in the primary group who had undergone PBSO was 3.1 years (SD = 2.4 years), versus a follow-up time of 2.1 years for the women who had not had the procedure (SD = 2.0 years). Findings indicated a decrease in overall mortality (hazard ratio = 0.24; 95% confidence interval = 0.08–0.71) and cancer-specific mortality (hazard ratio = 0.10; 95% confidence interval = 0.01–0.46) in women with inherited *BRCA1* and *BRCA2* mutations who elected to undergo PBSO.

The data provide hope that PBSO can reduce the cancer risk for women carrying the *BRCA1* or *BRCA2* mutations. The results supply more information, particularly for women considering genetic testing. Further investigation into optimal timing for this type of prophylactic procedure is warranted.

Domchek, S.M., Friebel, T.M., Neuhausen, S.L., Wagner, T., Evans, G., Isaacs, C., et al. (2006). Mortality after bilateral salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers: A prospective cohort study. *Lancet Oncology, 7,* 223–229.

Renal Cell Cancer Treatments Have Similar Outcomes in Younger and Older Adults

Oncologic procedures and outcomes are influenced by multiple factors, including tumor stage, comorbidities, and, potentially, patient age. Because renal cell carcinoma (RCC) is commonly a disease of older adults, researchers must determine whether more risks are associated with certain surgical procedures for adults older than 75 years. RCC often presents in the sixth or seventh decade of life, and surgical treatments are the only curative options currently available. Unfortunately, evidence suggests that patients with more comorbidities are treated less aggressively, and age often is used as a factor in determining treatment. Berdjis, Hakenberg, Novotny, Froehner, and Wirth (2006) sought to determine specifically whether age and comorbidities would be predictors of perioperative complications and mortality following surgery for RCC. Other studies have indicated that complications from cancer surgeries are not any more common in older adults than in younger patients.

During the study period (1993–2003), 1,023 surgeries were performed for RCC. Types of surgeries performed included radical nephrectomies and nephron-sparing surgeries. Of the 1,023 patients, 115 were older than 75 years. The mean age of the entire sample was 62. The researchers retrospectively reviewed the medical records of all 1,023 surgical patients to identify operative mortality and any early complications that arose within the first 30 days. A risk stratification system score, developed by the preoperative American Society of Anesthesiologists (ASA), also was used.

The tumor-node-metastasis 2002 tumor staging system was used. No significant differences were found between the two groups with regard to tumor stage or histologic grade. Common comorbidities identified were hypertension, diabetes mellitus, cardiac disease, cerebrovascular and respiratory diseases, and primary cancers. Results demonstrated that ASA scores were lower in younger patients. Furthermore, 31 of the 908 younger patients suffered early complications, whereas only two of the 115 older patients experienced early complications. Overall, perioperative mortality was found to be higher in older

patients. However, the findings indicated that a correlation existed between morbidity and mortality and increasing ASA scores but age was not a factor ($p < 0.05$).

Although patients older than 75 had greater comorbidities when compared to their younger counterparts, a significant difference in morbidity and mortality rates relating to RCC surgical treatments did not exist. In light of an excellent five-year survival rate for patients who have local RCC treated surgically, age alone should not drive treatment decisions. These findings support the fact that advanced age certainly should not be used as a determining factor to deny anyone RCC surgical treatment.

Berdjis, N., Hakenberg, O.W., Novotny, V., Froehner, M., & Wirth, M. (2006). Treating renal cell cancer in the elderly. *BJU International, 97,* 703–705.

Serum Vascular Endothelial Growth Factor Is a Prognostic Parameter in Ovarian Cancer

Patients with early-stage ovarian cancer have critical clinical decisions to make, and healthcare professionals need as many prognostic factors as possible to assist them. Decisions regarding adjuvant therapies for ovarian cancer usually are based on disease stage and tumor grade, and few prognostic factors exist. Vascular endothelial growth factor (VEGF) has been shown to parallel tumor growth and metastasis development. Previous experimental studies have found that VEGF is involved in various steps of ovarian carcinogenesis. The authors of the current study sought to determine the relevance of serum VEGF levels in early ovarian cancer.

Several previous studies had examined serum VEGF with relatively small sample sizes. The authors of the current study contacted authors of seven other studies and were able to gain data from authors of four of those seven studies to build on. The total sample size was 314 patients, including 45 new cases added by the current authors. Patients had epithelial ovarian cancer. Serum VEGF was measured in all patients prior to their primary surgeries. Patients had a mean age of 59 years.

Mean follow-up time of women in the study was 38.9 months. One hundred seventy-five patients died from cancer-related causes during the study. Serum VEGF, disease stage, residual tumor mass, tumor grade, patient age, and CA-125 levels were associated with overall survival. Higher VEGF levels were associated with decreased survival. A serum VEGF value of 380 pg/ml was established in the study as the "cutoff" value separating excellent from poor outcomes. The median serum VEGF value for patients with ovarian cancer was 407 pg/ml.

The results indicate that serum VEGF can be used as a prognostic factor for women with all stages of ovarian cancer. The parameter can assist women and their healthcare providers in making the most effective clinical decisions, especially when considering chemotherapy as an adjuvant treatment.

Hefler, L.A., Zeillinger, R., Grimm, C., Sood, A.K., Cheng, W.F., Gadducci, A., et al. (2006). Preoperative serum vascular endothelial growth factor as a prognostic parameter in ovarian cancer [E-pub ahead of print]. *Gynecologic Oncology.* Retrieved August 10, 2006, from http://dx.doi.org/10.1016/j.ygyno.2006.03.058

Michele D. Blakely, RN-C, MSN
Clinical Nurse Specialist
Wake Forest University
Baptist Medical Center
Winston-Salem, NC