

A look at HIV-related cancers: incidence, screening, and stem transplantation

At the 21st International AIDS Conference in Durban, South Africa, presenters reported on the incidence of lymphoma in HIV-positive patients receiving antiretroviral therapy, the value of screening for anal cancer in this population, and the possible role of reductions in the viral reservoir after stem-cell transplantation for hematologic cancers. Bruce Jancin reports.

HIV-related lymphoma rate remains sky-high despite ART

Key clinical point ART has had a major impact on the incidence of HIV-related non-Hodgkin lymphoma but no effect on Hodgkin lymphoma. **Major finding** The overall incidence of non-Hodgkin lymphoma in HIV-positive adults on ART is 287 cases per 100,000 person-years, varying by location and route of HIV acquisition. **Data source** A longitudinal analysis of non-Hodgkin lymphoma incidence in more than 210,000 HIV-infected adults on combination ART on 4 continents. **Disclosures** The European Union and the National Institutes of Health. The presenter reported having no financial conflicts of interest.

The good news about non-Hodgkin lymphoma in the setting of HIV infection is that the risk drops significantly after several years of antiretroviral therapy. The bad news is that the risk remains extraordinarily high compared with the risk in the general population, Mathias Egger, MD, reported at the conference.

Dr Egger was referring to a key finding in a new analysis of lymphoma trends in more than 210,000 HIV-positive adults on combination antiretroviral therapy (ART) during more than 1.1 million person-years of follow-up in North America, Europe, Latin America, and South Africa.

The non-Hodgkin lymphoma (NHL) incidence rate standardized to 40 years of age was 287 cases per 100,000 person-years. From a pre-ART baseline of about 500 cases per 100,000 person-years, it dropped “massively” within a year after going on ART. Even after 5 years of ART, however, the rate remained in the range of 60-200 cases per 100,000



Dr Egger

person-years, depending on geographic location and HIV transmission route. In contrast, the incidence rate among the general population of the US and Canada, which is among the world's highest, is less than 10 per 100,000 person-years, according to Dr Egger, professor of epidemiology and public health at the University of Bern, Switzerland.

The risk of developing NHL in the setting of HIV infection varied by continent. It was slightly higher in HIV-infected patients in North America than in Europe or South Africa, although the South African data are considered unreliable due to under-ascertainment of cancers. In Latin American HIV-infected adults, the NHL rate was lowest of all – 54% lower than in Europe after adjustment for current CD4 cell count, ART regimen and duration, and transmission risk group. The low NHL rate in Latin America was driven by a very low risk in HIV-infected women.

Across the world, NHL rates in patients on ART were consistently lowest in women, intermediate in heterosexual men, and highest in men who have sex with men.

The explanation for the regional variation in NHL trends might involve differing prevalences of Epstein-Barr virus-2 and other oncogenic viruses as well as differences in the completeness of cancer ascertainment, Dr Egger said.

While NHL is categorized as an AIDS-defining condition, Hodgkin lymphoma is not. Nonetheless, the risk of Hodgkin lymphoma is markedly increased in the setting of HIV infection. In one meta-analysis, it was increased by 11-fold, compared with that seen in the general population (*Lancet*. 2007;370[9581]:59-67).

In a study by Dr Egger and his coworkers of more than 41,000 HIV-infected European adults, the incidence of Hodgkin lymphoma was 49 cases per 100,000 person-years. Importantly, unlike in NHL, the cumulative incidence and mortality of Hodgkin lymphoma were not affected by ART (*Blood*. 2011;117[23]:6100-8).

The clinical implication of these trends in HIV-related lymphomas is clear: with more than 2 million new cases of HIV infection occurring annually worldwide, and with infected patients living far longer as ART transforms HIV infection into a chronic manageable condition, physicians can anticipate encountering a steadily growing number of patients with NHL and Hodgkin lymphoma, Dr Egger said.

Anal cancer in HIV-infected patients: to screen or not?

Screening for anal cancer in HIV-infected men or women should not be part of routine clinical practice at this time, according to Andrew Grulich, MBBS, PhD, professor of medicine and head of the HIV epidemiology and prevention program at the University of New South Wales in Sydney, Australia. “And for very good reason: When we have a condition with a prevalence that’s so high and a treatment with recurrence rates that are so high, we need to question our approach,” he said.



Dr Grulich

Some experts recommend anal cytologic screening or high-resolution anoscopy for HIV-positive men and women, but that strategy has not been incorporated into any national practice guidelines. Screening proponents point to the high incidence of anal cancer in persons with HIV infection. It’s the fourth most common cancer in HIV patients in the United States, behind the AIDS-defining cancers and lung cancer. Indeed, the anal cancer rate is 10-fold greater in HIV-positive women, heterosexual men, and injection drug users than in the HIV-negative general population, and 50-fold higher in HIV-positive gay and bisexual men. Screening proponents also draw an analogy between anal cancer screening and the screening and treatment of cervical intraepithelial neoplasia (CIN), which has been enormously successful in preventing cervical cancer. But Dr Grulich said he believes the cervical cancer screening analogy is faulty.

Colposcopy has a mean 90% specificity for diagnosis of HPV-related high-grade squamous intraepithelial lesions (HSIL) or cervical cancer, whereas high-resolution anoscopy as a diagnostic test has a specificity as low as 37% in HIV-positive persons. The prevalence of HSIL is 30%-40% in anal samples from HIV-infected homosexual men, compared with 1%-2% in cervical samples from HIV-negative women.

The rate of progression from CIN 3 to cervical cancer in women in the general population is about 1 in 80 per year. In contrast, the rate of progression from anal intraepithelial neoplasia (AIN)-2 or AIN-3 to anal cancer in HIV-

infected homosexual men is estimated at only 1 in 400-600 per year, probably because regression of anal lesions is quite common.

Moreover, although a single treatment of high-grade CIN is typically curative and entails little morbidity, destruction of AIN by means of heat, cold, or electricity has a 70% failure rate, carries substantial morbidity, and is not supported by any evidence that it actually reduces the incidence of anal cancer, Dr Grulich continued. “We’re in a bit of a quandary [about] what to do about anal cancer prevention. We really need research in order to move this field forward.”

He added that it’s worth keeping an eye on two ongoing studies that are addressing key questions on anal cancer in HIV-positive persons. The first is the National Cancer Institute-funded randomized ANCHOR trial is examining ablative therapy versus watchful waiting in HIV-infected patients with anal HSIL lesions; however, results of this large study aren’t expected until 2022 or 2023. (Dr Grulich heads the Study of the Prevention of Anal Cancer, aimed at identifying biomarkers that predict persistence of HSIL as a marker of anal cancer risk.)

The second study is a randomized, placebo-controlled, adequately powered trial of the 9-valent HPV vaccine in HIV-infected gay or bisexual men. At the 2016 meeting of the Conference on Retroviruses and Opportunistic Infections (CROI), Timothy J Wilkin, MD, of Cornell University, New York, presented the results of the phase 3 ACTG A5298 trial of the quadrivalent HPV vaccine in HIV-infected adults over age 26. The vaccine group had a 27% reduction in risk of persistent anal HPV compared with the placebo group, though it was not statistically significant because of the small study size. The 9-valent vaccine would prevent a broader range of oncogenic HPV types, said Dr Grulich, who reported receiving research funding from CSL Australia, Gilead Sciences, Viiv, and Hologic.

Is stem-cell transplant curative for HIV infection?

Key clinical point It may not be necessary to use donor stem cells that are homozygous for the CCR5 delta32 mutation to achieve enormous sustained reductions in the viral reservoir in HIV-infected patients undergoing allogeneic stem-cell transplantation for hematologic cancers. **Major finding** 2 of 3 patients in a European series who have survived for longer than 3 years after stem-cell transplantation with undetectable or only trace HIV in their blood received donor cells lacking the rare CCR5 delta32 mutation. **Data source** EpiStem, an ongoing observational study of HIV-infected patients who undergo allogeneic stem-cell transplantation for life-threatening hematologic cancers. **Disclosures** American Foundation for AIDS Research Consortium on HIV Eradication. The presenter reported having no financial conflicts regarding her presentation.

It does not seem to be necessary to use donor stem cells that are homozygous for the CCR5 delta32 mutation to

achieve enormous sustained reductions in the viral reservoir in HIV-infected patients who undergo allogeneic stem-cell transplantation for hematologic cancers. The 15 HIV-infected patients who have undergone allogeneic stem-cell transplant for life-threatening hematologic cancers under the auspices of the European EpiStem Consortium have uniformly demonstrated a profound and durable reduction in viral reservoir to a degree that has not been approached by any other investigational cure strategy, Annemarie Wensing, MD, said at the conference.

“We see an enormous reduction in the viral reservoir, and in two patients we cannot find any viable HIV in the blood using ultrasensitive tests. But we don’t know whether these patients are cured, because they are still on antiretroviral therapy,” said Dr Wensing of Utrecht University, The Netherlands.

Non-Hodgkin lymphoma and Hodgkin lymphoma are 7-9 times more prevalent in HIV-positive patients than in the general population. But allogeneic stem-cell transplantation is an even higher-risk treatment in HIV-positive patients with life-threatening leukemia or lymphoma than in the HIV-negative population. Only 6 of the 15 EuroStem patients remain alive. Eight died within 4 months of the procedure and another died 2.5 years after the transplant, all from progression of their cancer or as a result of opportunistic infections arising during the immunosuppressive chemoablation that’s central to stem-cell transplantation. However, 3 of the 15 patients have survived longer than 3 years. In 2 of them, no HIV can be detected in blood or intestinal tissue using ultrasensitive tests, while in the third there is “only a slight trace,” according to Dr Wensing, a clinical virologist.

EpiStem (the European Project to Guide and

Investigate the Potential for HIV Cure by Stem-Cell Transplantation) is a multinational collaboration of European oncologists, infectious disease physicians, and other specialists. It was formed in response to the successful outcome of allogeneic stem-cell transplantation for acute myeloid leukemia in HIV-positive Timothy Brown, more famously known as “the Berlin patient” (N Engl J Med. 2009;360[7]:692-8). He has thus far survived 7 years off antiretroviral therapy.

Much has been made of the fact that Mr Brown’s donor cells were homozygous for the CCR5 delta32 mutation, which confers natural resistance to HIV infection because it prevents the virus from infecting T cells. Only 1% or less of the population is homozygous for this mutation. But Dr Wensing is not convinced that using donor cells with the mutation is a prerequisite for success. Indeed, although 4 of the 15 EpiStem patients received stem cells from donors homozygous for the mutation and another got donor cells heterozygous for the CCR5 delta32 mutation, the other 10 patients received stem cells capable of being infected by HIV, yet all 15 experienced an enormous reduction in their viral reservoir. And 2 of the 3 patients who have survived longer than 3 years got stem cells without the CCR5 delta32 mutation.

Dr Wensing observed that a common feature shared by Timothy Brown and the 2 EpiStem patients who have trace or undetectable HIV in blood or tissue samples more than 3 years after transplant is that all 3 developed severe graft-versus-host disease in conjunction with their stem-cell transplantation. She suspects this may have helped them to clear the infection, a hypothesis she intends to pursue further as EpiStem gathers more patients.

Eventually, if patients continue to test negative for HIV using ultrasensitive tests, it will be time to have a discussion with patients and their treating physicians about whether they should continue on antiretroviral therapy. “In the end it’s the patients’ decision, but they should be very well counseled because it can have medical and also psychological consequences if HIV returns,” she said.



Dr Wensing