Hot News

Cancer in HIV Patients

Starting antiretroviral therapy (ART) with low CD4 counts raises the likelihood of certain cancers, but others increase with longer time on therapy, reflecting the rising risk associated with older age. Researchers in the USA looked at patterns of cancer incidence and timing after ART initiation (Yanik, et al. Clin Infect Dis. 2013;57:756-64). The analysis included medical records from 11,485 participants in eight U.S. HIV clinical cohorts who started ART between 1996 and 2011. Around 80% were male and they started treatment at a median age of 38 years. At the time of ART initiation, the median CD4 count was 202 cells/mm^3. Nearly half started a protease inhibitor regimen. The authors looked at incidence rates for AIDS-defining cancers (Kaposi sarcoma [KS], non-Hodgkin's lymphoma, and cervical cancer) and non-AIDS cancers. They separately assessed cancers caused by viruses, such as hepatocellular carcinoma caused by hepatitis B or C, lymphoma related to Epstein-Barr virus, and cervical or anal cancer caused by human papillomavirus (HPV).

A total of 457 new cases of cancer were reported during 46,318 person-years (PY) of follow-up (average three years of follow-up per person), for an incidence rate of 987 cases per 100,000 PY. The most common AIDS-defining cancer was KS at 304 cases per 100,000 PY, while the most common non-AIDS cancers were anal cancer for men and breast cancer for women (69 and 128 cases per 100,000 PY, respectively). Incidence rates for AIDS-defining and non-AIDS cancers were similar, at 515 and 466 per 100,000 PY, respectively. Incidence rates for KS and lymphoma (both non-Hodgkin's and Hodgkin's) were highest during the first six months after ART initiation, then fell steeply during the next six months, followed by a more gradual decline. The incidence rate for all other cancers combined increased from 416 cases per 100,000 PY at one year after ART initiation to 615 per 100,000 PY after 10 years on treatment. Rates of non-AIDS cancers rose with longer time on ART, with an average increase of 7% per year. Older age was a significant predictor of non-AIDS cancers, with risk doubling with each additional 10 years of age. Lower CD4 count at the time of ART initiation was associated with greater risk of KS, lymphoma, and HPV-related malignancies. In summary, KS and lymphoma rates were highest immediately following ART initiation, particularly among patients with low CD4 counts, whereas other cancers increased with time on ART, likely reflecting increased cancer risk with aging.

Improvements in ART over time "have not had dramatic effects on cancer incidence," as more people with HIV are now living long enough to develop cancer. "Our results underscore recommendations for earlier HIV diagnosis followed by prompt ART initiation along with ongoing aggressive cancer screening and prevention efforts throughout the course of HIV care," they advised. These findings also underline the somewhat arbitrary historical division between "AIDS-defining" and "non-AIDS" cancers. Non-Hodgkin's (AIDS-defining) and Hodgkin's (non-AIDS) lymphomas followed a similar pattern. Likewise, cervical cancer (AIDS-defining) and anal cancer (non-AIDS) are similar malignancies with the same viral cause and parallel disease progression.

Other new research revealed increases in malignancies related to viral infections and a higher risk of KS even after immune restoration. Italian researchers looked at the incidence of and risk factors for AIDS-defining and non-AIDS cancers, with the latter divided into virus-related and non-virus-related malignancies (Calabresi, et al. HIV Med. 2013;14:481-90). The authors conducted a retrospective cohort analysis of 5,090 HIV patients in northern Italy during 1999-2009. Cancer rates among HIV persons were compared to expected rates for the HIV-negative general population living in the same area using standardized incidence ratios (SIR).

A total of 416 cancers were recorded in 390 HIV patients during 32,390 PY of follow-up: 200 AIDS-defining cancers (48%);138 non-virus-related, non-AIDS cancers (33%); and 78 virus-related non-AIDS cancers (19%). Overall, people with HIV had a four-fold higher cancer risk than HIV-negative individuals (SIR: 4.2).The excess risk was largest for AIDS-defining cancers (SIR: 31.0), but was also significant for virus-related non-AIDS cancers (SIR: 12.3).The highest SIR figures were seen for KS among AIDS-defining cancers and for Hodgkin's lymphoma among virus-related, non-AIDS cancers. In contrast, the overall increased risk for non-virus-related, non-AIDS cancers was small (SIR: 1.6), indicating no difference. In a multivariate analysis, older age and CD4 count < 50 cells/mm^3 were the only independent predictors associated with all cancers.

Based on these findings, the authors concluded that among HIV-infected people, there is an excess of AIDS-defining cancers and also of non-AIDS-defining cancers, particularly those related to viral infections (Table 1). Ageing and severe immunodeficiency are the strongest predictors.

Another analysis of the same cohort (Albini, et al. AIDS Res Hum Retroviruses. 2013;29:1097-104),

Table 1.

Virus	Cancers
Epstein-Barr Virus	Nasopharyngeal carcinoma Primary cerebral lymphoma Burkitt's lymphoma Diffuse large B-cell lymphoma
Human herpes virus 8	Kaposi's sarcoma Multicentric Castleman's disease Primary effusive lymphoma
Human T-cell leukemia virus 1	Adult T-cell leukemia/lymphoma
Papillomavirus	Cervical carcinoma Anal carcinoma Oropharyngeal carcinoma
Hepatitis B and C viruses	Hepatocellular carcinoma
Polyomavirus	Merkel cell cutaneous carcinoma

found that SIR for non-virus-related, non-AIDS cancers increased over time. After stratifying by gender, however, only HIV-positive men had an excess risk for these types of cancer, with nearly twice the risk (SIR: 1.9).

People with HIV had higher rates of lung cancer (SIR: 3.6) and testicular cancer (SIR: 3.1), but rates of prostate cancer and breast cancer were similar to those of the general population. The only independent predictors of non-virus-related, non-AIDS cancers were older age and shorter duration or not using of ART, with CD4 count not reaching significance in a multivariate analysis. In summary, HIV-infected men showed a twofold increased risk of non-virus-related (non-AIDS-defining cancers) compared to the general population. However, the use of ART appeared to be beneficial in protecting against the development of these malignancies.

Finally, French researchers examined trends in the incidence of AIDS-defining cancers among people with HIV relative to the general population, looking at the effect of controlled viral load and restored immunity after starting ART, which became widely available in the mid-1990s (Hleyhel, et al. Clin Infect Dis. 2013; Epub ahead of print). The authors estimated age- and sex-standardized cancer incidence rates among patients enrolled in the French Hospital Database on HIV and in the general French population during four calendar periods: 1992-1996, 1997-2000, 2001-2004, and 2005-2009. The median CD4 count rose over time (from 259 cells/mm^3 during the pre-ART era to 413 cells/mm^3 during the late ART period) as ART coverage reached 86%. Standardized incidence ratios were calculated for all periods, and separately for patients on combination ART, those with CD4 counts ≥ 500/mm^3 for at least two years, and those with HIV RNA suppressed to < 500 copies/ml.

Although the incidence of AIDS-defining cancers fell significantly across the calendar periods, the risk remained consistently higher for people with HIV compared with the general population. Among HIV patients with restored immune function, the relative risk of KS remained significantly elevated (SIR: 35.4). The risk of non-Hodgkin's lymphoma was similar to that of the general population, but was diagnosed at a significantly younger age among people with HIV (about 11 years sooner). The incidence of all AIDS-defining cancers continued to fall, including cervical cancer, in the combination ART period, but the risk remained higher than in the general population in 2005-2009. In patients with stably restored immunity, KS remained significantly more frequent than in the general population. Age at KS and cervical cancer diagnosis was only slightly different between HIV-infected and general populations (–2 and –3 years, respectively), while the difference was more marked for non-Hodgkin's lymphoma (–11 years). These results do not favor the hypothesis of premature aging in HIV patients for KS and cervical cancer.

The rise in CD4 counts as ART use increases over time is likely to account in large part for the decrease in the burden of the three AIDS-defining cancers. However, the magnitude of the fall differs according to the cancer, gender, and HIV transmission group. The reason for this heterogeneity is unclear, but it might involve differences in the relation between immunodeficiency and cancer risk, or differences in the proportion of persons coinfected with the relevant oncogenic virus. Treated patients who achieved virological suppression and good immunological recovery did not have an increased risk of non-Hodgkin's lymphoma, leading to the belief that ART would be most beneficial to prevent the risk of cancer in HIV-infected patients if it restores or maintains CD4 counts > 500 cells/mm^3, thereby indicating the need for an earlier diagnosis of HIV infection and an earlier treatment initiation.

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Once-Daily Raltegravir Moving Ahead

Raltegravir is a highly potent antiretroviral agent, with arguably one of the most favorable adverse event profiles in the HIV armamentarium. However, its standard twice-daily (BID) dosing schedule makes it less convenient than once-daily (QD) options.

Although pharmacokinetic data suggest that QD raltegravir may provide adequate drug levels, the randomized phase III QDMRK trial (Eron, et al. Lancet Infect Dis. 2011;11:907-15) showed that 800 mg QD raltegravir failed to meet the criteria for non-inferiority when compared with 400 mg BID RAL in antiretroviral-naive HIV-infected individuals. 83% of patients in the QD arm achieved undetectable HIV viremia, in comparison with 89% in the BID arm. This was largely due to poorer efficacy among people with high baseline viral load (74 vs. 84%, respectively).

But raltegravir may be able to keep HIV under control if viral load is already suppressed. In the ODIS trial (Vispo, et al. HIV Clin Trials. 2010;11:197-204), Spanish researchers reported for the first time that a switch to 800 mg QD raltegravir maintained undetectable viremia successfully in patients previously treated under other less convenient regimens as long as prior nucleoside analogue resistance mutations were absent.

More recently, French investigators re-evaluated whether raltegravir QD was able to maintain virological control when people switched from a fully suppressive combination regimen. Almost all patients maintained viral suppression (Caby, et al. 14th EACS, Brussels. Oct 16-19, 2013. Abstract BPD1/7). This observational study enrolled 71 patients in Paris who had plasma HIV RNA < 50 copies/ml for at least six months. They had been on antiretroviral therapy for 14 years on average. Nearly one quarter switched from 400 mg BID raltegravir while the rest switched from other drugs and were integrase inhibitor-naive. In addition to once-daily raltegravir, 56% used tenofovir/emtricitabine and 18% used abacavir/lamivudine. The most common reason for switching to QD raltegravir was dyslipidemia (20%), followed by liver toxicity (15%) and lipodystrophy (13%). Overall, 96% of participants maintained undetectable viremia at 48 weeks. The three patients that failed selected viruses with raltegravir resistance associated mutations. All three had a prior history of nucleoside analogue failure.

In an effort to facilitate QD dosing, Merck is working on a new tablet that appears less affected by food than the current formulation. In an open study, researchers from the company tested the effect of food on a new 600 mg tablet formulation (Krishna, et al. 14th EACS, Brussels, October 16-19, 2013. Abstract PE10/17). The study enrolled 36 healthy volunteers that were randomly assigned to take either three of the marketed 400 mg raltegravir oral tablets or two of the reformulated 600 mg tablets, in either case receiving a total dose of 1,200 mg. The new formulation was found to be generally safe and well tolerated, with no clinical or laboratory serious adverse events reported and no discontinuations for this reason. Taken while fasting, 1,200 mg doses of the new tablet and the old tablet led to similar drug exposure levels. Moreover, steady-state 24 hour concentrations were virtually the same. The reformulated tablet was less affected by food, however. A low-fat meal reduced drug exposure by 71% using the old tablet versus 40% using the new tablet. In a press release issued to coincide with the European AIDS Conference, Merck indicated that it plans to initiate a phase III trial of QD raltegravir in early 2014.

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