1. Record Nr. TD20012262

Autore	SUARDI, ELISA
Titolo	HIV-ASSOCIATED CANCERS: ROLE OF IMMUNE PARAMETERS AND RELATION WITH THE OUTCOME OF CHEMOTHERAPY [Tesi di dottorato]
Editore	Università degli Studi di Milano, 2019-03-01
Lingua di pubblicazione	Inglese
Formato	Tesi di dottorato
Livello bibliografico	Monografia
Note	diritti: info:eu-repo/semantics/openAccess In relazione con info:eu-repo/semantics/altIdentifier/hdl/2434/628815
Sommario	Background: HIV positive patients present a higher risk of cancer compared to the HIV-negative population. Three tumors, namely Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and invasive cervical cancer (ICC) occurs with particularly high incidence in HIV-positive patients, and have been classified as AIDS-defining malignancies (ADMs). However, a risk excess is observed for both ADMs and non-AIDS defining malignancies (NADMs). Beside co-infection with oncogenic virus, the pathogenic pathways underlying the development of infection-related and non infection-related cancer in PLWH are sustained by a complex network of interactions between various components of the immune system, with cytokines and other pro-inflammatory agents mediating those interactions. However, these mechanisms have not been fully characterized. Aim: To shed light on this topic, we conducted 3 studies with the following aims: - Natural Killer cell populations in HIV associated lymphoma: Natural Killer (NK, CD56+) cells exert anti-cancer and anti-viral actions and their number and function is impaired during HIV infection. In HIV-negative patients with Hodgkin Lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL), NK cell constitute a higher percentage of circulating lymphocytes and are associated

with a better outcome. We aimed to evaluate the NK cell population in HIV-associated lymphomas. - Sex-based differences in factors associated with HPV infection and intraepithelial lesions in a cohort of HIV-positive patients: We aimed to assess the factors associated with HPV infection and with squamous intraepithelial lesions (SILs) in a cohort of HIV-positive patients with focus on gender differences, and possible factors linked with the capability to clear HPV infection, thus influencing the progression of SILs towards cancer. - Association of immune activation markers and CD4/CD8 ratio with the development of virus related and non-virus related cancers in HIV-positive patients: High levels of peripheral T-cells immune activation and low CD4/CD8 ratio in HIV-positive patients have been associated with comorbidities, increased risk of serious events and deaths, despite effective highly active antiretroviral therapy (HAART). Thus, we aimed to assess the association of peripheral immune activation markers (CD8+CD38+ T-lymphocytes) and CD4/CD8 ratio with the onset of infection-related and non-infection related cancers in a cohort of HIV-positive patients virological suppression. We further investigated possible association of CD8+CD38+ T-cells and CD4/CD8 ratio with overall survival of HIV-positive patients with virus-related cancer. Results: Association of immune activation markers and e CD4/CD8 ratio with the development of virus related and non-virus related cancer in HIV-positive patients: We collected clinico-pathologic and treatment data from a prospective series of HIV-positive patients with virus related and non-virus related cancers. We enrolled 140 HIV-positive patients, 115 with virus-related cancer and 25 with non-virus related cancers. We evaluated the association of CD4/CD8 ratio and CD8+CD38+ percentage at the time of first evaluation at our centre with the onset of virus ad non-virus related cancers in uni- and multivariable analyses, in relationship to other HIV-related criteria (CD4+ current and nadir, HIV-RNA, length of HIV infection, cART). Patients with virus-related cancer were more frequently males (p=0.002) and men who have sex with men (MSM) (p=0.003) compared to patients with non-virus related cancers. Further, at the time of cancer diagnosis, patients with virus-related disease were younger (p<0.0001), with a shorter time from HIV-diagnosis (p=0.04)and more frequently naïve to HAART (p=0.009); from an immunological perspective, pre-diagnostic levels of CD8+CD38+ T-cells were higher (p=0.05) and CD4/CD8 ratio was lower (p=0.01) in patients with virus related compared with non-virus related cancer. Natural Killer cell populations in HIV associated lymphoma: Clinical characteristics at lymphoma diagnosis have been prospectively collected at the National Centre for HIV Malignancy at Chelsea & Westminster Hospital, London, since 1986. We reviewed data of 615 HIV-positive patients including 360 lymphomas with full lymphocyte subset analysis at lymphoma diagnosis. The percentage of NK cells was significantly higher in patients with HL (median 9%) than in DLBCL (6%) and other NHL subtypes (p=0.009). The total NK cell count was significantly higher in patients with undetectable HIV-RNA(p<0.0001) but only weakly correlated with CD4 cell count (PearsonsR2 =0.11). For 156 patients with DLBCL, the 5-year OS was 64% (95%CI 56-72%) and in univariate analysis neither total NK-cell population (log rank p=0.14) not NK-cell % (log rank p=0.84) were prognostic variables for OS. In multivariate Cox model the only variable associated with OS was the International Prognostic Index (IPI) (log rank p<0.001). In conclusion, the percentage of NK-cells was reduced in HIV-associated NHL, in contrast with previous reports in

	HIV-negative patients, and this could contribute to lymphoma development in these patients. The NK-cell population was strongly influenced by effective ARV therapy but only marginally associated with CD4 counts. Nevertheless, NK-cell populations were not predictive of outcome in DLBCL. Sex-based differences in factors associated with HPV infection and intraepithelial lesions in a cohort of HIV-positive patients:We enrolled 472 patients. Anal/cervical brushing samples were collected for HPV-PCR detection/genotyping and cytologic abnormalities at baseline and follow-up visits. Viro-immunological data were recorded at the time of brushing. HPV infection($p<0.001$), SIL ($p<0.001$), HPV persistence ($p<0.001$) and SIL progression ($p=0.018$) were all associated with male sex. Among females, HPV was associated with higher HIV-RNA ($p=0.002$) and SIL was independently associated with lower CD4+ count (AOR: 0.998; 95%CI: 0.997-1). In the males group, HPV was associated with MSM (AOR: 3.801, 95% CI: 1.82-7.95) while AIDS diagnosis (AOR: 0.387 95% CI:0.176-0.851) and older HIV infection (AOR: 0.996 95% CI: 0.992-0.999) were negatively associated with HPV infection; males with SIL were younger (AOR 0.973, 95% CI 0.95-0,997), more MSMs ($p=0.04$) and with higher levels of immune-activation (CD38+CD8+%) ($p=0.013$) compared to SIL-negative males. In conclusion, the natural history of HPV and SIL is largely influenced by risky behaviors and immune-activation in males, particularly in recently HIV-infected patients, while it appears to be driven by immune-suppression in women. Given the high incidence of HPV infection in both men and women, we suggest that vaccination has to be strongly recommended to all HIV independently form the age and gender.
Localizzazioni e accesso	http://memoria.depositolegale.it/*/http://hdl.handle.net/2434/628815