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Prevalence and predictors of malignancies in HIV patients: results of a retrospective multicentric Italian cohort

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SUMMARY

We report the sharp reduction in the incidence of AIDS defining cancers in a multicentric, retrospective study carried out since 1991 and involving six Infectious Diseases Units spread across Italy. However, due to the parallel increase in non-AIDS defining cancers, cancer incidence was not reduced. Focusing on predictors of death in HIV-positive patients with neoplastic disease, multivariate models revealed that males as well as drug abusers were independently associated with a poor clinical outcome.

Keywords: Predictors, malignancy, HIV.

INTRODUCTION

Since the introduction of combined antiretroviral therapy (cART), the epidemiology of cancer among people living with HIV (PLWH) has been significantly modified [1]. The efficacy and safety of cART both decreased the risk of acquired immunodeficiency syndrome (AIDS) and contributed to prolonged survival of HIV infected patients, thus increasing the mean age of PLWH [2, 3]. In this scenario, the sharp decline in incidence of AIDS-defining cancers, such as Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, was counterbalanced by the increased risk of developing non-AIDS defining cancers (NADCs), which currently represent a major cause of morbidity and mortality in PLWH [4, 5]. HIV-1 infection and co-infection with Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV), lead to a persistent inflammation status, somewhat resistant to the benefits of cART [6, 7]. This state of incomplete immune recovery, often associated with prolonged survival and persistently inadequate lifestyles, raises the risk for PLWH to develop NADCs, more frequently anal cancer, Hodgkin's lymphoma (HL), liver cancer and lung cancer [6, 7].
Our aim was to characterize the prevalence of both AIDS defining cancer and NADCs in a large cohort of patients monitored across Italy in real life clinical settings. To this aim, we performed a case-control study among all consecutive PLWH

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enrolled for management of HIV infection. Furthermore, we tried to identify predictors of malignancies in this large and heterogeneous study cohort.

PATIENTS AND METHODS

We performed a retrospective multicentric evaluation of all HIV infected patients diagnosed with both AIDS and non-AIDS defining neoplasms at six Infectious Disease Units spread throughout Italy (Ancona, Chieti, Firenze, Genova, Perugia, Pescara) from January 1st 1991 to the end of 2013. Cases were compared with an equal number of controls without neoplasia followed at the same Institutions, matched for length of HIV infection, age, CDC staging and CD4 T-cell counts at enrolment. Data were explored by descriptive statistics such as mean (SD) for continuous and frequencies for categorical variables. T-Test and Chi-square test were adopted for univariate analysis that were confirmed by multivariate logistic regressions. All statistical analyses were performed using the Stata 14.2.

RESULTS

Three-hundred and fifty-five consecutive cases of HIV infected patients diagnosed with any

Table 1 - Main features of cases and controls.

	Overall N=710	*Cases 355 (50.0%)*	*Controls 355 (50.0%)*	*p value**
Sex, male, n(%)	507 (73.0)	240 (70.6)	267 (75.2)	0.2
Age, mean (SD)	48.3 (10.8)	48.3 (10.9)	48.3 (10.8)	1.0
Drug addiction, n(%)	166 (25.0)	73 (23.0)	93 (26.9)	0.2
AIDS, n(%)	250 (50.6)	182 (51.9)	68 (47.6)	0.4
Smoke, n(%)	298 (57.5)	169 (59.9)	129 (54.7)	0.2
Death, n(%)	136 (21.2)	101 (30.1)	35 (11.5)	<0.001
CD4 <200 cell/mmc, n(%)	319 (49.4)	158 (51.0)	161 (47.9)	0.4
HBV coinfection, n(%)	100 (21.2)	83 (25.5)	17 (11.5)	0.001
HCV coinfection, n(%)	159 (27.3)	85 (25.9)	74 (29.0)	0.4

Notes: (*) p-values were referred to a chi-square test for frequencies and t-Test for means.

Table 2a - AIDS defining tumor, univariate descriptive analyses with demographic, immune-virological and hepatitis analyzed parameters.

	AIDS defining tumor 177 (50.3%)	*Non AIDS defining tumor 175 (49.7%)*	*p value**
Sex, male, n(%)	133 (76.9)	104 (63.4)	0.007
Age at tumor diagnosis, mean (SD)	42.7 (10.7)	42.7 (11.1)	1.0
Drug addiction, n(%)	33 (20.0)	39 (25.8)	0.2
Smoke, n(%)	80 (60.2)	89 (59.7)	0.9
Death, n(%)	60 (35.7)	38 (23.0)	0.011
LyCD4 <200 cell/mmc at tumor diagnosis, n(%)	91 (54.8)	57 (36.3)	0.001
cART naïve (at diagnosis or pre-treatment waiting), n(%)	100 (58.5)	49 (28.7)	<0.001
HBV coinfection, n(%)	28 (17.2)	55 (34.6)	<0.001
HCV coinfection, n(%)	35 (21.2)	49 (30.6)	0.053

Notes: (*) p-values were referred to a chi-square test for frequencies and t-Test for means.

malignancy were collected from the six involved centres since 1991, including approximately an equal proportion of AIDS (50.3%) and non-AIDS defining tumors. In particular, the diagnosed tumors were: NHL (130 cases, 36.8%), KS (57 casese, 16.2%), HL (20 cases, 14.5%), primary CNS lymphoma (6 cases, 1.7%), hepatocellular carcinoma (8 cases, 2.3%), cervical or anal cancer (49 cases, 13.8%), Monoclonal gammopathy of undetermined significance (29 cases, 8.2%), leukemia (3 cases, 0.8%), other unspecified solid tumor (51 cases, 14.5%). In three cases the origin of the tumor was not specified.

Table 2b - AIDS defining tumor, multivariate logistic analyses.

	OR 95%CI	*p value**
Sex, male	1.90 (1.02 – 3.55)	0.045
Age at tumor diagnosis	1.00 (0.97 – 1.03)	1.0
Drug addiction	0.83 (0.32 – 2.18)	0.7
CD4 <200 cell/mmc at tumor diagnosis	1.56 (0.90 – 2.69)	0.1
cART naïve (at diagnosis or pre-treatment waiting)	2.62 (1.45 – 4.73)	0.001
HBV coinfection	0.28 (0.15 – 0.52)	<0.001
HCV coinfection	0.99 (0.39 – 2.48)	1.0

Main features of cases and controls are reported in Table 1: mean age at tumor diagnosis was similar in cases and controls (48.3±10.9 vs 48.3±10.8 years, respectively, p=1.0); drug addiction was the major risk factor for HIV infection and was similar in both groups (23.0% vs 26.9%, respectively, p=0.2); a higher proportion of cancer patients had HBV coinfection (25.5% vs 11.5%, p=0.001). Seventy percent of tumors occurred in males (Table 1); 51.9% of patients were diagnosed with AIDS in advance of malignancy, while 19.0% were diagnosed with HIV and AIDS at the same time of tumor diagnosis. One hundred-one (30.1%) tumor patients died at the time of data collection, a much higher proportion than among cases (30.1% vs

Table 3 - Death, univariate and multivariate logistic analysis.

	Univariate descriptive analysis			*Logistic multivariate analysis*	
	Death 136 (21.2%)	*Alive 505 (78.8%)*	*p-value**	*OR (95%CI)*	*p value*
Sex, male, n(%)	107 (79.9)	361 (71.8)	0.060	3.66 (1.33 – 10.06)	0.012
Age at tumor diagnosis, mean (SD)	45.1 (9.7)	42.0 (11.2)	0.014	1.02 (0.98 – 1.05)	0.4
Drug addiction, n(%)	55 (44.4)	96 (19.7)	<0.001	3.55 (1.12 – 11.25)	0.031
Smoke, n(%)	53 (69.7)	243 (55.7)	0.023	1.09 (0.51 – 2.29)	0.8
AIDS, n(%)	70 (63.1)	172 (48.2)	0.006	1.87 (0.86 – 4.07)	0.1
AIDS defining tumor, n(%)	60 (61.2)	108 (46.0)	0.011	1.01 (0.49 – 2.09)	1.0
CD4 <200 cell/mmc, n(%)	84 (66.1)	214 (45.4)	<0.001	1.05 (0.50 – 2.19)	0.9
cART naïve (at diagnosis or pre-treatment waiting), n(%)	46 (44.7)	121 (40.5)	0.5	2.17 (0.92 – 5.11)	0.077
HBV coinfection, n(%)	19 (18.6)	80 (22.4)	0.4	0.44 (0.18 – 1.04)	0.062
HCV coinfection, n(%)	46 (42.2)	110 (24.1)	<0.001	2.08 (0.60 – 7.25)	0.3

Notes: (*) p-values were referred to a chi-square test for frequencies and t-Test for means.

11.5%, p<0.001) (Table 1). We performed univariate and multivariate analyses to assess predictors of AIDS defining tumor and deaths (Tables 2a, 2b and 3). Male sex (p=0.007), LyCD4 counts <200 cells/mmc (p=0.001), being cArt naïve (p<0.001) were all associated with AIDS defining (Table 2a). Instead, HBV coinfection resulted associated with non-AIDS defining tumors (p<0.001), HCV coinfection being near significant (p=0.053) (Table 2a). Deaths among AIDS (35.2%) and non-AIDS defining tumor patients (35.7% vs 23.0%) were significantly different (p=0.011) (Table 2a). At multivariate models of logistic regression, male sex (OR=1.90, p=0.045) and being cART naïve (OR=2.62, p=0.001) appeared associated, while HBV coinfection reduced the risk (OR= 0.28, p<0.001) (Table 2b).
Predictors of death at the time of data collection were: male sex (p=0.06); higher mean age at tumor diagnosis (p=0.014); being drug abusers (p<0.001), CD4 T-cell counts <200 cells/mmc at diagnosis of malignancy (p=0.001), HCV co-infection (p<0.001), AIDS diagnosis (p=0.006), diagnosis of AIDS defining tumor (p=0.011), smoke (p=0.023) (Table 3). At multivariate model of logistic regression, only male sex (OR=3.66, p=0.012) and being drug abuser (OR=3.55, p=0.031) held an independent prediction, whereas not being treated with cART and not being HBV coinfected were near significant (p=0.077 and p=0.062, respectively) (Table 3).

DISCUSSION

The higher prevalence of cancer among male HIV patients in this series is well aligned with other data in the literature and may be related to the simultaneous presence of more general risk factors for malignancy in this setting, such as a high proportion of men who have sex with men (MSM), exposed to oral or anal human papillomavirus (HPV), and a higher proportion of injection drug users, exposed to HBV/HCV-contaminated blood and needles, as well as a higher proportion of cigarette smokers [8].
The lower CD4 T-cell counts observed at the time of tumor diagnosis could be in relation with two different issues: first, the greater is the immune suppression, the greater is the oncogenic potential of viral co-infections predisposing to cancer development. Second, it is well known that the immune deregulation caused by neoplastic cells might reduce the recovery in CD4 T-cell counts, leading to a higher proportion of cases of Hodgkin lymphoma, one of the most frequently observed non-AIDS-related cancers [9]. Furthermore, 19% of the patients enrolled were diagnosed with AIDS and cancer at the same time, enforcing the concept that earlier HIV diagnosis as well as aggressive cancer screening and prevention are mandatory to reduce the burden of those diseases in our country. The age of patients at the onset of cancer was significantly lower than the age of matched controls (all HIV infected) and the age of the general population for the same neoplasia [10]. This phenomenon may be related to persistent inflammation sustained by HIV, despite near complete viral suppression, a trait responsible for other manifestations of the disease burden observed in HIV patients treated with cART [2].
Furthermore, in our analysis HBV appears to be related to non-AIDS defining tumors. Several evidences showed that HBV may infect other tissues besides the liver and it can play an oncogenic role through replication also in extra-hepatic reservoirs, leading to chronic inflammation, with inhibition of p53, and immune stimulation of B-lymphocytes [11, 12].
Although increased risk of hepatocellular carcinoma and NHL are well established, more evidences correlated HBV to the development of other solid tumors [12-14]. In this setting of patients, HBV could amplify HIV oncogenic role in non-AIDS defining tumors however, further investigations should be performed to confirm this correlation.
Finally, the higher mortality reported in patients with HIV and cancer is in line with other data in the literature and should be considered as a mandatory input to improve the extent of deployment and the efficacy of HIV screening campaigns; thus, aging in PLWH should be addressed as a further indication for targeted screening campaigns. Moreover, new diagnostic and therapeutic approaches as those reported by Beretta et al. should be implemented [15]. A multidisciplinary attitude, involving other health specialists such as pharmacists, geneticists, and lab specialists, should be provided in order to maximise the effect of cART and anti-neoplastic agents and ultimately improve patients' outcome [15].
Thus, improvements in early diagnosis of HIV in-

fection may once more have a deep impact on the reduction of mortality in HIV infection through the increased prevention of cancer related mortality.

The strength of our study dwells on the number of medical centres involved and in their diffusion across the nation, so it is representative of the real conditions faced by clinicians daily involved with the care of aging PLWH. On the other hand, the main limitation resides in the number of patients enrolled which is not sufficient for a robust analysis. Therefore, further investigations as well as collecting data from larger cohorts, should be performed to verify and confirm our findings.

CONCLUSIONS

Our retrospective study revealed a considerably high proportion of NADCs, apparently on the rise in recent years. The unexpectedly higher proportion of mortality among drug abusers, confirmed by multivariate model, independently to HCV/HBV co-infections, suggests the need for the improvement of oncologic screenings in this high-risk group.

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