HIV Infection and Non-AIDS-Defining Malignancies: An Outpatient Clinic Experience

Infecção VIH e Neoplasias Não Definidoras de SIDA: Experiência de um Centro

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ABSTRACT

Introduction: Human Immunodeficiency Virus infected patients have an increased risk for developing different types of cancer. After the introduction of highly active antiretroviral therapy (HAART), and consequent increased survival, a shift has been seen in the spectrum and evolution of HIV infection related diseases, particularly oncological ones, with a tendency to increase non-AIDS-defining malignancies (NADM) as opposed to AIDS defining malignancies.

Material and Methods: Characterization of the Human Immunodeficiency Virus infected patients with a non-AIDS defining malignancy diagnosis, followed over 16 years at an outpatient clinic in Lisbon through the review of medical records and retrospective evaluation of demographic, epidemiological, clinical and laboratorial parameters, treatment and mortality.

Results: Of the 1042 patients evaluated, there were 34 Non-AIDS defining malignancy cases identified, mostly in men (78%), with a median age of 55 years. The most common cancers were: lung (20.6%), bladder (17.6%), prostate (8.8%), and anal carcinoma (5.9%). The mean time between Human Immunodeficiency Virus infection and non-AIDS-defining malignancy diagnosis was 6.8 ± 4 years. At the time of non-AIDS- defining malignancy diagnosis the majority of patients (78.8%) was receiving HAART for a mean period of 5.7 ± 3 years, most of whom were immune and virologically controlled (64%). There were 45.5% deaths, mainly in patients with lung cancer (20%).

Conclusion: Given the risk of developing a non-AIDS-defining malignancy in Human Immunodeficiency Virus-infected patients, it is essential to continue to invest in prevention strategies, promote smoking cessation as well as vaccination programs, as well as applying screening protocols adjusted to this population.

Keywords: Acquired Immunodeficiency Syndrome; Antiretroviral Therapy, Highly Active; HIV Infections; Neoplasms.

RESUMO

Introdução: Os doentes infectados pelo Vírus da Imunodeficiência Humana têm um risco elevado de desenvolver diferentes tipos de Neoplasias. Com a introdução da terapêutica anti-retroviral de alta potência, e consequente aumento da sobrevida, assistimos a uma mudança do espectro das patologias relacionadas com a infecção, nomeadamente das doenças Oncológicas, com aumento das Neoplasias Não Definidoras em deterimento das Definidoras de SIDA.

Material e Métodos: Caracterização dos doentes com infecção Vírus da Imunodeficiência Humana e diagnóstico de Neoplasias Não Definidoras acompanhados ao longo de 16 anos na Consulta de Medicina/Imunodeficiência do Hospital de São José, através da consulta dos processos clínicos e avaliação retrospectiva dos aspectos demográficos, epidemiológicos, clínico-laboratoriais, tratamento e sobrevida.

Resultados: Nos 1042 doentes avaliados, foram identificados 34 casos de Neoplasias Não Definidoras, principalmente em homens (78%) e com idade mediana de 55 anos. As neoplasias mais frequentes foram: pulmão (20,6%), bexiga (17,6%), próstata (8,8%) e canal anal (5,9%), sendo o tempo médio entre o diagnóstico da infecção pelo Vírus da Imunodeficiência Humana e da Neoplasias Não Definidoras de 6,8 ± 4 anos. Na altura do diagnóstico da Neoplasias Não Definidoras a maioria dos doentes (78,8%) estava sob terapêutica anti-retroviral de alta potência, em média desde há 5,7 ± 3 anos, encontrando-se imunovirologicamente controlada. No total verificaram-se 45,5% óbitos, sobretudo em doentes com Neoplasia do pulmão (20%).

Conclusão: Perante o risco de desenvolvimento de Neoplasias Não Definidoras nos doentes infectados pelo Vírus da Imunodeficiência Humana, torna-se fundamental o investimento em estratégias de prevenção, promoção de cessação tabágica e vacinação, bem como aplicação de protocolos de rastreio ajustados a esta população.

Palavras-chave: Infecção por VIH; Neoplasias; Síndrome de Imunodeficiência Adquirida; Terapêutica Anti-Retroviral.

INTRODUCTION

HIV (Human Immunodeficiency Virus) infected patients have a high risk, higher than general population, for the development of different types of cancer.[1-4] After the introduction of highly active antiretroviral therapy (HAART) and ensuing increased survival, a shift has been observed in the range and evolution of HIV infection-related disorders, mainly in oncological disorders, with a tendency towards an increase of non-AIDS-defining malignancies (NADM) rather than AIDS-defining malignancies (ADM).[2-8] Previous reviews indicate a two to four times higher cancer frequency *vs.* general population, with a variable incidence according with age, gender, ethnicity and geographical region, being the most frequent Hodgkin's lymphoma, lung cancer and oncogenic virus-related carcinomas as hepatocellular carcinoma and anal cancer.[3,4,9,10] As NADM generally affect younger patients, with an atypical and more aggressive presentation, inducing a quick progression of the disease, with high relapse rates and bad therapy response.[11-13]

Regarding etiopathogenesis, data are still scarce

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and controversial. As in general population, some behaviours and lifestyles (tobacco and alcohol abuse, sunlight exposure) seem to be involved.[7,14] The influence of immunosuppression status is less understood, in line with what happens with transplanted patients or patients under chronic immunosuppressive therapies.[9,15,16] A recent French prospective study showed that the risk of cancer progressively increases for CD4+ T-lymphocyte counts below 500 cells/mm^3 and even higher when below 50 cells/mm^3.[15] In addition, an Australian study with transplanted patients showed an enhanced risk with a similar NADM pattern in these patients, suggesting that immunosuppression is itself the responsible for the increase of that risk.[16] Again, HIV seems to produce itself a direct action on different cell mechanisms, contributing for the development of cancer. Some of these mechanisms include proto-oncogene activation, the interference on cell cycle regulation, tumor suppressor genes inhibition, among others.[12,17] Co-infection with other oncogenic virus (B and C-hepatitis, Epstein-Barr – EBV and Human Papillomavirus - HPV) raises cancer development, due to viral replication and infection persistence enhancement, producing a quicker progression of its natural history.[16,18,19] Finally, the use of anti-retroviral therapy, particularly non-nucleoside reverse transcriptase inhibitors (NNRTI), has been considered as an additional potential carcinogenic factor.[9,20]

Despite cancer being currently a major cause for mortality in HIV-infected patients[21] there are in most cases no specific guidelines for screening and early treatment.[19] In the case of European AIDS Clinical Society some screening protocols are recommended, mainly for anal, breast, cervical, colorectal, liver and prostate cancer.[22] In this context, prevention includes mainly information campaigns, tobacco cessation promotion and immunization.[2]

Regarding cancer treatment in these patients, it is not generally different from treatment in general population, although we must consider not only cancer's primary location, as well as patient's health condition, possible drug interactions and cumulative toxicities.[12]

In order to give a contribution for NADM knowledge and characterization, as well as possible risk factors, the characterization of a group of HIV-infected patients has been carried out, followed by the NADM subsequent diagnosis, followed over 16 years at the Medicine/ Immunodeficiency Outpatient Department at the *Hospital de São José – Lisboa, Portugal*.

MATERIAL AND METHODS

Characterization of HIV-infected patients with a NADM diagnosis, followed over 16 years (1997 - 2012) at the Medicine / Immunodeficiency Outpatient Department at *Hospital de São José, CHLC-EPE* – database and clinical records, retrospective assessment of the following: gender, age, ethnicity, HIV type and transmission category, immunological and virological evaluation, risk factors for cancer development (tobacco, alcohol abuse, HPV and B and C hepatitis co-infection), time of evolution of HIV infection until cancer diagnosis, presence, type and duration of anti-retroviral therapy (ART) until cancer diagnosis, cancer type and histology, therapy (surgery, chemotherapy, radiotherapy, hormonal therapy or others) and mortality.

The patients with cancer clinical history previous to HIV-infection diagnosis, as well as those that cancelled the follow-up or that were transferred to another outpatient department without any cancer confirmed diagnosis were excluded from our study. Cancer diagnosis has been based in clinical suspicion as well as in clinical, laboratory, radiological and/or histopathological data.

We should refer that data were difficult to obtain, with some gaps in non-digitalized clinical information

In order to compare survival between groups of patients, Kaplan-Meier estimate and Breslow test have been used. A significance level $\alpha = 0.05$ has been considered. Data statistical analysis used SPSS® software version 21 (SPSS Inc, Chicago, IL).

RESULTS

We have followed 1.042 HIV-infected patients over 16 years (1997 - 2012) with a mean follow-up of 6.5 years (minimum 0.003 - maximum 16 years). From these, 33 (3.2%) patients had a confirmed diagnosis of NADM; Table 1 presents demographic and clinical/laboratory characteristics referred to HIV-infection.

Median age at the time of HIV diagnosis were 51 (23 -75), most patients were male (78.8%). Caucasian ethnicity as well as HIV-1 were clearly predominant (97% and 93.9%, respectively), including one patient of black ethnicity (3%) and two cases of HIV-2 infection (6.1%). Regarding transmission category, sexual contact was the most frequent transmission route, mainly heterosexual (72.7%). Transmission associated with intravenous drug use was present in 5.2%.

Regarding the level of immunosuppression and according with the first known CD4 T-lymphocyte count, mean count was 368 ± 308 cells/mm^3 and median was 289 (19 – 1,500) cells/mm^3.

Thirty-four NADM patients were identified, with two NADM diagnosis in the same patient (bladder cancer and basal cell carcinoma from the nose). We should also remark one patient whose ADM primary diagnosis (skin Kaposi's sarcoma) led to a NADM early staging and diagnosis (lung cancer) – patient number 7, Table 2.

HIV infection mean evolution time until NADM diagnosis was 6.8 ± 4 years, longer than the time between the first medical visit and NADM diagnosis (mean 4.6 ± 4 years). Two patients had a previous established NADM diagnosis, in another hospital, both three years upon HIV infection diagnosis (patient number 19 and 22, Table 2).

At the time of NADM diagnosis, patients had a median age of 55 (31 - 73). The youngest patient with a stage IV sclero-nodular Hodgkin's lymphoma diagnosis had an

Table 1 - Demographic and clinical/pathological characteristics of HIV-infected patients with NADM

Characteristics	*n*	%
Number of patients	33	
Age at HIV diagnosis (years)		
Median	51	
Interval	23 - 75	
Gender		
Female	7	21.2%
Male	26	78.8%
Ethnicity		
Caucasian	32	97.0%
Black	1	3.0%
Infection type		
HIV 1	31	93.9%
HIV 2	2	6.1%
Transmission route		
Heterosexual	24	72.7%
Drug addiction	5	15.2%
Homosexual	3	9.1%
Unknown	1	3.0%
Exposure to ART		
Yes	24	72.7%
Yes, but period of time unknown	2	6.1%
No	7	21.2%
Average time until the NADM diagnosis (years) (*n* = 24)	6 ± 3	
First CD4 count (cells/mm^3)		
Median	289	
Interval	9-1500	

NADM. Non-AIDS defining malignancy; ART. Antiretroviral therapy

irregular follow-up, with very low therapy compliance. At that time and although having a known HIV infection with only two years of evolution, already presented a severe immunosuppressive condition (CD4-T lymphocyte count 55 cells/mm^3) and detectable HIV-1 viral load (113,196 copies/ml, 5.5 log) - (patient number 26, Table 2).

From an immunological point of view, the patients presented on average CD4 T-lymphocyte count of 512 ± 254 cells/mm^3 and most patients (64%) were stable and with undetectable viremia.

At the time of our study, 26 patients (78.8%) were on ART, from which 24 were on average from 5.7 ± 3 years. From these 26 patients, 54% followed a therapy plan with protease inhibitors (PI) and 46% with NNRTIs (Table 1 and 2).

Regarding NADM type, lung cancer was the most frequent (7 patients, 20.6%) – mostly in smokers (71.4%) – followed by bladder (17.6%), prostate (8.8%) and anal cancer (5.9%). The remaining oncological disorders and histological types are presented in Table 3.

Regarding cancer staging at the time of diagnosis, we should remark that four patients (12%) already presented

Table 2 - Clinical/pathological characteristics of our group of patients

Patient number	Gender	Virus	Age when HIV diagnosed (years)	Age when NADM diagnosed (years)	1st CD4 count (cells /mm³)	CD4 when NADM (cells /mm³)	Viral load at NADM (copies/ml)	ART with NNRTI/PI	ART until NADM (years)	NAFM risk factor	NADM type	Therapy	Death
1	M	HIV1	59	68	823	1021	< 20	PI	ND	Smoking	*Lung*	Palliative care	Y
2	M	HIV1	53	66	1500	822	< 20	NNRTI	3		*Lung*	RTX	N
3	M	HIV1	41	48	524	326	25722		0	Smoking; HCV	*Lung*	UD	Y
4	M	HIV1	30	38	506	554	< 40	PI	8	Smoking; HCV	*Lung*	CTx + RTx	Y
5	M	HIV1	45	53	146	929	< 50	NNRTI	9	Smoking	*Lung*	CTx + RTx	Y
6	M	HIV1	49	49	454	580	< 40	NNRTI	8	HCV	*Lung*	Paliative care	Y
7	M	HIV1	46	46	413	615	< 20	NNRTI	2	Smoking	*Lung*	Lobectomy	N
8	M	HIV1	54	63	427	974	< 20	NNRTI	10	Smoking	*Bladder*	TUR	N
9	M	HIV1	64	67	500	537	< 20	NNRTI	3		*Bladder*	HTx + RTx	Y
10	M	HIV1	51	51	111	111	50445		0	HCV	*Bladder + BCC (Nose)*	TUR	Y
11	M	HIV1	56	63	114	465	< 40	NNRTI	7		*Bladder*	Radical cystoprostatectomy	N
12	M	HIV1	72	73	262	465	28	NNRTI	0.5		*Bladder*	Refused	Y
13	M	HIV1	32	34	703	617	< 20	NNRTI	2		*Bladder*	Intravesical interferon	N
14	M	HIV1	62	67	515	879	< 40	NNRTI	5		*Prostate*	HTx	N
15	M	HIV1	63	68	355	546	< 40	PI	6		*Prostate*	HTx	N
16	M	HIV1	43	51	19	496	< 20	NNRTI	9		*Prostate*	Radical prostatectomy	N
17	M	HIV1	23	34	289	295	17319	PI	11	HCV	*Anal*	RTx + CTx	N
18	M	HIV1	27	42	276	ND	ND		0	HPV	*Anal*	UNS surgery	N
19	M	HIV1	60	60	12	ND	ND		0		*Colo-rectal*	Sigmoidectomy	N
20	M	HIV1	57	65	276	581	< 20	IP	8		*Colo-rectal*	Left hemicolectomy	N
21	M	HIV1	65	73	132	412	< 20	IP	9	Alcohol abuse	*Gastric*	Total nephrectomy	Y
22	F	HIV1	75	77	222	456	< 40	IP	2		*Gastric*	Subtotal gastrectomy + CTx	N
24	F	HIV1	60	60	335	370	4089		0		*Breast*	Mastectomy	N
25	F	HIV1	58	66	126	730	91	IP	8		*Breast*	Tumorectomy + RTx + HTx	N
27	F	HIV2	51	54	25	99	< 40	IP	0.4		*Conjunctival*	Conjunctival excision	Y
26	M	HIV1	29	31	202	55	113196	IP	2		*Hodgkins' lymphoma*	CTx	N
23	M	HIV1	71	72	31	31	129895	IP	0.4		*Kidney*	Left nephrectomy	Y
28	F	HIV1	31	41	995	340	7525		0	Smoking; HCV	*Laryngeal*	Laryngectomy + RTx	N
29	M	HIV1	29	43	448	513	< 20	IP	7	HBV	*BCC (Nose)*	Refused	N
30	M	HIV1	49	54	250	262	1246	IP	6	HBV	*Penile*	Partial penectomy	Y
31	M	HIV1	44	55	77	673	< 20	NNRTI	11	Smoking	*Tongue*	Hemiglossectomy + Gingivectomy + RTx	Y
32	F	HIV1	25	36	450	446	< 40	IP	ND	Smoking; HCV	*Tonsil*	UD	Y
33	F	HIV2	63	64	641	678	< 40		0		*Uterine*	UD	Y

NADM. Non-AIDS-defining malignancy; ART. Antiretroviral therapy; NNRTI. Non-nucleoside reverse transcriptase inhibitor; PI.Protease inhibitor; HCV. Hepatitis C virus; HBV. Hepatitis B virus; HPV. Human papillomavirus; BCC. Basal-cell carcinoma; CTx. Chemotherapy; RTx. Radiotherapy; HTx. Hormonal therapy; Y. Yes; N. No; UD. Undetermined; UNS. Unspecified.

Table 3 - Type of NADM

Type of cancer	*n*	%
Lung	7	20.6%
Non-small cell adenocarcinoma	2	
Squamous cell carcinoma	2	
Small cell carcinoma	1	
Undetermined	2	
Bladder	6	17.6%
Invasive transition cell urothelial carcinoma	4	
Low-grade papillary urothelial carcinoma	1	
In situ carcinoma	1	
Prostate	3	8.8%
Adenocarcinoma		
Anal	2	5.9%
Squamous cell carcinoma		
Breast	2	5.9%
Invasive ductal carcinoma	1	
Invasive lobular carcinoma	1	
Colo-rectal	2	5.9%
Well-differentiated adenocarcinoma		
Gastric	2	5.9%
Adenocarcinoma		
Skin	2	5.9%
Basal cell carcinoma		
Conjuntival	1	2.9%
Invasive squamous-cell carcinoma		
Hodgkin's Lymphoma	1	2.9%
Stage IV sclero-nodular		
Kidney	1	2.9%
Renal cell papillary carcinoma		
Laryngeal	1	2.9%
Squamous cell carcinoma		
Penile	1	2.9%
Squamous cell carcinoma		
Tongue	1	2.9%
Invasive squamous cell carcinoma		
Tonsil	1	2.9%
Moderately-differentiated squamous cell carcinoma		
Uterine	1	2.9%
Não especificado		
TOTAL NADM	34	100.0%
Total number of patients	33	

NADM. Non-AIDS-defining malignancy

an advanced disease, particularly with lung and gastric cancer. In these patients, disease started with distance metastasis signs, mainly in the liver but also with brain, bone and kidney invasion (Table 4).

Nine patients presented HCV (7) or HBV co-infection (2) and one patient presented HPV infection, which has developed in an anal cancer. Different additional risk factors were identified: tobacco (27%) and alcohol abuse (3%), intravenous drug use (15.2%).

Treatment of different types of cancer included: surgery (37%), chemotherapy (CTx - 14%), radiotherapy (RTx- 19%) and hormone therapy (HTx – 14%) in isolated or combined way, as it is presented in Table 2 and 4. However, we should remark that some patients had only an indication for palliative care (5%).

Fifteen patients died (45.5%), mostly patients with invasive lung cancer (20%) – Fig. 1.

The median age of deceased patients was 56 (36 - 78) and the median time of evolution of known HIV infection was eight (0.5 - 12) years. The youngest patient died at the age of 36, at the same year of diagnosis of a squamous cell carcinoma of the tonsil, with an undetermined treatment as this patient finally died at another hospital. Regarding immunological and virological staging, these patients presented on average CD4 counts of 475 ± 277 /mm^3, 66.7% of which with undetectable HIV viral load. Two female HIV-2 infected patients died with conjunctival and cervical cancer, respectively.

We only identified three death causes: the cancer itself, H1N1-infection (one patient) and a post-surgical nephrectomy death occurring during admission to the ICU. The characteristics of the remaining deceased patients are presented in Table 4.

DISCUSSION

Considered as enhanced risk disorders in HIV-infected patients, NADM are currently a major cause of morbidity/mortality in these patients.[21] The most frequent include Hodgkin's lymphoma, lung cancer and oncogenic virus-related carcinomas as hepatocellular carcinoma and anal cancer.[1,3,4,9,10] Head and neck, colorectal, prostate, penile and kidney cancer also present an increased risk in HIV-infected patients.[4,9,10,23]

In our analysis, lung cancer was the most prevalent, followed by bladder, prostate and anal cancer. Head and neck cancer included laryngeal, tongue and tonsil cancer patients.

Regarding lung cancer, this is currently the third most common cancer cause in these patients, only preceded by ADM as Kaposi's sarcoma and non-Hodgkin's lymphoma.[24] In line with most clinical review series[1,12,16,25-27] we also found a male and smoker predominance and adenocarcinoma and squamous cell as most common histological types which added to a tendency for a late diagnosis and already with distance invasive evidence, which conferred a worse outcome with a high mortality rate. Genitourinary cancer was also highly prevalent in this study (bladder, prostate and kidney). According with previous reviews, although bladder cancer is most prevalent in transplanted immunosuppressed patients[16] data regarding HIV-infected patients are scarce. However, younger age, with male predominance and the presence of haematuria seem to be the most common clinical presentation. Patients usually present moderate immunosuppression and a disease confined to the initial location, while the most common histological type is transitional cell urothelial carcinoma. Smoking habit is included as a risk factor and ART does not seem to contribute.[28] In our study, bladder cancer patients had a similar presentation, except regarding staging, which was more advanced and with a higher number of patients with an invasive carcinoma. We also identified three patients with prostate cancer and one patient with kidney cancer; in line with previous studies, these presented similar characteristics as in general population. It does not seem to exist any influence of HIV infection on PSA levels, on cancer clinical presentation, staging or therapy,.[29] However, we should remark that some studies describe a slight increase of kidney cancer incidence in this population, mainly renal cell carcinoma, although the underlying mechanisms are not entirely understood.[1,30,31]

Neoplasms associated with oncogenic virus-related co-infections are also more prevalent in HIV-infected patients. HPV infection, whose chronic infection is promoted by the accompanying HIV infection, is a major risk factor for the development of anal, penile and conjunctival cancer, among others. Although anal cancer is uncommon in general population, there is an increased risk in HIV-infected patients, particularly in homosexual.[7] In this context and although there are no guidelines specifically oriented to this population, it may be recommendable to obtain a cytology at the time of HIV diagnose, with biannual follow-up until two negative tests are obtained, beyond annual inspection and digital rectal examination and possible anoscopy and biopsy in the presence of changes.[19] We found two patients with anal cancer in our study, both in homosexual-behaviour young patients, one of them with a HPV co-infection. In addition, penile cancer, whose risk is also increased in patients with HIV and HPV co-infection,[1] represents a NADM clinical case.

Despite the percentage of patients presenting a co-infection with B and/or C hepatitis (27%), we did not find any patient with a hepatocellular carcinoma.

We should also remark that, although Hodgkin's lymphoma is considered as the most frequent NADM[12] related with EBV co-infection, we only found one patient in our study. In addition, despite a bad outcome associated with this type of cancer as with severe immunosuppression (CD4 count of 55 cells/ mm^3), this patient had a good response to chemotherapy, in 12 years follow-up upon cancer diagnosis.

We also found patients with gastrointestinal cancer in our study, mainly gastric and colorectal cancer, both

Table 4 - Clinical/pathological characteristics, type of cancer, therapy and cause of death in our group of NADM-diagnosed patients

Patient number	Gender	Age at NADM (years)	Age at time of death (years)	CD4 count at NADM (cells/ml)	Viral load at NADM (copies/ml)	NADM risk factors	Type of NADM	Metastasis	Therapy	Cause of death
1	M	68	68	1021	< 20	Smoking	*Lung*		Palliative care	NADM
2	M	48	48	326	25722	Smoking; HCV	*Lung*	Liver	UD	NADM
3	M	38	39	554	< 40	Smoking; HCV	*Lung*	Liver and brain	CTx + RTx	NADM
4	M	53	54	929	< 50	Smoking	*Lung*	Liver and bone	CTx + RTx	UD
5	M	49	49	580	< 40	HCV	*Lung*		Palliative care	UD
6	M	67	71	537	< 20		*Bladder*		HTx + RTx	NADM
7	M	51	51	111	50445	HCV	*Bladder + BCC (nose)*		TUR	NADM
8	M	73	74	465	28		*Bladder*		Refused	NADM
9	M	73	73	412	< 20	Alcohol	*Gastric*	Lung and kidney	Total nephrectomy	Nephrectomy post-surgical
10	M	72	75	31	129895		*Kidney*		Total nephrectomy	UD
11	F	54	58	99	< 40		*Conjunctival*		Conjunctival excision	H1N1 Flu
12	M	54	55	262	1246	HBV	*Penile*		Partial penectomy	UD
13	M	55	56	673	< 20	Smoking	*Tongue*		Hemiglossectomy + Gingivectomy + RTx	UD
14	F	36	36	446	< 40	Smoking; HCV	*Tonsil*		UD	UD
15	F	64	65	678	< 40		*Uterine*		UD	UD

NADM. Non-AIDS-defining malignancy; HCV. Hepatitis C virus; HBV. Hepatitis B virus; BCC. Basal-cell carcinoma; CTx. Chemotherapy; RTx. Radiotherapy; HTx. Hormonal therapy; TUR. Transurethral resection; UA. Undetermined.

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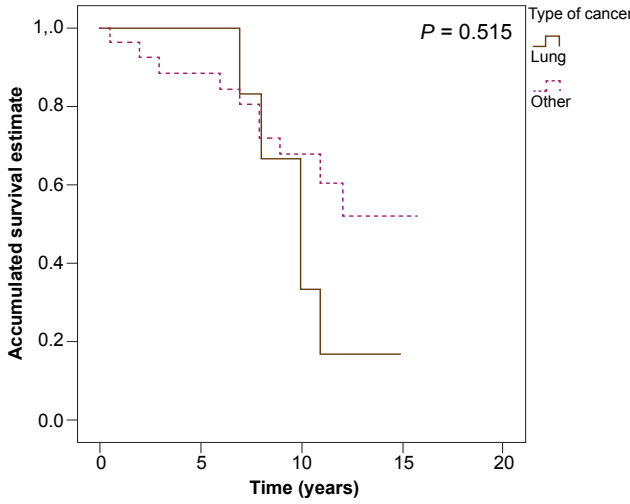

Figure 1 - Kaplan-Meier estimate of stratified survival function by type of cancer

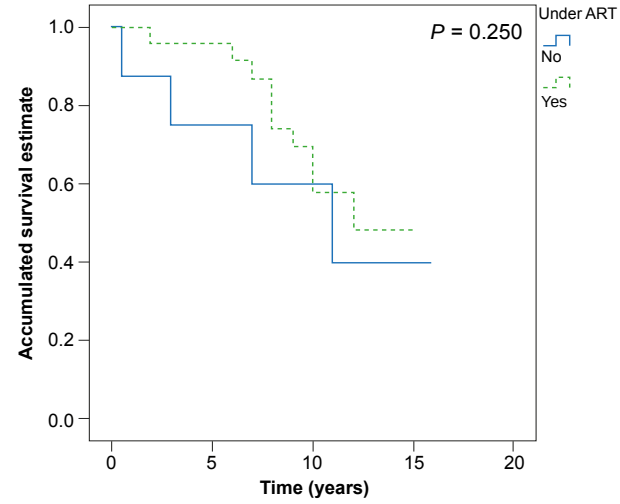

Figura 2 - Kaplan-Meier estimate of stratified survival function by ART

more prevalent in HIV-infected population than in general population.[2,32,33]

It is important to remark the two deadly cancer-affected HIV-2-infected female patients in our study. The first patient presented a conjunctival cancer, also closely related with HPV infection and promoted by sunlight exposure and ageing.[23] Among HPV-related neoplasms, this is considered as one of the most invasive in immunosuppressed patients. However, it is independent from HIV-transmission route, CD4 cell count or time of evolution of underlying HIV infection.[34] This patient was of black ethnicity with HIV-2 infection diagnosed three years before, with a severe immunosuppression (CD4 count of 99 cells/ mm^3) and under ART with a PI, although with bad compliance to therapy. Upon invasive squamous cell histology, she underwent a conjunctival excision, dying four years later when admitted to the ICU due to influenzae H1N1 infection. The second HIV-2 patient presented a satisfactory immunovirological control and without the need for therapy, with a cervical cancer diagnosis at the age of 64.

Finally, we should remark two breast cancer patients. According with literature, the aetiological relation with HIV is not clear. While some studies describe the development of a disease with a tendency towards a more aggressive, earlier and with worse outcome,[35] others did not find any difference related with the presentation form when compared with general population.[36] In our study, we found two patients with cancer diagnosed at the age of 60 and 65, with no invasion evidence and with good response to therapy.

Regarding the mechanisms responsible for the incidence increase of these cancers in HIV-infected patients, data are scarce and controversial, a multifactorial aetiology being suggested.

Due to our study's retrospective and observational characteristics, as well as the small dimension of our group of patients and the absence of a control group (which were the major constraints of our study), we may not establish any correlations, mainly regarding the oncogenic risk factors involved. However, we should remark that patient's young age at the time of a NADM diagnosis (median of 55), the incidence of patients with invasion evidence at NADM presentation (12%) as well as the high mortality rate (45.5%) found are in line with literature data regarding cancer's earlier presentation, more aggressive and with worse outcome in HIV-infected patients.

As regards HIV itself, immunosuppression and viremia level, as well as the impact of the use of ART on the risk of development of a NADM, most patients were immunovirologically controlled and under ART (54% PI/ 46% NNRTI). However, an immunosuppression evolutive assessment has not been made (with only two determinations per patient) nor regarding previous therapy programs, for no conclusion can be reached concerning potentially carcinogenic effects of any of these parameters (Fig. 2 and 3). In addition, the presence of certain behaviours and lifestyles as smoking (27.3%), alcohol abuse (3%) and oncogenic viral co-infection (HCV, HBV, HPV) may have contributed to the development of some of these neoplasms.

CONCLUSION

Strategies oriented towards reducing morbidity and mortality of oncological disorders in HIV-infected patients are crucial, due to the risk of early development of different types of cancer in these patients. Therefore, we must keep developing prevention strategies through Information campaigns, general measures as smoking cessation promotion and immunization campaigns, as well as using screening protocols adjusted to HIV-infected patients.

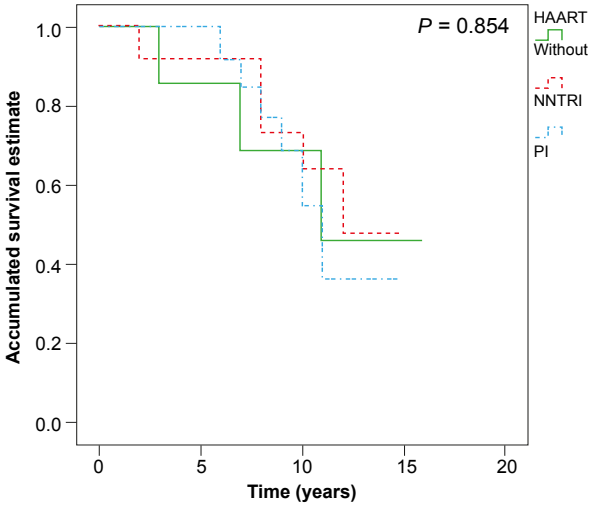

Figure 3 - Kaplan-Meier estimate of stratified survival function by therapy. HAART: highly active antiretroviral therapy.

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CONFLICTS OF INTEREST

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Maria do Carmo FEVEREIRO

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