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Malignancies in HIV-infected patients – incidence and predictors of survival in a Romanian health care facility

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Abstract: *Objective.* To estimate incidence and survival in HIV-infected patients with malignancies.

Methods. Retrospective study on patients with malignancies from a single HIV center between January 2007 and December 2014. Malignancies were classified in ADMs (AIDS-defining malignancies) and nADMs (non AIDS-defining malignancies) (CDC 1993). Statistical analysis was performed using STATA 20.

Results. From 12,298 person-years (PY), 91 (3.2%) were diagnosed with malignancies (incidence 7.39/1000 PY): 57 (62.6%) ADMs and 34 (37.3%) nADMs. Median age (IQR) at HIV and cancer diagnosis was 32 years (1-70) respectively 34 years (34-74). The most common ADMs were: non-Hodgkin's lymphoma NHL 31 (54.3%), Kaposi Sarcoma KS 17 (29.8%) and cervical cancer 9 (15.7 %). Among nADM, Hodgkin's lymphoma (HL) was the most frequent: 10 cases (29.4%). Patients with ADM had significantly lower nadir and median CD4 cell count/mm^3 at cancer diagnosis compared to NADM (47 *vs*. 91 and 123 *vs*. 306 ($p<0.01$) and higher median HIV viral loads log10 (5.3 *vs*. 3.4). Kaplan-Meier survival estimates showed that patients with NHL had significantly worse survival than those with HL or KS ($p=0.03$). All-cause annual death rate was 12.8% and significantly decreased to 11.1% and 7.6% for patients on cART and a combination of cART and chemotherapy respectively ($p< 0.01$).

Conclusion. Incidence of malignancies slightly increased over the years. ADM were more frequent than nADM. The mortality rate was high, but chemotherapy and cART improved survival rates in both groups.

Key Words: HIV infection, ADMs, nADMs, incidence, survival.

BACKGROUND

Human immunodeficiency virus (HIV) and malignancies were considered to be related since the first cases of HIV infection were diagnosed [1]. Due to immunosuppression induced by HIV and the continuous viral replication, the risk of developing malignancies is considered higher than in the general population because of the direct pro-oncogenic effects of the virus and the altered capacity of the immune cells to control the oncogenic processes [2 - 5]. In addition, the persistent chronic immune activation, demonstrated by high plasma levels of inflammatory biomarkers, especially interleukin-6 (IL-6), is also considered to be associated with an increased risk of cancers. It leads to abnormal function of the immune cells with a prolonged and auto-induced immune activation, accelerating the chaotic maturation of pre-malignant cells [5 - 7]. However, it seems that even if these factors may influence the incidence of viral-related malignancies in HIV-infected patients, they have limited effect on other types of cancers [3, 8].

Due to their high incidence in HIV-infected patients, Kaposi Sarcoma (KS), non-Hodgkin's lymphoma (NHL) and invasive cervical cancer (ICC) were classically defined as AIDS-related malignancies (ADMs), all the other types of cancers being considered non-AIDS defined malignancies (nADM) [9]. Data from literature suggested that the incidence of both ADMs and nADMs is higher among HIV-infected patients

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compared to the general population, especially in case of viral-related malignancies [3, 10-12]. Moreover, during last years, the ADM/nADM classification was considered out-of-date, more authors tending to classify cancers into viral-related and non-viral-related malignancies [2, 5, 7, 10, 13, and 14].

Both ADMs and nADMs diagnosed in HIV-infected patients were associated with high incidence, an increased mortality rate and shorter survival compared to the general population, but combined antiretroviral treatment (cART) decreased the morbidity and mortality in HIV-infected patients, reducing the risk of viral-related malignancies [15 - 18]. Moreover, recent studies suggested that early initiation of cART, before the immune system is severely depressed, may be associated with a significant decrease in the incidence of infection-related cancers (e.g. KS and NHL) [19, 20]. On the other hand, the risk of cancer due to long term exposure to cART was not studied enough, so there is a need for more studies to be performed [19].

HIV infection is still associated with a higher risk for nADMs and a slightly increase of mortality in patients diagnosed with cancer [21]. Taking into consideration that cART significantly increased survival, HIV-infected individuals are exposed to other traditional cancer risk factors (e.g. smoking, alcohol and injecting drug use, viral co-infections (HPV, HCV, HBV) and sun exposure. In addition, during the last decades, HIV-infected populations are ageing, which is a well-known phenomenon associated with high risk of malignancies [15, 22, 23]. Lung cancer is one of the most often diagnosed nADM, especially due to high rates of smoking, but also due to immunosuppression and chronic inflammation related to HIV. It was also suggested that lung cancer outcome may be worse in HIV-infected patients than in the general population [24].

Even if in the cART era the risk of cancers decreased due to suppression of HIV viral replication, the persistence of ADMs, especially in low and middle - income countries can be explained by late presentation, treatment fatigue or abandonment and/or lack of adherence

At the end of 2016, Romania reported 14.349 persons living with HIV. An important number of these patients were infected with F1 clade, by parenteral route during their first years of life. They are long-time survivors, but also long time exposed to antiretroviral therapy and start to experience "therapeutic fatigue". Since 2011, Romania reported an important increase in the number of patients newly diagnosed with HIV due to injecting drug use (IDU). The majority of these patients are using injectable heroin or a new category of psychoactive substances, known as "legal highs" or "ethnobotanical drugs". In addition, during last year's more and more men having sex with men (MSM) were diagnosed with HIV infection, 2016 being the first year when the percent of MSM diagnosed with HIV was higher than the IDU's [25, 26].

Even if Romania has a long experience in management of HIV-infected patients, data regarding malignancies in these population are scarce.

OBJECTIVE

We aimed to assess the incidence and survival in patients with HIV infection and malignancies from a Romanian tertiary health care facility and to evaluate their socio-demographic and clinical characteristics.

METHODS

Patient population

We performed a retrospective study on HIV-infected patients diagnosed with malignancies admitted and followed-up at "Victor Babes" Clinical Hospital for Infectious and Tropical Diseases Bucharest between January 2007 and December 2014. This center is the second largest infectious diseases and HIV specialized clinic in Romania.

Demographic, epidemiological, clinical characteristics, nadir and most recent CD4 cell counts and plasma HIV viral loads at the time of cancer diagnosis were obtained from routine clinical databases until 31 December 2014.

All patients signed an informed consent at the admission at the hospital that they can be involved in a research study.

Laboratory methods

Malignancies were classified as ADMs (AIDS defining malignancies) or nADMs (non AIDS defining malignancies) according to CDC classification Atlanta 1993. All cancers were confirmed by histological exams and followed-up in collaboration with the oncologist.

CD4 cell counts were determined by four color flow cytometry using the BD MultiTest™ CD3/CD8/CD45/CD4 (Becton Dickinson, San Jose, CA, USA) in the dual platform with hematology analyzer. HIV viral load was determined with a commercial nucleic acid amplification test (COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test Version 2.0, Roche Molecular Systems, Branchburg, NJ, USA), with a lower detection limit of 20 copies of HIV RNA/mL and a linear range between 20 and 10000000 copies HIV RNA/mL

Statistical analysis

Individuals were followed from the date of cancer diagnosis until the date of death or last follow-up of 31st December 2014. Comparisons of categorical variables were made using chi-squared test or Fisher's exact test, as appropriate. Comparisons of continuous variables, such as CD4 count, age and viral load were made using t test or

Mann - Whitney test. Comparisons in survival between different cancer types were analyzed using Kaplan Meier methods.

Analyses were performed using STATA version 20 (College Station, Texas, USA}. A p value of less than 0.05 was considered to show a statistically significant difference.

RESULTS

Out of 12,298 person-years of follow-up (PYFU), 91 individuals (3.2%) were diagnosed with malignancies, with an incidence of 7.39/1000 PY. More than half of them, 57 (62.6%), were diagnosed with ADMs and 34 (37.3%) with nADMs. The incidence of malignancies was variable during the study period, with a peak of 1.2% in 2008 as shown in Figure 1.

The characteristics of the patients diagnosed with ADM and nADM are presented in Table 1.

Most HIV infected patients with cancer were males (58.2%), with a median age at HIV diagnosis of 32 years [inter- quartile range (IQR) 19-43] and at cancer diagnosis of 34 years [IQR: 25-45]. The median time between HIV and the cancer detection was 2 years but 42.2% were diagnosed with HIV and cancer simultaneously. More than half of the patients 50 (54.9%) acquired HIV infection by heterosexual contact, 27 (29.7%) by parenteral mode in early childhood and 8 (8.8%) were injecting drug users. There was no statistically significant difference in the modes of HIV acquisition between patients with ADMs and nADMs, but there were no nADMs diagnosed in the MSM group.

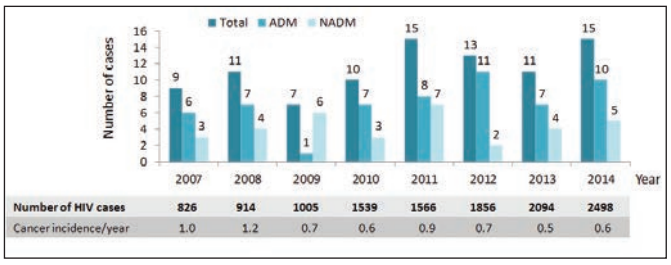


Figure 1. Distribution of ADMs and nADMs by study year.

The median (IQR) nadir CD4 cell count and CD4 cell count at cancer diagnosis were low 63 (20-131) cells/mm^3 and 147 (55- 346) cells/mm^3 respectively, and the median HIV-RNA was high 4.8 (2.2 – 5.6) log10 copies/mL.

There were some notable differences between ADM and nADM group of patients. Patients with ADMs had lower nadir and current CD4 cell counts compared to those with nADMs (47 *vs.* 91, 123 *vs.* 306), respectively and higher HIV plasma viral load (5.3 *vs.* 3.4 log10 copies/mL) ($p < 0.01$).

Patients with nADMs had more frequent prior AIDS-defining events and were more often on cART before the cancer diagnosis.

Co infections with hepatitis B and C were similar in both groups.

The overall mortality rate was high, 41.7%, with no statistically significant difference between the two groups.

The three most frequent types of cancer were: non-Hodgkin's lymphoma NHL 31 (34.0%), Kaposi

Table 1. Characteristics of HIV-infected patients at time of cancer diagnosis for ADMs and nADMs

Demographic and clinical characteristics		Total n=91	ADMs n=57	nADMs n=34	*P value*
Gender - male n (%)		53 (58.2)	34 (59.6)	19 (55.8)	0.72
Age (years) at HIV diagnosis median (IQR)		32 (19, 43)	28 (22, 43)	32 (11, 41)	0.49
Age (years) at malignancy diagnosis median (IQR)		34 (25, 45)	33 (26, 43)	37 (22, 46)	0.95
Time (years) between HIV and malignancy median (IQR)		2 (0, 8)	1 (0, 6)	3 (0.8, 10.3)	0.09
Modes of HIV acquisition n (%)					
sexual		50 (54.9)	31 (54.3)	19 (55.8)	0.88
parenteral		27 (29.7)	15 (26.3)	12 (35.2)	0.36
injecting drug use		8 (8.8)	5 (8.7)	3 (8.8)	0.99
men having sex with men (MSM)		6 (6.6)	6 (10.5)	0 (0.0)	0.05
HCV positive	n (%)	11 (2.0)	7(12.2)	4 (11.7)	0.94
HBV positive	n (%)	15 (16.4)	9 (15.7)	6 (17.6)	0.81
Prior AIDS defining events	n (%)	38 (41.7)	16 (28.0)	22 (64.7)	**< 0.01**
cART > 6 months prior to cancer diagnosis	n (%)	45 (49.5)	21 (38.8)	24 (70.5)	**< 0.01**
CD4 cell count/mm^3 at cancer diagnosis median (IQR)		147 (55, 346)	123 (51, 225)	306 (141, 520)	**< 0.01**
Nadir CD4 cell count/mm^3 median (IQR)		63 (20. 131)	47 (20, 125)	91 (19, 239)	**< 0.01**
HIV-RNA $\log_{10}$ in plasma (copies/mL) median (IQR)		4.8 (2.2. 5.6)	5.3 (3.6. 6.0)	3.4 (1.6. 5.0)	**0.01**
All-cause mortality	n (%)	38 (41.7)	21 (36.8)	17 (50.0)	0.21

Table 2. Comparison between CD4 cell count and HIV viral load for the most frequent types of cancers

	NHL n=31	KS n=17	HL n=10	*P value*
Nadir CD4 cell count/mm^3 median (IQR)	41 (19, 105)	103 (25, 170)	91 (66, 277)	**<0.01**
CD4 cell count/mm^3 at cancer diagnosis median (IQR)	115 (21, 233)	114 (61, 228)	263 (166, 359)	0.41
HIV-RNA $\log_{10}$ at cancer diagnosis median (IQR)	5.33 (5.13, 6.05)	5.29 (5.07, 6.09)	5.00 (1.61, 5.11)	0.06

Table 3. Types and number of nADMs diagnosed in HIV-infected patients at "Victor Babes" Hospital, Bucharest, between 2006 and 2014

Types of nADMs	N (%)
Hodgkin's lymphoma	10 (29.4)
Skin and soft tissue cancers	8 (23.5)
Lung cancer	3 (8.8)
Breast cancer	3 (8.8)
Liver cancer	3 (8.8)
Lymphoblastic leukemia	2 (5.8)
Anal cancer	1 (2.9)
Testicular cancer	1 (2.9)
Esophageal cancer	1 (2.9)
Pancreatic cancer	1 (2.9)
Astrocytoma	1 (2.9)

Sarcoma KS 17 (18.6%) and Hodgkin's lymphoma HL 10 (10.9%). Some cases from the personal iconography are illustrated in Figure A-F.

Table 2 shows the immunological and virological status in patients with the most frequent diagnosed cancers. Compared to HL and KS, NHL was associated with significant lower nadir CD4 cell count and the highest HIV plasma viral load at cancer diagnosis.

In this study we found that the lowest CD4 cell count was associated with cerebral lymphoma 86 cells/mm^3, [IQR: 41-154], whereas patients with nADMs (other than HL), had higher median CD4 cell count, 309/mm^3 [IQR: 92-532] at cancer diagnosis.

The most common ADMs were non-Hodgkin´s lymphoma 31 subjects (54.3%), followed by Kaposi Sarcoma 17 (31.4%) and cervical cancer in 9 (15.7%).

Among NHL the majority of patients 13 (41.9%) were diagnosed with diffuse large B-Cell lymphoma (DLBCL), 3 with Burkitt's lymphoma (BL), 6 with primary cerebral lymphoma (PCL) and 8 were not histologically classified.

Among nADMs, Hodgkin's lymphoma was the most frequent in 10 patients (29.4%), followed by skin and soft tissue malignances in 8 (23.5%) and breast and liver cancer in 3 cases each (Table 3).

The median follow-up time of the study population was 4.4 years.

Survival estimated by Kaplan-Meier methods showed no statistically significant differences between

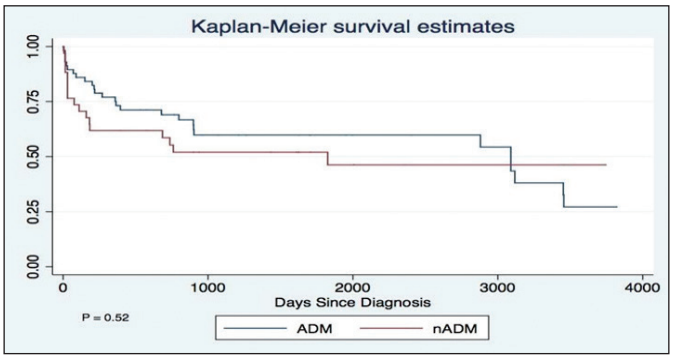


Figure 2. Seven years survival estimates after cancer diagnosis in patients with ADM and nADM.

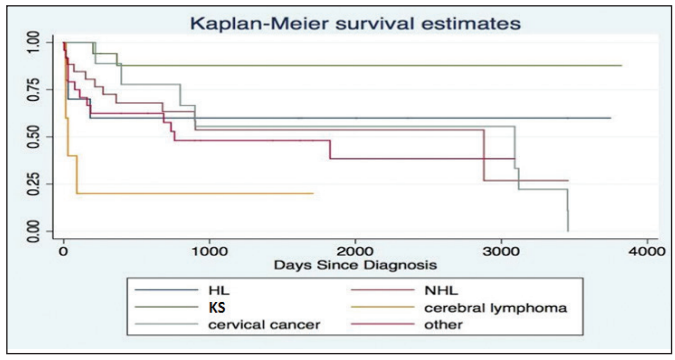


Figure 3. Kaplan-Meier survival curves according to specific cancer types.

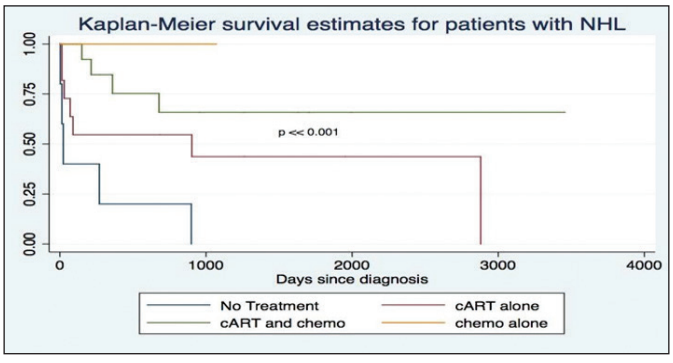


Figure 4. Survival time comparison in patients diagnosed with NHL (on cART, cART and chemotherapy and without treatment).

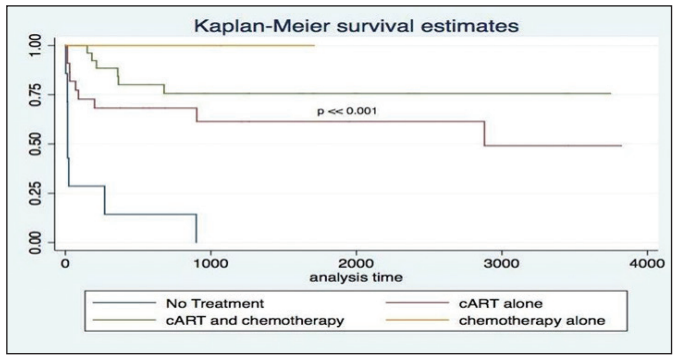


Figure 5. Survival estimates in patients with all type of cancers (on cART, cART and chemotherapy or without treatment).

patients with ADMs compared to nADMs (p=0.52) (Fig. 2). However, patients diagnosed with NHL had a shorter survival compared to those diagnosed with HL or KS (p=0.03) (Fig. 3).

Survival time in patients with NHL was significantly lower in the absence of cART and chemotherapy compared to those who received cART (Fig. 4).

All-cause annual death rate was 12.8% and it significantly decreased to 11.1% in patients on cART and to 7.6% in patients who received combined cART and chemotherapy (p< 0.01) (Fig. 5).

DISCUSSION

In this study, we report a high incidence of cancers among HIV-infected patients from a Romanian tertiary health care facility, almost two thirds of them being AIDS-related (ADM). The incidence was variable during the study period with a slightly descendent trend over the years, but with no statistical significance. Even if the study was performed in cART era, and patients had access to almost all types of antiretroviral drugs, the number of cancers diagnosed per year didn't decrease significantly. This could be explained by several facts: most of our patients were diagnosed as late presenters (CD4 cell counts < 350 cells/mm^3) or with advanced HIV disease (CD4 cell count < 200 cells/mm^3), the lack of adherence in the cART treated group and/or by treatment fatigue and abandonment in patient belonging to the parenterally infected cohort. nADMs were less frequent in our study population, because of the younger age of the study population and the lower additional risk of the traditional cancer risk factors. Recent studies showed that due to increased life expectancy and ageing of the HIV population, the incidence of HIV associated co-morbidities, including cancers in higher [27, 28].

The incidence of nADMs has increased due to chronic inflammation in the context of abnormal immunologic function in association with viral co-infections and the presence of other risk factors (e.g., smoking). The incidence of ADMs has significantly decreased after the introduction of cART followed by immunologic function recovery and viral load suppression. Despite the global availability of efficient cART, the incidence of both ADMs and nADMs is still higher in HIV infected patients than in general population, viral co-infections and traditional cancer risk

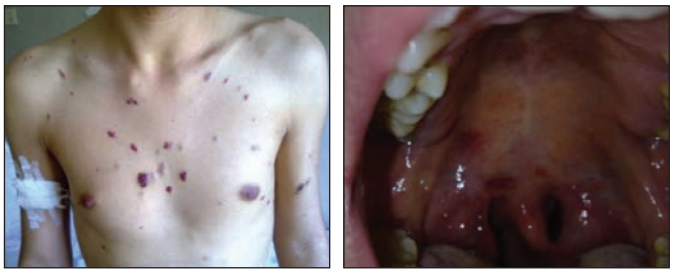
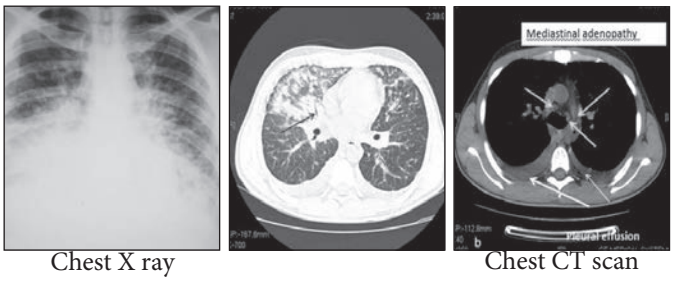


Figure A. Multiple KS lesions in a 26 year- old man with AIDS and disseminated KS.



Chest X ray Chest CT scan

Figure B. Multiple bilateral pulmonary opacities and pleural effusions in a patient with AIDS and disseminated KS.

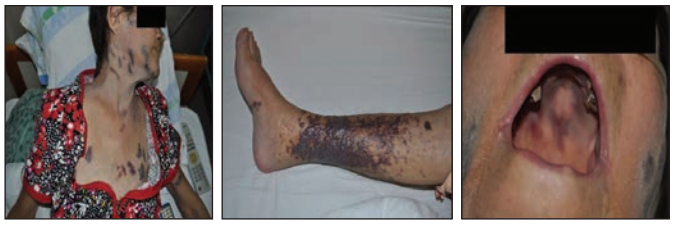


Figure C. Multiple skin and soft palate lesions in a 66 year-old woman with AIDS and disseminated KS disease.

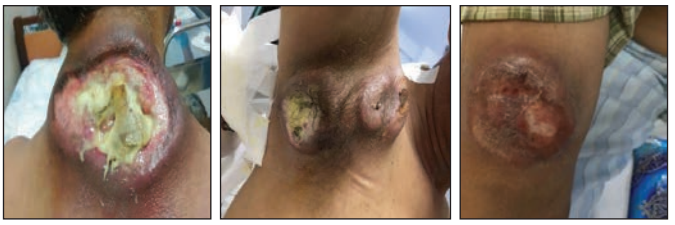
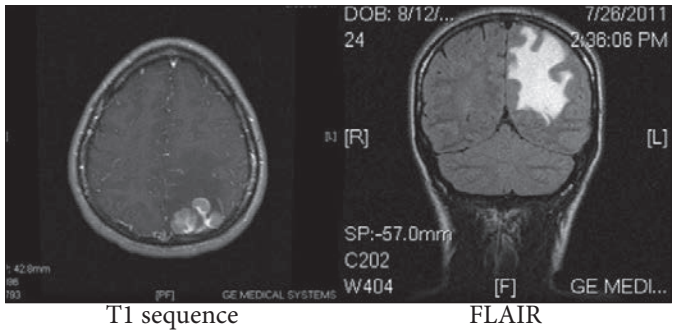
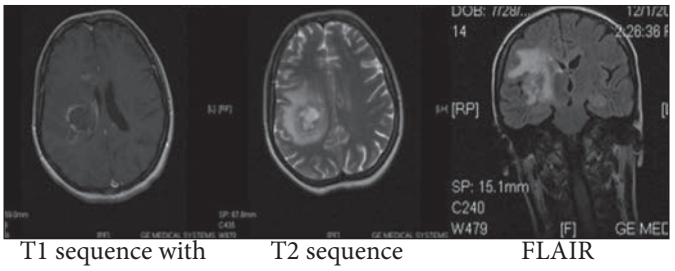


Figure D. Non-Hodgkin's cutaneous B cell lymphoma in a 47 year-old HIV infected man; Multiple ulcerated lesions on the neck, axilla and arms.



T1 sequence FLAIR

Figure E. Brain MRI in a 23 year-old woman with HIV infection and primary cerebral lymphoma (left temporal and parietal lesion).



T1 sequence with contrast T2 sequence FLAIR

Figure F. Brain MRI in a 27 year-old woman with AIDS and multiple brain lymphoma.

factors playing also an important role in this process [5, 28 – 30].

More than half of our patients acquired HIV by heterosexual contact and almost a third of them were infected by parenteral mode with F1 clade during their first years of life. Moreover, due to these epidemiological particularities and the existence a large cohort of patients who grew up with HIV, being multiple experienced to initial, more toxic ART regimens, potential carcinogenetic effects can be expected [25, 26, 31]. There are recent studies who aim to demonstrate the influence that drugs currently used as first line therapy may have on the increased incidence of cancer. [5, 32, 33].

Taking into consideration that the number of Romanian IDUs and MSMs infected with HIV significantly increased during last decade, we can expect that the incidence of nADMs will also rise due to associated risk factors (e.g. high risk of HPV and HCV infection among MSM, tobacco use, injectable drugs) [34, 35].

Non-Hodgkin's lymphoma, Kaposi sarcoma and Hodgkin's lymphoma were the most frequent cancers in our study population, known as virus-related (EBV, HHV8). DLBCL was the most frequent NHL, similar to the general population, but even if less common Burkitt's lymphoma remains the most aggressive B cell lymphoma. [36].

Lung cancer is one of the most important causes of morbidity and mortality in HIV-infected patients, risk factors like: age, tobacco use, immunodeficiency, lung infections, chronic inflammation and oncoviruses being considered to be responsible for the high incidence [37]. It was suggested that HIV-infected patients tend to use more often tobacco compared to the general population, leading to a greater risk of lung cancer. In addition, it seems that pulmonary malignancies are correlated with younger age in persons with HIV infection and the risk remains higher than in the general population even after quitting smoking [37-42]. However, lung cancer was diagnosed only in few patients in our study, maybe due to the short study period, and the shorter time frame for additional traditional risk factors.

Patients diagnosed with ADMs were more often severe immunosuppressed and with high HIV viral load, while among nADM, HL had the lowest median CD4 cell count. Interestingly, there are a few studies who suggested a possible relationship between severe immunosuppression and nADMs [43-46]. The correlation between low CD4 cell count and high risk of ADMs is well-known, but more studies suggested recently a possible relationship between severe immunosuppression and nADMs, especially for the infection-related cancers [43]. The lower CD4 cell count is, the higher is the risk of infection-related nADM [11, 31]. Moreover, surveillance of malignant and pre-malignant cells may be influenced by HIV-immunosuppression, explaining the correlation between low CD4 cell count and nADM unrelated to infection [5, 44, 45]. Similarly to other studies, our patients diagnosed with NHL and KS had a high HIV-viral load [46].

Although we observed a wide variety of cancers in the deceased patients, lymphomas (especially NHL) were the most common. The median survival in our study population was similar for patients diagnosed with ADMs and nADM, but was significantly lower for patients diagnosed with NHL compared to HL and KS. This finding is somehow contrasting with recent published data who showed an increased survival in patients with ADMs in cART era due to immunological recovery, while in nADMs the survival was lower despite higher CD4 cell count at cancer diagnosis [47]. Survival in patients with nADMs was lower for patients who developed malignancies during the first years of the study period, suggesting the effectiveness of chemotherapy and cART during last decade [48-52]. Patients diagnosed with NHL had the lowest survival in our study, despite immunological recovery under cART. During the last years of the study, the incidence of BL seemed to increase, while DLBCL and PCL were diagnosed less often, explaining somehow the low survival with NHL in cART era [48, 53]. KS and HL were diagnosed in patients with higher nadir CD4 cell count compared to NHL, which lead to a better outcome, as suggested in other studies [48]. We also consider necessary a comparison between survivals in different types of cancer diagnosed in HIV-infected patients and in general population, knowing that usually HIV-infected patients develop more aggressive clinical forms and histological subtypes [48].

The concomitant use of cART and chemotherapy was associated with higher survival rates. Antiretroviral treatment significantly influenced survival and reduced the mortality rates, in all types of cancer and particularly in NHL. To mention that during the study period (before the publication of the results of the START trial) [54], cART was recommended only in patients with CD4 cell count bellow 350/mm^3 or in the later years of less than 500/mm^3.

Immunological recovery under cART allowed the use of more aggressive chemotherapy for longer periods with more favorable results, despite the higher risk of drug-drug interactions and toxicities related to treatment [55].

There are some limitations of this study. The study was performed in a single Romanian HIV center in a relative short study period (7 years), so it might not reflect the exact distributions of malignancies occurring all over the country. We couldn't adjust our study for traditional cancer risk factors because information about tobacco use, alcohol use or family history for cancers were not systematically collected.

The strength of our study is represented by the fact that, in our knowledge, it included the largest number of patients diagnosed with HIV infection and cancers in Romania.

CONCLUSIONS

The incidence of malignancies per year increased slightly over the study period, suggesting that the risk of both ADMs and nADMs remains higher in HIV-infected patients. ADMs were diagnosed more often than nADMs, especially in late presenters. nADMs were less frequent than reported in literature, probably due to a younger median age of the study population and a shorter time of exposure to traditional cancer risk factors. The mortality rate was high, but chemotherapy and cART improved the survival rates in both groups. Effective prevention methods, early detection of viral co-infections and early and more effective cART could reduce the cancer incidence in our HIV population.

Conflict of interest. The authors declare that there is no conflict of interest.

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