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Research

Malignancies Spectrum in the Era of Modern HAART

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Abstract

Background

In the current highly active antiretroviral therapy (HAART) era, studies suggest AIDS defining malignancies (ADM) are decreasing and non-AIDS defining malignancies (NADM) are increasing. We aimed to review all types of malignancies and risk factors in our HIV cohort over a period of ten years.

Methods

This was a retrospective cohort study of all malignancy diagnoses and risk factors collected (2004-2014) from two teaching hospitals in the Midlands, United Kingdom. The demographic data and clinical features were collated and the primary end point of survival analysed. Secondary endpoints included risk factors for ADM compared to NADM.

Results

111malignancy diagnoses 63 (54%) ADM and 48 (46%) NADM identified. Survival was worse once diagnosed with a NADM. About half of the ADM and a third of the NADM had a new HIV diagnosis at the same time or soon after the malignancy diagnosis. Haematological malignancies were the commonest malignancy in both groups. Oncogenic virus was an independent predictor of ADM risk .

Conclusions

Despite new and improved HAART regimens, ADM remain high in newly diagnosed HIV individuals and NADM are on the rise in those on longstanding HAART with stable HIV. Not only continuing HIV testing in new ADM as per the indicator conditions, but it is also important to increase HIV testing in new diagnoses of NADM such as all haematological malignancies and lung cancer.

Key Words: Malignancy; HIV; AIDS; Non-AIDS; Antiretrovirals

Background

The development of highly active antiretroviral therapy (HAART) for management of HIV is one of the greatest success stories in modern medicine. Three decades on, HIV has transformed from a disease with high mortality to a disease which is chronic and needs long term management. Although HIV positive individual can be expected to have a near-normal life expectancy, malignancy still remains the commonest cause of death in this cohort[1], it is important to have a high suspicion of malignancy and thoroughly investigate for the same when an individual present with new symptoms. Although the introduction of HAART has resulted in a dramatic decline in the incidence of AIDS-defining malignancies (ADM), Non-AIDS defining malignancies (NADM) such as Hodgkin's lymphoma and lung cancer have increased significantly since the use of HAART[2,3,4]. The high rates of ADM in the pre-HAART era were attributable to severe immunosuppression associated with other HIV related opportunistic infections[5,6]. The rising incidence of NADM can be explained by the prolonged survival and overall ageing HIV cohort brought about by the introduction of HAART[5,6].There is an increasing number of HIV patients, stable on HAART presenting with symptoms that

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can be attributed to a malignancy. To our knowledge there have been few studies that have specifically looked at the changing malignancy pattern in HIV infected individuals in the modern era of HAART which consists of new and less toxic antiretroviral therapies[7]. In addition, clinicians should also recognize 'Indicator Conditions' for HIV and aim to test patients to aid early diagnosis of HIV[8]. Our aim is to review all types of malignancies in the era of modern HAART over a period of ten years and risk factors in our HIV cohort in two Teaching University Hospitals.

Materials and Methods

Retrospective case notes review was carried out on all malignancy diagnoses in the HIV cohorts at the Nottingham University Hospitals NHS Trust and the University Hospitals Coventry and Warwickshire NHS Trust in the United Kingdom for the period 2001-2014. Squamous cell carcinoma and basal cell carcinoma of the skin were excluded. All other malignancies diagnosed after the HIV diagnosis or a malignancy diagnosis which then led to an HIV test and subsequent HIV diagnosis were included. Malignancies were divided into ADM (Kaposi's sarcoma, Non-Hodgkin's lymphoma and cervical cancer) and all other malignancies were included in the NADM category. Ethics committee approval was not required as this was a retrospective collation of data obtained during routine review of individuals. The primary end point was survival. Secondary endpoints included risk factors associated with differences between the ADM and NADM groups.

Statistical analysis included univariate and multivariate analysis using GraphpadInstate 3, version 3.10 and SPSS version 21. The Chi squared test was used for analysis of categorical variables and the one-way analysis of variance (ANOVA) test was used to compare continuous variables. The primary end point of survival was assessed using Kaplan-Meier analysis. Factors which had a P value of less than 0.15 by univariate analysis and factors of interest were included in the multivariate analysis which was carried out by binary logistic regression. All P values were considered statistically significant if $P<0.05$.

Results

The total HIV cohort included 678-1647 individuals per year (an average of 1202 per year) over a period between 2004 and 2014, of which 111 individuals were diagnosed with a malignancy. The 111 individuals provided 318 person-years of follow up to the 1st July 2014 or death. Of those with malignancy, 84 (76%) were men and 27 (24%) were women. The mean age at malignancy diagnosis was 44 years [+/- 11.8 years standard deviation (SD)]. Overall 47% were White, 46% Black African and 7% other. The mode of HIV transmission was 62 (56%) heterosexual, 34 (31%) men who have sex with men (MSM) and 15 (13%) other or unknown. The mean CD4 and viral load at the time of malignancy diagnosis were 260 cells/mm3(+/- 231.7 SD) and log10 5.08 copies/ml (+/- 5.62 SD) respectively (table 1).

Table 1. Baseline characteristics of the AIDS defining and non-AIDS defining groups.

Characteristics		**ADM**		**NADM**	
		No	%	No	%
Gender					
	Male	53	84	31	65
	Female	10	16	17	35
Oncogenicvirus					
	Yes	37	59	9	19
	No	26	41	39	81
Time from HIV to malignancy diagnosis ≤5 years					
	Yes	52	83	28	58
	No	11	17	20	42
CD4<500 at malignancy diagnosis					
	Yes	55	87	36	75
	No	3	5	9	19
Nadir CD4<100					

	Yes	29	46	18	38
	No	28	44	25	52
Time from starting HAART to malignancy diagnosis ≤5 years					
	Yes	57	90	34	71
	No	5	8	12	25
Viral load ≥100000 at malignancy diagnosis					
	Yes	40	63	40	83
	No	17	27	4	8
Death					
	Yes	24	38	24	50
	No	39	62	24	50
On HAAR Tattime of malignancy diagnosis					
	Yes	52	83	36	75
	No	10	16	12	25
Ageofmalignancy diagnosis in years					
	<30	8	13	3	6
	31-40	25	40	18	38
	41-50	16	25	14	29
	51-60	7	11	6	13

The majority of malignancies were ADM 62 (56%) compared to NADM 49 (44%). There were 5 times as many men compared to women in the ADM group and 3 times more men compared to women in the NADM group (table 2). Non-Hodgkin's lymphoma (NHL) was the most common ADM (58%) and haematological malignancies including Hodgkin's lymphoma were the most common (43%) in the NADM group followed by lung cancer (12%) (table 2). Median age at malignancy in the ADM group was 39 years (range 27-74 years) and in the NADM group was 44 years (range 25-81 years). Time from HIV to malignancy diagnosis in ADM was 2.8 years and 6.8 years in the NADM group. The mean CD4 count at malignancy diagnosis in the ADM and NADM groups were 213 cells/mm3 (+/- 166.8 SD) and 320 cells/mm3 (+/- 285.5 SD) respectively. A viral load of greater than 100 000 copies/ml was found at malignancy diagnosis in 18 (29%) of the ADM and 8(16%) of the NADM compared to an undetectable viral load on HAART at malignancy diagnosis which was found in 22 (35%) and 24 (49%) respectively. Thus the mean CD4 count was lower and the majority of viral loads were higher in the ADM cases compared to NADM. A diagnosis of HIV was at the same time or soon after the malignancy diagnosis in 29 (47%) ADM and 14 (29%) NADM. This showed that nearly half the ADMs were diagnosed alongside a new HIV diagnosis.

Overall, there were 48 (43%) deaths, of which 24 (39%) were in the ADM group and 24 (49%) were in the NADM group. The NADM deaths had a mean CD4 count of 207cells/mm3 (+/- 222 SD) and 42% (10/24) had undetectable viral loads on HAART at the time of malignancy diagnosis. The mean CD4 count was 189cells/mm3 (+/- 182 SD) and 46% (11/24) had an undetectable viral load on HAART at time of malignancy diagnosis in the ADM group. Mean follow up from malignancy to death was 128 days (+/-263.8 SD) and 247 days (+/-366.9 SD) respectively for ADM and NADM. This showed that despite better controlled HIV on HAART, mortality was higher with NADM diagnoses.

In univariate analysis, gender, oncogenic virus, time from HIV to malignancy diagnosis of ≤5 years, CD4 count <500 at malignancy diagnosis, time from starting HAART to malignancy diagnosis of ≤5 years and a viral load of ≤100000 copies/ml were more frequently associated with ADM compared to NADM (Table 3).

In multivariate analysis, oncogenic virus and time from HIV diagnosis to malignancy of 5 years or less remained as independent predictors of ADM risk (Table 3).

Table 2. Malignancies categorised by AIDS defining malignancies (ADM), non-AIDS defining malignancies (NADM) and gender

Type of malignancy		Male		Female		Total
		No	%	No	%	
ADM						
Non-Hodgkinslymphoma(NHL)		32	86	5	14	37
Kaposi'ssarcoma(KS)		21	91	2	9	23
Cervix		0	0	3	100	3
	Subtotal	**53**	**84**	**10**	**16**	**63**
NADM						
Other Haematological, including Hodgkins		15	71	6	29	21
Lung		5	83	1	17	6
Head&Neck		2	50	2	50	4
Anal		4	100	1	0	5
Breast		0	0	4	100	4
Gynaecological		0	0	3	100	3
Uppergastrointestinal		2	100	0	0	2
Gallbladder		1	100	0	0	1
Hepato cellular carcinoma		1	100	0	0	1
Prostate		1	100	0	0	1
	Subtotal	**31**	**65**	**17**	**35**	**48**
GrandTotal		**84**	**76**	**27**	**24**	**111**

Table 3. Factors associated with AIDS defining malignancies compared to non-AIDS defining malignancies.

Variable		Univariate			Multivariate	
Gender	**RR**	**95% CI**	**p**	**OR**	**95%CI**	**p**
	1.7	1.01-2.86	0.025	2.1	0.78-5.84	0.142
Oncogenic virus	2.0	1.45-2.80	<0.0001	5.6	2.14-14.69	<0.0001
Time fromHIV to malignancy diagnosis ≤5 years	1.8	1.11-3.02	0.006	2.0	0.55-7.36	0.293
CD4<500 at malignancy diagnosis	2.4	0.89-6.53	0.029	1.9	0.39-9.69	0.416
Nadir CD4<100	1.2	0.83-1.64	0.422			
Time from starting HAART to malignancy diagnosis ≤5 years	2.1	1.00-4.52	0.016	2.0	0.41-10.15	0.381
Viral load ≥100000 at malignancy diagnosis	0.6	0.45-0.84	0.013	1.8	0.63-5.30	0.269
Death	0.8	0.57-1.14	0.248			
On HAART at time of malignancy diagnosis	1.3	0.79-2.12	0.337			

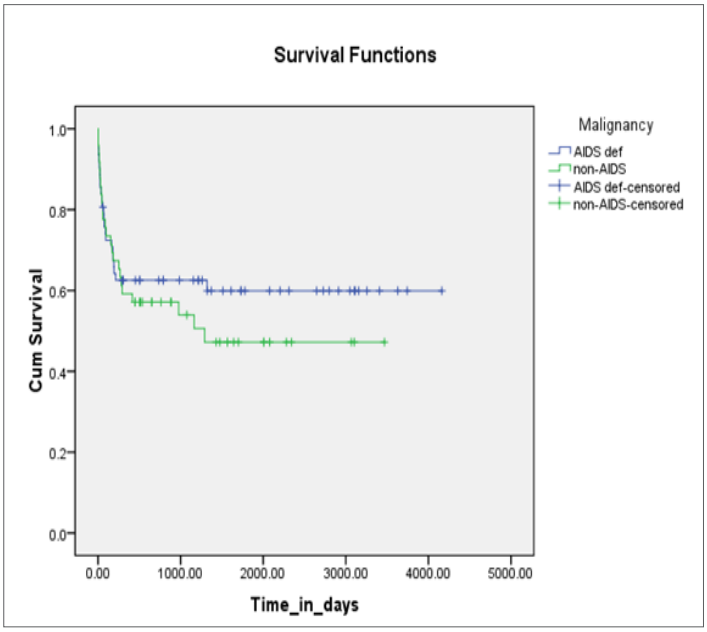

Figure 1: Kaplan-Meier survival curve following malignancy diagnosis for AIDS defining compared to non-AIDS defining malignancies.

Discussion

Our study shows that AIDS defining malignancies are a continued risk despite commencement of HAART and improvements in immune function. Equally, some individuals with HIV are living longer due to HAART and therefore surviving long enough to develop Non AIDS defining malignancies. The majority of cancers in our study were ADM as was the case in other studies[9] but some have in recent years shown a higher incidence of NADM[10].Direct comparison of the change in NADM incidence over time in studies is difficult to compare as many studies were in the pre-HAART era[2]. The process of ageing due to better survival with HAART and the prolonged exposure to immunosuppression may cause the rise in NADM incidence[2]. Some studies mention an increase in NADM incidence while others do not[11,12,13,14]. Studies from Africa showed an increase in incidence of ADM such as KS and cervical carcinoma as opposed to NHL, due to the high female population in the malignancy demographic in Africa[7]. The majority of studies have compared rates of NADM to the pre-HAART era which may reflect the resulting different conclusions. Not all studies have taken into account the ageing of the HIV population, which may also add to the expected rise in NADM. It is worth noting that the commonest malignancies in both ADM and NADM groups were the haematological malignancies[15]. We found a high rate of Hodgkins lymphoma in the NADM group, similar to rates shown in several other studies in the past[16,17,18,19].

In our study, survival was better in the ADM group following HIV diagnosis, which may be due to the availability of better HAART regimens, virological suppression and improved immune response. However, despite stable HIV on HAART, once a NADM was diagnosed, the prognosis tended to be worse with a greater number of deaths compared to the ADM group[10]. There was a significant difference between CD4 in the ADM group and NADM group as shown in other studies[10], however no significant difference was noted with age or death between the two groups[5].

Whilst gender, CD4 count, time from starting HAART to malignancy diagnosis and viral load were significantly associated with the likelihood of ADM more than a NADM diagnosis in univariate analysis, it did not remain significant in multivariate analysis[19]. This may reflect the small study sample size.

The presence of an oncogenic virus or the likelihood of being on HAART for 5 or less years were strong predictors of an ADM diagnosis compared to a NADM in multivariate analysis. A shorter duration of HIV is more likely to cause ADM than NADM as shown in previous studies[5]. It is noteworthy that in our study there was no association between CD4, viral load, gender or time from starting HAART to malignancy diagnosis and a greater likelihood of an ADM occurring when adjusted analysis was carried out. This may again reflect the small sample size.

Our study has several limitations; the sample size is small, leading to a low number of person years. We were unable to calculate the incidence rates because of difficulty in obtaining the denominator (overall HIV numbers during the study period).

The study has the potential for certain biases. Those in the HIV cohort are subject to closer monitoring and may have led to earlier diagnoses of malignancies. The under-representation of women in the study may have led to certain malignancies such as cervical and breast cancer showing lower incidence than expected.

Conclusion

Our study shows that cancer remains an important cause of morbidity and mortality specifically AIDS defining malignancies soon after an HIV diagnosis and non-AIDS defining malignancies in stable HIV, specifically in those who have been on HAART for many years. The presence of an oncogenic virus in a newly diagnosed HIV positive individual can be a predictor of an AIDS defining malignancy. Routine HIV testing in newly diagnosed malignancies should be widened to include all malignancies and not just those defined as indicator conditions in current HIV testing guidelines[20].

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