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HIV-Infected Men with an Elevated Level of Serum Cystatin C have a High Likelihood of Developing Cancers

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Abstract

Background: HIV-infected individuals are at high risk for morbidity and mortality regardless of good infection control with highly active antiretroviral therapy (HAART). The residual inflammation after apparent good infection control with HAART may be responsible for an increased risk of mortality including cancers. Serum cystatin C is not only a sensitive marker for renal dysfunction but also a potential marker for inflammation, which may suggest that this marker is something more than a measure of renal function.

Materials and methods: A total of 520 HIV-infected men under good infection control with HAART were enrolled in a 3-year prospective cohort study. The incidence of cancers was investigated with special reference to serum cystatin C level. Cumulative incidence of cancers over time was analyzed by Kaplan-Meier methods. A Cox proportional hazards model was used to calculate the Hazard Ratio (HR) of developing cancers, adjusted for age, smoking habit, CD4 cell count, serum albumin, estimated glomerular filtration rate below 60 mL/min/1.73m^2, C-reactive protein, and presence of comorbidities including diabetes mellitus, hypertension, and hepatic viral infection.

Results: During the follow-up, cancers developed in 14 (2.7%) subjects. Death occurred in 4 from cancers. The Kaplan-Meier estimate for cancer incidence significantly increased in patients with serum cystatin C elevation (≥ 1.0 mg/L). The HR (95% confidence interval) of cancer incidence was 3.56 (1.08-11.2) for elevation of serum cystatin C, although other markers of inflammation were not significant.

Conclusion: The examination of serum cystatin C may enable earlier recognition of cancers among HIV-infected individuals.

Keywords: Chronic kidney disease; Highly active antiretroviral therapy; Inflammation; Mortality

Introduction

The introduction of highly active antiretroviral therapy (HAART) has markedly reduced AIDS-related death and opportunistic infectious diseases, which had been the main causes of mortality among human immunodeficiency virus (HIV)-infected subjects in the pre-HAART era [1-3]. However, the causes of mortality have shifted to non-AIDS diseases in the contemporary HAART era, most of which are commonly associated with aging [4]. The major causes of death include non-AIDS-defining cancer and cardiovascular disease (CVD), and these deaths are reported to occur at an earlier age in the HIV-infected population than in the general population [5-7]. Previous studies suggest that HIV-infected subjects are at greater risk for morbidity and mortality than HIV-uninfected subjects, partly because HIV-infected subjects often have high prevalence of chronic comorbidities including diabetes mellitus (DM), hypertension, kidney disease, and liver disease [8,9].

The residual immune-insufficiency and inflammation after apparent good infection control with HAART may also be responsible for an increased risk for such age-associated diseases in treated HIV patients, as shown by the prognostic value of the CD4 cell count and other inflammatory markers [10]. Inflammatory markers are elevated in HIV-infected individuals and remain unaltered after HIV-RNA levels are suppressed by HAART [11], which in part may reflect the existence of persistent immune activation [12]. A large body of evidence supports the notion that inflammation plays a role in poor prognosis including cancers in the general population [13-15]. Thus, evaluation of some biomarkers of inflammation may be important for early identification of those at increased risk for critical illness in well-controlled HIV-infected populations.

In general, serum cystatin C level is a well-known biomarker for early kidney disease; however, it may be a clinical marker for the existence of systemic inflammation as well. In fact, serum cystatin C levels increased rapidly after HAART interruption and were correlated with several inflammatory markers [16]. Serum cystatin C provides prognostic information beyond its role as an index of kidney function and may be a better overall measure of the spectrum of pathophysiologic abnormalities [17-19].

Here, we conducted a 3-year prospective cohort study among men under good infection control with HAART to test the impact of elevated serum cystatin C on the development of cancers.

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Materials and Methods

Study design

This study was a prospective cohort study with the aim of ascertaining the relationships between baseline clinical characteristics, laboratory data, and the new onset of cancer during a follow-up of 3 years. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board (approval certificate no. 681-09-1-13). Informed consent was obtained from all participants.

Study population

A total of 520 ambulatory HIV-infected men (mean age: 47.6 ± 11.4) were recruited at the time of routine outpatient HIV care at Tokyo Metropolitan Komagome Hospital and underwent baseline examination between February and April, 2008. Subjects were followed for at least six visits per year over a 3-year period. All subjects received HAART and had undetectable HIV-RNA level (<50 copies/mL) at baseline. 'Having cancer at baseline' was included in an exclusion criterion. No other inclusion and exclusion criteria were set for the study. Virological and immunologic control was well maintained in all subjects throughout the study period. There were no dropouts due to missing data during the follow-up period. The mean duration of follow-up was 3.10 (range, 3.04 - 3.20) years. Tenofovir disoproxil fumarate, abacavir, and zidovudine were used in 278 (53.5%), 98 (18.8%), and 96 (18.5%) subjects, respectively. Likewise, atazanavir/ritonavir, lopinavir/ritonavir, fosamprenavir/ritonavir, and efavirenz were used in 189 (36.3%), 65 (12.5%), 8 (1.5%), and 234 (45.0%) subjects, respectively.

Measurements

Non-fasting blood and urine samples were collected for analysis as part of routine clinical visits. Serum cystatin C and serum creatinine (Cr) was measured in all subjects. Serum cystatin C was measured using the latex agglutination-turbidimetric immunoassay (IATRO Cys-C; Mitsubishi Chemical Medicine Corporation, Tokyo, Japan), with a cut-off value of 1.0 mg/L. Accordingly, serum cystatin C elevation was defined as ≥ 1.0 mg/L. Estimated Glomerular Filtration Rate (eGFR) based on serum Cr was calculated using the 3-variable Japanese equation constructed by the Japanese Society of Nephrology: eGFR (mL/min/1.73 m^2) = 194 × Serum $Cr^{-1.094}$ × $Age^{-0.287}$ × 0.739 (if female) [20]. CD4 cell counts in HIV-infected subjects were determined using a specific monoclonal antibody and fluorescence-activated cell-sorter analysis. HIV-RNA level was measured using the Roche Amplicor HIV Monitor assay based on reverse transcription-polymerase chain reaction (Roche Molecular Systems, Tokyo, Japan; lower detection limit, 50 copies/mL). Other laboratory variables were measured using standard methods as described previously [21].

The electronic medical charts of all subjects were reviewed to determine the presence of comorbidities such as hypertension, DM, and hepatic viral infection. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg, or the use of antihypertensive agents at baseline. DM was defined as a diagnosis of DM prior to baseline, or the use of oral antidiabetic agents or insulin at baseline. Hepatitis B virus (HBV) infection was defined as a positive HBV surface antigen test, and hepatitis C virus (HCV) infection was defined as a positive reactive HCV antibody test.

Statistical analysis

All data are expressed as the mean ± standard deviation unless otherwise stated. Comparisons between 2 groups were performed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Cumulative curves of incident cancers were prepared by the Kaplan-Meier method, stratified by the presence or absence of serum cystatin C elevation (≥ 1.0 mg/L). The log-rank test was used to analyze difference between the curves. A second analysis was conducted using a Cox proportional hazards regression model to examine the hazard ratio (HR) of developing cancers. For the HR, 95% confidence interval (95% CI) was calculated. The following covariates were evaluated by univariate analysis as they were previously shown or clinically relevant to be risk factors associated with the development of cancer: age, current smoking habit, CD4 cell counts, serum albumin, renal dysfunction (eGFR< 60 mL/min/1.73m^2), C-reactive protein (CRP), and coexistence of DM, hypertension, and hepatic viral infection. Subsequently, a multivariate model included covariates which were set at a value of $P \leq 0.10$ on univariate analysis. All statistical analyses were conducted using JMP 8.0 (SAS Institute Japan, Tokyo, Japan). P values < 0.05 were considered statistically significant.

Results

Baseline demographic and clinical characteristics

Table 1 summarizes the comparative data between patients who developed cancers and those who did not. Hypertension and DM were present in 125 subjects (24.0%) and 41 subjects (7.9%), respectively. HBV antigen-positive and HCV antibody-positive patients were 38 (7.3%) and 24 (4.6%), respectively. A decrease in eGFR below 60 mL/min/1.73 m^2 and serum cystatin C elevation (≥ 1.0 mg/L) were present in 48 (9.2%) and 47 (9.0%), respectively. Mean age was significantly higher in patients with these features than in those without. Differences

	Overall (n=520)	Cancer (+) (n=14)	Cancer (-) (n=506)
Age, years	47.6 ± 11.4	60.6 ± 11.1*	47.2 ± 11.2
Hypertension (+), no. (%)	125 (24.0)	4 (28.6)	121 (24.2)
DM (+), no. (%)	41 (7.9)	1 (7.1)	40 (8.0)
Smoking (+), no. (%)	303 (58.7)	9 (64.3)	294 (58.7)
HBV (+), no. (%)	38 (7.3)	0 (0)	38 (7.6)
HCV (+), no. (%)	24 (4.6)	2 (14.3)	22 (4.4)
CD4 cell count, cells/μL	439 ± 208	364 ± 203	441 ± 208
Serum albumin, g/dL	4.44 ± 0.30	4.15 ± 0.38*	4.44 ± 0.30
Total cholesterol, mg/dL	198 ± 43	169 ± 37*	199 ± 43
eGFR, mL/min/1.73 m^2	84.0 ± 20.5	68.9 ± 28.1*	84.4 ± 20.1
eGFR < 60 mL/min/1.73 m^2	48 (9.2)	3 (21.4)	45 (9.0)
Serum cystatin C ≥ 1.0 mg/L	47 (9.0)	6 (42.9)*	41 (8.2)
Mean serum cystatin C, mg/L	0.80 ± 0.26	1.06 ± 0.78*	0.79 ± 0.23
C-reactive protein, mg/dL	0.41 ± 1.21	1.53 ± 3.49*	0.38 ± 1.07

Data are expressed as mean ± standard deviation.

Abbreviations: no: number; DM: diabetes mellitus; HBV: hepatitis B virus; HCV: hepatitis C virus; eGFR: estimated glomerular filtration rate.

*Asterisk indicates significant difference between the groups with and without cancer ($P < 0.01$).

Table 1: Baseline demographic and clinical characteristics of HIV-infected men.

in mean serum cystatin C level and the proportion of patients with serum cystatin C elevation were significant between patients who developed cancer and those who did not.

Incidence of cancers in the 3-year follow-up period

Cancers developed in 14 (2.7%), and all-cause death in this cohort was 10 (1.9%), including 4 from cancers. There were 4 colon, 3 lung, 1 pancreas, 1 bile duct, 1 oropharynx, 1 buccal mucosa, 1 testicular, 1 tongue, and 1 hepatocellular cancer and 1 case of Hodgkin lymphoma. One patient developed 2 types of cancer. All participants completed the 3-year follow-up study.

Cumulative incidence of cancers

Figure 1 presents the Kaplan-Meier curve of the cumulative proportion of patients who developed cancers, according to the presence or absence of serum cystatin C elevation. The Kaplan-Meier estimate significantly increased in patients with an elevated level of serum cystatin C (≥ 1.0 mg/L).

An association of serum cystatin C elevation with the development of cancers

The results of the multivariate analyses are summarized in Table 2. Age, CD4 cell count, smoking habit, eGFR<60 mL/min/1.73 m^2, serum albumin, CRP, and the presence of comorbidities including DM, hypertension, and hepatitis virus infection were assessed using univariate analysis. Age, serum albumin, and CRP met the entry criteria of a *P* value ≤ 0.10. The multivariate analysis demonstrated that the HR (95% CI) of cancer incidence was 3.56 (1.08 - 11.2) for serum cystatin C elevation and 1.11 (1.05 - 1.19) for age.

Discussion

This study highlighted the clinical significance of serum cystatin C elevation beyond its role as an index of a decrease in renal function among HIV-infected men under good infection control with HAART.

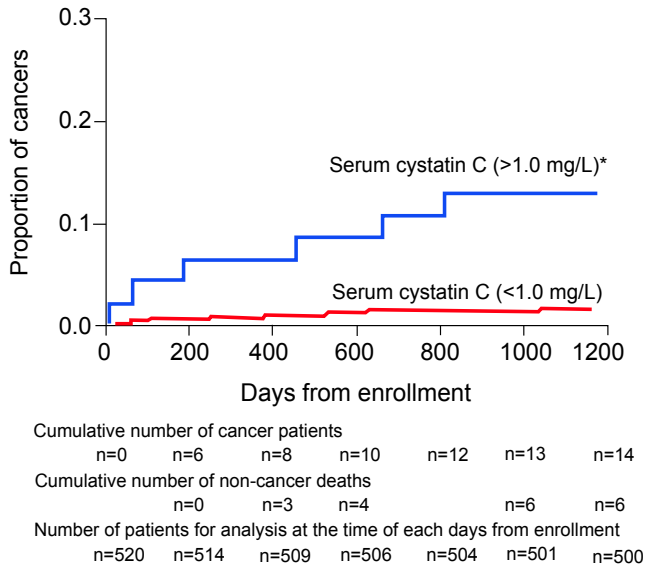

Figure 1: Kaplan-Meier estimate of cancers according to the presence or absence of elevated serum cystatin C at baseline. The difference between the 2 groups was highly statistically significant (*P* < 0.0001). Elevated serum cystatin C was defined as ≥ 1.0 mg/L. Asterisk (*) indicates log-rank test, *P* < .0001.

	Univariate analysis		Multivariate analysis	
Variates	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, per year	1.12 (1.06-1.19)	<.0001	1.11(1.05-1.19)	0.0003*
Hypertension (+)	1.27 (0.35-3.81)	0.6880	-	-
DM (+)	0.95 (0.05-4.80)	0.9653	-	-
HBV or HCV infection (+)	1.29 (0.20-4.74)	0.1556	-	-
Smoking (+)	1.29 (0.45-4.20)	0.6426	-	-
CD4 cell count, cells/μL	0.997 (0.994-1.001)	0.1390	-	-
Serum albumin, g/dL	0.13 (0.06-0.41)	0.0013	0.26 (0.06-1.44)	0.1202
eGFR < 60mL/min/1.73 m^2 (+)	2.73 (0.62-8.74)	0.1637	-	-
Serum cystatin C elevation (+)	8.01 (2.64-23.0)	0.0006	3.56 (1.06-11.2)	0.0408*
C-reactive protein, mg/dL	1.27 (1.05-1.42)	0.0200	1.18 (0.96-1.38)	0.1052

The multivariate Cox proportional hazards model was adjusted for age, serum albumin, and C-reactive protein, all of which showed significance (*P* ≤ 0.10) in the univariate analysis. Asterisk (*) indicates that the parameter is significantly associated with the incidence of the outcome.

Abbreviations: DM: diabetes mellitus; HBV: hepatitis B virus; HCV: hepatitis C virus; eGFR: estimated glomerular filtration rate

Table 2: Hazard ratios for cancer incidence in HIV-infected men.

Our results have suggested an impact of serum cystatin C elevation on the probability of cancers in HIV-infected subjects under good infection control with HAART.

Serum cystatin C is not only a sensitive marker for renal dysfunction, but also a potential marker for inflammation, which may suggest that this marker is something more than a measure of renal function [22,23]. Underlying inflammation has become one of the leading causes of morbidity and mortality in HIV-infected subjects while HAART is routinely employed [24]. Common comorbidities of HIV-infected patients including DM, hypertension, chronic kidney disease (CKD), and hepatic viral infection may exacerbate the inflammatory status in HIV-infected subjects. Chronic inflammation is considered to play a key role in the pathogenic process in cancer [15,25]. Our multivariate analysis has shown a significant association between serum cystatin C elevation and incident cancer, after adjusting for relevant covariates including age, serum albumin and CRP which were significant in the univariate analysis. CKD is a proinflammatory state, and likely associated with cancer risk [26]. Thus, serum cystatin C elevation may reflect the wide spectrum of abnormalities, including predisposition to cancer, accompanying renal dysfunction [15,27]. In fact, some reports have shown that the mRNA expression of cystatin C in malignant extracted tumor tissues was increased compared with that in normal tissues, and that increased extracellular levels of cystatin C correlated significantly with high risk of poor outcome in cancer patients [28,29]. Taking this together with our results, serum cystatin C may be of significant value in providing prognostic information for cancers among HIV-infected individuals.

CRP, an acute phase protein, which is generated in liver cells in response to systemic or local inflammation and tissue damage, is a widely used in everyday practice. Previous reports have demonstrated that elevated CRP is important in the diagnosis, prognosis, and cause of cancers, including lung and colon [30-32], with which the majority

in our subjects developing cancers was affected. In addition, low serum albumin concentration is considered to be a risk or poor prognosis factor for colon cancer [33,34]. Nevertheless, our multivariate analysis showed that neither an elevation in CRP nor a decrease in serum albumin were not statistically associated with the incidence of cancers, although both parameters were significant in univariate analyses. From this point of view, serum cystatin C may be more specific in order to alert clinicians to possible cancer incidence in HIV-infected individuals, as compared to such conventional inflammation markers.

In the contemporary era of HAART, epidemiological studies reveal that the incidence of AIDS-defining cancers (ADCs) has decreased, whereas the rate of non-AIDS-defining cancers (NADCs) is rising and now accounts for the majority of cancers in HIV-infected persons [35,36]. In our cohort, 2.7% developed cancers, all of which were classified into NADCs. In particular, colon and lung cancers were the most common, which was comparable to previous reports [36]. It is worth noting that the diversity of cancers observed in our study, which could be comparable to the fact that HIV-infected subjects have higher incidence of NADCs such as anal, Hodgkin lymphoma, liver, lung, melanoma, oropharyngeal, leukemia, colorectal, and renal than the general population [37]. Clinicians have to take into account not only the rising incidence of NADCs but also the diversity of the cancers observed among HIV-infected subjects.

Several limitations must be considered in this study. First, this study did not compare the impact of serum cystatin C on cancer incidence with serum interleukin-6, which is an inflammatory marker involved in pathophysiologic processes including carcinogenesis. Second, we were unable to provide detailed patient characteristics including a prior diagnosis of AIDS, prior serious non-AIDS events, CD4 nadir, and time since starting HAART. Third, the statistical robustness of this study may be limited owing to the small number of incidence of cancers.

In conclusion, our study shows that the presence of serum cystatin C elevation is a risk factor for cancer in HIV-infected men on HAART with their infection under good control. Monitoring of serum cystatin C level may enable earlier recognition of cancers in subjects with HIV infection.

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