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Preventive Effect of Korean Red Ginseng on Cancers in AIDS Patients

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We have treated 130 human immunodeficiency virus-1 (HIV-1) infected individuals with Korean red ginseng (RG) since late 1991. CD4+T cell and CD8+ T cell counts using flow cytometry have been routinely measured nearly every to 3~6 months. Other immunnological markers have been measured for them. This study was attempted to evaluate whether Korean red ginseng (RG) intake has positive effects on survival and the prevention of cancer in HIV-1 infected individuals. Among total number of patients who were diagnosed with HIV-1 antibody positive by Dec. 31, 1992, 64 cases expired by Dec. 31, 1996. The patients were divided into two groups, those with the intake of RG (n=21) and those without it (n=43), and the incidence of cancer was compared between the two groups. Data on cancer were collected via medical records. The duration of RG intake in 21 patients was 13.4±10.6 months (range, 3~44; median, 11.5). The causes of death were AIDS (n=48), suicide (n=10), diseases other than AIDS (n=4), and accident (n=2). Cancers were confirmed in 8 (16.6%) of 48 who were expired by AIDS. Excluded 16 cases of death caused by diseases other than AIDS, the cancer incidence between two groups with RG intake and without it showed significant difference; 5.0% (1/20) versus 25.0% (7/28), respectively (Relative risk, 0.20; $P<0.01$). These results, as nationwide data, suggest that long-term intake of RG may have a preventive effect on cancers in AIDS patients.

Key Words: Cancer, AIDS, Korean red ginseng, CD4+T cell

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INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) infected patients with severe immune dysfunction are susceptible to opportunistic pathogens and malignancies due to decreased immune surveillance. So far, Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and invasive cervical carcinoma which are clearly associated with AIDS are considered as AIDS-defining illness in HIV-1 infected patients[1]. High incidence of other malignancies such as anal cancer might be associated with HIV infection[2]. The probability of developing cancer in AIDS patients is correlated with baseline CD4+cell counts. In case of KS which has been observed most frequently in AIDS patients, its etiology remains unknown, although it's pathogenesis has been partly described[3]. In patients with baseline CD4+cell counts less than 100×10^6/l, the relative risk of further KS is two fold higher than in patients with that counts more than 200×10^6/l, suggesting that immunesuppression could play an important role in cancer occurrence, either directly or indirectly[4,5].

To assess whether RG has an immune enhancement in HIV-1 infected individuals, we have followed up about 130 individuals since late 1991[6~8]. The significant decrease in serum soluble CD8 antigen (sCD8) to nearly normal level and maintenance of β_2-microglobulin in the HIV -1 infected individuals treated with RG over 5 years was observed[9].

Ginseng has been used by man for thousands of years in the Orient, and Chinese medicine describes it as both a tonic for restoration of strength and a panacea[10]. It is widely used in contemporary Oriental medicine and there are 5 to 6 million ginseng users in the United States[11]. Ginseng is classified pharmacologically as a adaptogen[12] that helps the body adapt to stress and corrects adrenal and thyroid dysfunction[13,14]. There are many kinds of ginseng according to years and location of cultivation. Korean red ginseng (RG) is made via the process of steaming and drying from 6-year-old-root ginseng under the monopoly of Korean Tobacco and Ginseng Corporation (KTGC)[10]. It is known as best quality product among many different kinds of ginseng cultivated in Korea except wild mountain ginseng.

There are a number of reports that RG has an anti-carcinogenic effect in mice[15] and continuous intake of ginseng might reduce the risk of human cancer[16]. Moreover, Yun et al[17] reported that ginseng intake has a preventive effect against various cancers depending on the number of intake. Of several different types, red ginseng was known to be most effective. There is a report that the anti-carcinogenic effect of red ginseng may be related to the augmentation of NK activity[18]. In mice, it was reported that Korean ginseng enhances cell-mediated immune response, while humoral immune response was suppressed[19]. In case controlled clinical trial for third degree gastric cancer patients, the considerable increase of T cell percentage and significant response of DNCB skin test were noted[20].

Although ginseng has a beneficial effect as a health promoting food, there is no known comprehensive marker on the effect of ginseng in human trial. In view of this, we have thought that AIDS would be a model disease for the evaluation of immune enhancement and anti-carcinogenic effect by ginseng because AIDS patients have high incidence of cancers compared to general population[4,5], and such definite disease progress markers as the decrease in CD4+T cell counts[21] and increase in serum sCD8[22], and so on. As preliminary data, we report there are definite differences in cancer incidence and some difference of survival between two dead AIDS patients group treated with RG and without. These data suggest that long- term intake of RG has a preventive effect against cancers in AIDS patients .

MATERIALS AND METHODS

1) Population

We have tried RG for 130 HIV-1 infected individuals from Nov. 1991 to Dec. 1996. The proportions of patients treated with RG among HIV patients diagnosed each year were as follows; 33% (1/3), 33% (3/9), 32% (7/22), 49% (18/37), 61% (33/54), 49% (22/45), 40% (31/77), 10% (8/78) and 8% (7/90), in 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, and 1994, respectively. As first RG trial of our study, 44 patients were enrolled for the study after written consents of patients and hematoimmunological findings were checked by 3 months interval. First pilot study was done for 6 months. The details on RG trial are described elsewhere[6~8]. The second trial was started from October 1992. There were new enrollments for RG trial up to 1994. The trial is ongoing, in part, for the same target population.

Since the first HIV-1 case in late 1985, all cases of HIV infection after diagnosis have been registered and controlled under the government in Korea. Most patients with CD4+T cell less than 500/ul come to have azidothymidine (AZT) treatment from early 1991. Total 245 HIV-infected individuals were reported by December, 1992[23].

We analyzed data on the patients diagnosed in 1986 ~ 1992 of which the proportion of patients treated with RG is over 30% each year. As of December 31, 1996, 64

HIV-1 infected patients expired and all of them were included in this study.

2) Demographic characteristics

Sex ratio of male to female is 55:9. Mode of transmission is 11 homosexuals and bisexuals, 8 blood product recipients, 43 heterosexuals, and 2 others. Regional distribution of patients were 29 (45%) in Pusan and Kyungnam, 23 (37%) in Seoul, Kyungki and Incheon, 6 (10%) in Kyungbook and Daegu, 3 (5%) in Cheonnam and Kwangju, and 3 (5%) in others. Twenty-one patients were treated with RG (Table 1). Thirty-five patients were treated with AZT. Of them, 29 were treated for more than three months; 16 and 13, in group with RG and without, respectively. Other anti-retroviral drugs such Videx (ddI), Zalcitabine, and protease inhibitors as were not tried for these patients because those were not imported in Korea. All diagnosis for cancer was done at the university hospitals. Two suspected cancers were not included in data analysis.

3) Duration of Korean red ginseng intake

The duration of RG intake in 21 patients was 13.4±10.6 months (range, 3~44; median, 11.5). The survival from HIV diagnosis in group with RG treatment was 60±26 months (range, 4~112; median, 63) compared to 29±26 months (range, 1~83; median, 21) in group without RG (n=30, except 12 cases of suicide and accident) ($P<0.001$). Except the deaths other than AIDS, the duration of AZT intake in group with RG and without RG were 18±18 months (n=18; range, 0~58) and 8.0±18 (n=17; range, 0~70) ($P<0.05$) (Table 2). Survival of 12 patients including 10 who committed suicide and two accidents was 15.6 months (range, 2~50) and they did not take AZT or RG.

4) CD4+T cell count

CD4+T cell count measurements with every 6 months' interval were done at the Center for AIDS research and Department of Clinical Pathology, Asan Medical Center. CD4+T and CD8+ T cells were measured by FACScan (Beckton-Dickinson, California, USA) flow cytometer after staining of whole blood with phycoerythrin and fluorescein isothiocyanate (FITC)-conjugated antibodies for CD4 and CD8 antigen, respectively (Simultest reagent, Beckton-Dickinson)[7]. CD4+T cell count was not measured in 11 patients after HIV dignosis.

5) Statistical analysis

Data were expressed as mean±standard deviation. Comparisons between groups were performed using student t-test and Chi-square test.

RESULTS

1) Cause of death

Causes of death were as follows; 10 suicides, 2 accidents, 4 diseases other than AIDS-defining illness (CDC), and 48 AIDS. Four kinds of disease were cardiac arrest, renal insufficiency, peritonitis, and cerebral infarction. Two accidents were traffic accident and drowning in the sea as overseas sailor. Patients were divided into 2 groups with the RG intake (n=21) and without it (n=43). The ratio of male to female were 19:2 in group with RG and 36:7 in group without it ($P>0.05$). Mean ages at HIV diagnosis were 35.6±9.6 years in group with RG and 36.5±11.3 years in group without it ($P>0.05$) (Table 2).

2) Type of cancer

As of December 1996, eight cases (15.4%) of cancer were diagnosed among only 53 male AIDS patients out of 64 dead patients of 245 HIV-1 infected patients diagnosed up to December 31, 1992. The kinds of cancer were 2 gastric cancers, 2 rectal cancers in homsexuals, 1 NHL and 1 nasopharyngeal cancer in overseas sailor, 1 KS and 1 pancreatic head cancer (Table 3). Apart from 8 confirmed cases of cancers, 1 CNS lymphoma and 1 abdominal mass were suspected in 2 patients without RG intake.

3) Comparison of cancer incidence

Cancer incidences in two groups with RG intake and without it were as follows; 1/21 (4.8%) (TSJ in Table 3) and 7/43 (16.3%) (Relative risk; 3.5, $P>0.05$), respectively. If 16 patients died of causes other than AIDS itself including 10 patients who committed suicide were excluded, they showed significant difference; 1/20 (5.0%) versus 7/28 (25.0%) (Relative risk; 0.20) ($P<0.01$). There was no significant difference in the cancer incidence by AZT treatment itself; with versus without, 2/28 (7.1%) vs. 6/36 (16.6%) (Odds ratio; 2.3, $P>0.05$). The only cancer patient among 21 patients with RG intake expired of cerebral infarction 73 months later after diagnosis in 1989. But, he had an esophageal candidiasis history in October 1984. That suggest that he might be already infected with HIV at that time.

DISCUSSION

HIV infection is known to significantly increase the incidence of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL)[24]. And primary central nervous system

(CNS) lymphoma, Hodgkin's disease, cervical and anal cancers are also increased[24,25]. KS is one of the major clinical manifestations of AIDS, involving 15% of all people in the United States reported to have AIDS[26]. The increases of KS and NHL in AIDS patients are closely associated with immunodeficiency. For example, organ transplant recipients on long-term immunosuppression therapy have more than 100 times the incidence of NHL and 150 to 500 times of KS, respectively, than in an age-matched population[27]. KS preferentially affects homosexual men and risk varies by geographic area, suggesting there is an environmental cofactor for KS in addition to HIV[4,5]. Recently, Chang et al[3] identified herpes-like DNA sequences in AIDS-associated KS. It is also called as human herpesvirus-8 and now considered to be causative agent of KS[28]. Cervical cancer and anal cancer have a less certain association with HIV infection and immunodeficiency, although epithelial dysplasia at these site does seem to be HIV-related. There is a report that HIV-1 can transform human T cell via integration and up-regulation of c-*fos/fps*[29] as HTLV-1 can be randomly integrated in a large number of HTLV-1- associated T-cell lymphoma.

Although the sample size of this study is small, it is interesting to observe several different types of cancers were detected among them. They were KS[30] and NHL, which were common to AIDS patients, but such unusual ones as rectal, gastric, pancreatic, and nasopharyngeal cancer were detected. Apart from suspicious CNS lymphoma in our data, there is a confirmed case in Korean homosexuals with AIDS diagnosed in 1995[31]. In view of this, two cases of gastric cancer and one case of pancreatic head cancer in our data could not have any association with HIV infection. However, these cancers were diagnosed at clinically late AIDS stage. Therefore, it cannot be concluded that they do not have any association with HIV infection.

In all the analyses the patients with the longer survival period were more likely to receive treatment. In our data, with higher baseline CD4+T count, the survival from diagnosis in group with RG was much longer than that in group without it. The former was also treated for longer period with AZT than that in the latter. On the other hand, it is noted that AZT has little intrinsic anti-neoplastic efficacy as a single agent[32]. As improved therapies including AZT for the treatment of HIV infection and its complications result in prolonged survival, cancer may become an increasingly significant problem[33]. In spite of longer survival, cancer incidence in the former was much less than that in the latter. The survival from baseline CD4+T cell 200/ul also showed some differences in the two groups (Table 2). In detail, the difference of survival period between the group with the combination of RG and AZT (n=16, 33.2 months) and group with AZT only (n=12, 21.5 months) might be caused by RG itself.

Our data show also significant difference in cancer incidence between two groups with RG and without it. These data could be a reliable evidence that red ginseng has strong anti-carcinogenic effect for human[16]. In regard to anti-carcinogenic effect of red ginseng, it was reported that ginsenoside-Rh2 has growth inhibitory effect on cancer cells[34] and ginsenoside-Rg3 and -Rb2 have inhibitory effect on tumor metastasis[35]. In our cases, the mean total amount (minimum 486 g, mean 1988 g) of RG intake during the study period (59.9±26.1 months) would be much higher than any other retrospective research[16]. In addition, we have already observed significant increase in CD4+T cell percentage and count in asymptomatic HIV-infected individuals treated with KRG for 6 months[7,8].

HIV-1 infection is characterized by a chronic state of immune hyperactivation in patients. It is mediated by Tat and the CD28 pathway[36]. One of important facts observed in long-term treated patients with RG is the dramatic decrease in serum soluble CD8 antigen (sCD8) to nearly normal level[6]. Though there is a report that the anticarcinogenic effect of RG may be related to the augmentation of NK activity[18] as one mechanism of RG against cancer, the decrease in sCD8 level denotes not only elimination of prerequisite for HIV replication but also the increase in CD8- positive cytotoxic T cell (CTL) activity. Not only CD4+T cell but also CD8+ T percentage are increased in mice[37] and HIV-1 patients[8] with ginseng intake. The CD8+ cell activity remains strong in long-term survivors[38]. The increase in body weight by RG intake[7] partly supports that main action mechanism of ginseng might come from similar structure to adrenal cortex hormones reported already[13,14,39,40]. We have measured body weight gain as a significant marker. In extreme cases, moon face like after long term steroid hormone treatment was observed. The increase of CD4+T cell count in patients with baseline CD4+T cell more than 200/ul is better than that less than 200/ul over 5 years. Especially, the two HIV-1 infected individuals among about 20 patients treated with RG over 36 months have showed the reversion of CD4/CD8+T cell and immunologically normal level[9].

Our study experience with RG over 5 years strongly suggests that ginseng has a beneficial effect on the prognosis of HIV-1 infected individuals. At present, long-term trial of RG in HIV patients is ongoing process, the duration of RG intake in some cases is over 60

months. They have showed positive responses in CD4+T cell counts, β_2-microglobulin and sCD8. Therefore, further follow up study would be required for correct evaluation on the effect of survival of HIV-infected patients treated with RG and is also needed to elucidate the correlation between cancer prevention and red ginseng intake.

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Table 1. Demographic characteristics of dead AIDS patients among 244 HIV-infected patients diagnosed in 1986- 1992 by December 31, 1996

	N=64
Sex	
Male: female	55 : 9
Age (yr.)	36±11
<30	18
30~39	26
≥40	20
Year of HIV diagnosis (%)*	
1992	14 (18)
1991	9 (20)
1990	13 (24)
1989	12 (32)
1988	10 (45)
1986~1987	6 (50)
Mode of transmission	
Homo/bisexual	11
Blood product recipient	8
Heterosexual	43
Other/Unknown	2
AZT treatment	
Yes	35
No	29
Korean red ginseng	
Yes	21
No	43
Survival after HIV diagnosis (mo)	37.4±29.4
Median	38

(%)*; death rate (No. of death x100/No. of HIV-infected patients diagnosed each year in Korea)

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Table 2. Comparison of demographic and immunologic profile of patients treated with Korean red ginseng (RG) and without it

	RG treatment	
	with	without
No. of patients	21	43
Age at HIV diagnosis	36±10	37±11
No. with AZT	18	17
No. of AIDS with AZT	17	14
Duration (mo)	18±18[a]	8±18[a]
Survival from HIV diagnosis (mo)	59.9±26.1	26.4±24.4
Range	4 ~ 112	1 ~ 68
Median	63	20
Survival from CD4+T cell 200/ul to death (mo)	27.8±16	24.4±19
Median	30	18
Baseline[b] CD4+T cell count	271±151	224±211
Median	234	170
No.	21	21[c]
Cause of death		
AIDS	20	28
Suicide	0	10
Accident	0	2
DOTA[d]	1	3
No. of cancer/No. of AIDS (%)	1/20 (5.0)	P<0.01 7/28 (25.0)

[a]; P<0.05, [b]; CD4+T cell count at RG start, [c]; except the number of suicide, accident cases, and cases which CD4+T cell was not measured, [d] ; death caused by diseases other than AIDS

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Table 3. Type of cancer diagnosed in expired AIDS patients in Korea.

Subject	Sex age	Survival[a] (month)	Mode of HIV transmission	Type of cancer (month before death)	Clinical state (CD4+T cell/ul)	Duration with AZT (month)
SMO	M 31	7	Heterosexual	Kaposi's sarcoma (7)	AIDS (<50)	0
SHP	M 36	43	Heterosexual	NHL[b] (oral cavity) (1)	AIDS (19)	1
YTK	M 43	11	Heterosexual	Pancreatic head cancer (7)	AIDS (<100)	0
SKO	M 53	1	Heterosexual	Gastric cancer (6)	AIDS	0
CIK	M 50	51	Heterosexual	Gastric cancer (1)	AIDS (66)	21
SHJ	M 33	20	Homosexual	Rectal adenocarcinoma (0)	AIDS (56)	0
JUK[c]	M 27	2	Homosexual	Rectal cancer (0)	(231)	0
TSJ[d]	M 54	73	Heterosexual	Nasopharyngeal cancer Eccrine gland adenocarcinoma (scalp) (2)	(370)	>12

Survival[a]; months from HIV diagnosis, NHL[b]; Non-Hodgkin's lymphoma, JUK[c]; the case of suicide, TSJ[d]; treated with AZT for more than 12 months and with Korean red ginseng for total 18 months (daily 5.4 grams), and he already had admission history with esophageal candidiasis, one of primary HIV infection sign, and gastric ulcer on 60 months before HIV diagnosis. On death, he also showed hilar and mediastinal lymphadenopathy and cerebral infarction