Effect of Radiation Therapy to Immunological and Virological Status in HIV/AIDS-Cancer Patients, Preliminary Report

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Objective: *To describe effects of radiation therapy (RT) on immunological status (CD4 cell counts) and disease progression among HIV-positive cancer patients.*
Material and Method: *This prospective observational study was conducted among HIV-positive cancer patients who received RT for curative intention of cancer in five selected hospitals in Thailand. All subjects received external beam radiation therapy, according to standard clinical practice guidelines of RT. Blood samples were taken 4 times for complete blood count, CD4 cell count and plasma HIV RNA viral load (HIV-VL) assays before and in the last week of RT, then three and six months after completion of RT.*
Results: *This preliminary study reported immunological status and HIV-VL before and the last week of RT, among 29 HIV-positive female cancer patients enrolled from August 22, 2009 to June 30, 2010. The median age was 38 years (range 30-54). 27 patients (93 percent) had invasive cervical cancer. 26 patients (90 percent) were on antiretroviral treatment (ART). The mean baseline white blood cell (WBC) count, lymphocyte percentage were 6,771.7 cells/μL and 31.7 percent respectively. The mean baseline CD4 cell count and CD4%, 387.8 cells/μL and 17.5 percent respectively. In the last week of RT, 25 subjects (86 percent) had CD4 count less than 200 cells/μL. The last week, mean WBC count, and mean lymphocyte percentage decreased to 3,902.8 cells/μL and 17.5 percent respectively. Mean CD4 count number decreased to 157.7 cells/μL, but the mean CD4 % did not change. Four patients (14 percent) had increased HIV-VL after RT, of these two were not on ART and two were on ART for more than 1 year.*
Conclusion: *The CD4 cell count was not a good surrogate for prediction of immunologic status of HIV-positive cancer patients during RT.*

Keywords: *Cancer, Observational study, Radiation therapy, HIV, AIDS, CD4*

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Due to the increased survival and decreased opportunistic infections effects of anti-retrovial therapy (ART), incidence of malignancies in HIV-positive patients appears to increase. With widely use of ART, AIDS defining malignancies are decreasing but non-AIDS defining malignancies are increasing[1-3]. HIV status does not affect cancer treatment plan in the current standard guidelines[4,5]. Radiation therapy (RT) is usually administered for HIV-positive cancer patients instead of surgery if it is suggested by guidelines. However, RT always causes hematological side effects through bone marrow suppression. A previous study showed that RT significantly reduced total lymphocyte count on higher radiation dose among HIV-positive cancer patients, mean lymphocyte count were decrease

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from 1,247 cells/μL before RT to, 88 cells/μL after radiated 40 gray(Gy) $p < 0.001$[6]. Total Lymphocytes including T-lymphocyte, B-lymphocyte and natural killer cells are also affected. CD4 T-cell which is a component of T-cell lymphocyte is used to determine the immunological status whether to initiate antiretroviral drug or failure of treatment of HIV positive patients. Effects of RT on CD4 and progression of HIV in radiated patients have not been well described. This study aimed to compare the CD4 cell counts, CD4% and HIV-VL in HIV-positive cancer patients, before and after the radiation therapy.

Material and Method

This prospective observational study was conducted in the Therapeutic Radiology and Oncology Unit of five hospitals: Rajavithi Hospital, Siriraj Hospital, Maha Vajiralongkorn Cancer Center, Chonburi Cancer Center, and Maharaj Nakorn Chiang Mai Hospital. The study protocol was approved by the ethics review committees of all respective hospitals. This preliminary report presented the results of patients recruited from August 22, 2009 to June 30, 2010.

To be eligible for the study, patients had to be serologically positive for HIV antibodies and histologically confirmed for malignancies with age between 18 - 65 years old. All subjects must not have previous malignancy or RT before being enrolled in the study. All RT treatment plans were curative intention using external photon beam in conventional fraction(fx); 180-200 centigray/fx and 5 fx /week, at least 40 Gy. The external electron beam, brachytherapy and concurrent chemoradiation were applied according to standard guidelines.

The exclusion criteria were patients who had CD4 count less than 200 cells/μL at baseline and were antiretroviral-naive, or patients with metastatic stage, or patients with two primary cancers, or those who received RT for palliative intention.

The CD4 cell count and CD4% as well as plasma HIV RNA viral load (HIV-VL) were assessed at baseline (within 7 days before RT), in the last week of RT, at three months and six months after completion of RT. The CD4 assays were performed using flow cytometry technique. HIV-VL was assayed using Branched DNA (b-DNA) or Abbott real-time Polymerase Chain Reaction (PCR) using standard pathological laboratory. Each patient was tested using the same technique in the same laboratory throughout the study.

This preliminary report compared the results between baseline and the last week of RT. Data were obtained and categorized CD4%, CD4 counts and HIV-VL according to recommendations of ART guideline[7-10]. Statistical analysis was carried out using STATA version 8.0 for descriptive statistics including number, percent, mean and median (range).

Results

This preliminary study reports data from August 22, 2009 to June 30, 2010; thirty-two patients were recruited. Two patients had progression of cancer and treatment were changed to palliative treatment; one patient did not have second blood sample taken at last week of RT. Twenty-nine patients were included in this preliminary analysis. The patients were all female with median age of 38 years (range 30-54). Twenty-six patients were receiving ART. Three ART-naive patients were evaluated by infectious physicians and ART was not initiated at the time of RT. Twenty-seven (93.1%) cases had invasive cervical cancer, one had breast cancer and one had nasopharyngeal cancer. The characteristics of patients were showed in Table1.

The median RT dose was 5,400 cGy, (range 5,000-7,000 cGy) by conventional fraction. All invasive cervical cancer patients received intracavitary brachytherapy and 15 patients received concurrent chemoradiation with platinum-based chemotherapy according to standard guidelines.

Table 2 compared certain parameters in the last week of RT with baseline. Mean white blood cell (WBC) decreased 2,868.9 cells/μL and mean lymphocyte count decreased by 14.2%. Median CD4 count decreased from 322 to 109 cells/μL, but the mean CD4% did not decrease.

Twenty-six patients (89.6%) had decreased CD4 count and 25 patients had CD4 count decreased to below 200 cells/μL. One patient had CD4 cell rise from 331 to 1,568 cells/μL after starting over-dose of GPO-VIR S-30™ (stavudine 30 mg+lamivudine 150 mg+nevirapine 200 mg) 4 tablets a day and developed hepatitis and drug eruption. Seven patients (24.1%) had decreased CD4%, 4 of whom the percentage of CD4 decreased more than 3%.

From Fig. 1, twenty-six patients received ART, 18 patients (75.0%) had baseline HIV-VL less than 50 copies/mL which remained suppressible after RT. Eleven patients had detected HIV-VL at baseline (more than 50 copies/mL). Four patients had HIV-VL increased after RT, 2 on ART and 2 not on ART. Four patients with baseline HIV-VL more than 50 copies/mL, had suppressed HIV-VL (less than 50 copies/mL) at the last week of RT and the duration of ART was shorter than 3

Table 1. Characteristics of HIV-infected cancer patients (n = 29 cases)

Characteristics	Number	%
Sex		
Female	29	100.0
Age (years)		
30-39	19	65.5
40 and over	10	34.5
Baseline CD4 count (cells/μL): median (range) = 331 (30-989) cells/μL		
< 200	7	24.1
200-349	10	34.5
350-499	3	10.4
≥ 500	9	31.0
Baseline percentage of CD4 (cells/μL): median (range) = 17 (3.5-36.1) cells/μL		
Less than 15%	10	34.5
15% and over	19	65.5
Baseline HIV-RNA viral load (copies/mL): median (range) = 50 (40-74,370) copies/mL		
< 50	18	62.0
50-999	2	7.0
1,000-100,000	9	31.0
Duration of ART before RT (months)		
0 (Non-ART)	3	10.4
less than 3	8	27.5
3-12	3	10.4
more than 12	15	51.7

RT = Radiation therapy
ART = Antiratroviral treatment

Table 2. Baseline and post-radiation therapy immunologic parameters (n = 29 cases)

	Baseline	last week of RT
	mean (range)	mean (range)
white blood cell count (cells/μL)	6,771.7 (3,400-16,500)	3,902.8 (2,010-12,100)
percentage of lymphocyte (%)	31.7 (14.0-52.0)	17.5 (4.6-41.0)
percentage of CD4 (%)	17.5 (3.5-36.1)	17.6 (6.0-48.0)
CD4 count (cells/μL)	387.8 (30-989)	157.7 (26-1,568)

RT = Radiation therapy

months. One patient, who did not receive ART, had no significant change of HIV-VL.

Discussion

All participants were female and most of them had invasive cervical cancer (92.3%). In Thailand, invasive cervical cancer is the most common cancer in female population, both among HIV-negative and HIV-positive patients.

The mean WBC and mean percentage of lymphocyte decreased in all patients as a hematologic side effect of the conventional fraction of RT that reduced lymphocyte count of HIV-positive patients and most of patients had post-RT less than 1,500 cells/μL[6]. The mean CD4% were not affected by the conventional fraction of RT, but the mean CD4 count decreased because the total WBC and lymphocyte were decreased. The used of CD4 count as a standard criteria

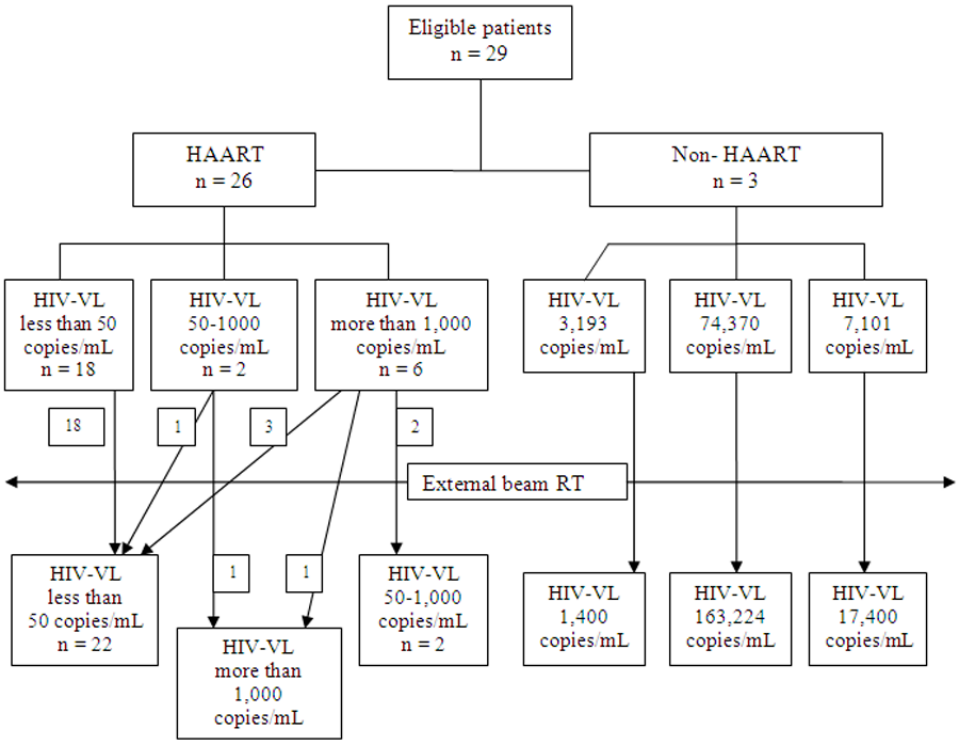

Fig. 1 Baseline and post-radiation therapy of HIV RNA viral load

for diagnosis of immunologic failure and changing antiretroviral regimen (absolute CD4 count increases less than 50 cells/μL after 1 year of ART, or absolute CD4 count decreases more than 30%, or CD4% decreases more than 3%) [9], may not be applicable during RT. The CD4 % might be the only predictive immunologic marker that was not decreased during radiation treatment. However, effects of RT on CD4% have not been well described the progression of HIV in radiated patients.

The HIV disease status appeared to be stable in patients who received ART and had pre-RT HIV-VL less than 50 copies/mL. Patients who immediately started ART before RT also had good virological outcome. The optimal virologic control by administration of ART before RT may prevent the progression of HIV disease during RT. Increase of HIV-VL > 1-$\log_{10}$ was observed in only one patient.

Conclusion

The CD4 count, which was the most commonly used marker for immunosuppression of HIV-positive patients seemed not useful in the setting of patients who had been receiving RT. The maximum suppression of HIV viral load was a better predictor of progression of HIV/AIDS during radiation therapy.

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Potential conflicts of interest

None.

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ผลการศึกษาเบื้องต้นของผลกระทบจากการฉายรังสีต่อภาวะภูมิคุ้มกันและปริมาณไวรัสเอชไอวีในผู้ป่วยมะเร็งที่ติดเชื้อเอชไอวี/ผู้ป่วยเอดส์

ปฐมพร ศิรประภาศิริ, เอกสิทธิ ธาราวิจิตรกุล, นันทน์ สุนทรพงศ์, ซ่อแก้ว โตวณะบุตร, ถนอมศักดิ์ อเนกธนานนท์, เอกภพ หมื่นนุช, ฐาปนา ตั้งชีวินศิริกุล

วัตถุประสงค์: *เพื่อศึกษาผลกระทบของการฉายรังสีต่อภาวะภูมิคุ้มกัน และการดำเนินโรคของเอชไอวีในผู้ป่วยมะเร็งที่ติดเชื้อเอชไอวี*

วัสดุและวิธีการ: *การศึกษาแบบสังเกตการณ์ในผู้ป่วยมะเร็งที่ติดเชื้อเอชไอวี/เอดส์และได้รับการฉายรังสีในโรงพยาบาล 5 แห่งของประเทศไทย ตั้งแต่เดือนสิงหาคม พ.ศ. 2552 ถึงเดือนมิถุนายน พ.ศ. 2553 ผู้ป่วยทุกรายต้องได้รับการฉายรังสีภายนอกแบบหวังผลให้โรคมะเร็งหายขาดตามมาตรฐานการฉายรังสี ตรวจเลือดเพื่อหาปริมาณเซลล์เม็ดเลือดขาว ซีดี 4 และปริมาณไวรัสเอชไอวีในกระแสเลือดก่อนและสัปดาห์สุดท้ายของการฉายรังสี และในการตรวจติดตามหลังการฉายรังสีเสร็จสิ้น 3 และ 6 เดือน*

ผลการศึกษา: *การศึกษาเบื้องต้นรายงานภาวะภูมิคุ้มกัน และปริมาณเอชไอวีไวรัสในกระแสเลือดก่อนและสัปดาห์สุดท้ายของการฉายรังสีในผู้ป่วย 29 ราย ตั้งแต่เดือนสิงหาคม พ.ศ. 2552 ถึง มิถุนายน พ.ศ. 2553 โดยผู้ป่วยทั้งหมดเป็นเพศหญิง ค่ามัธยฐานของอายุเท่ากับ 38 ปี (ช่วงอายุระหว่าง 30-54 ปี) ป่วยเป็นมะเร็งปากมดลูก 27 ราย ผู้ป่วย 26 รายกำลังได้รับยาต้านไวรัส ค่าเฉลี่ยของจำนวนเซลล์เม็ดเลือดขาว และร้อยละของเม็ดเลือดขาวลิมโฟไซท์ เท่ากับ 6,771.7 เซลล์ต่อไมโครลิตรและร้อยละ 31.7 จำนวนเม็ดเลือดขาวซีดี4 และร้อยละของเม็ดเลือดขาวซีดี 4 ก่อนการฉายรังสีเท่ากับ 387.8 เซลล์ต่อไมโครลิตรและ ร้อยละ17.5 ตามลำดับ ภายหลังการฉายรังสีผู้ป่วย 25 ราย มีจำนวนเลือดขาวซีดี4 ต่ำกว่า 200 เซลล์ต่อไมโครลิตร ค่าเฉลี่ยของเม็ดเลือดขาวลดลงเหลือ 3,902.8 เซลล์ต่อไมโครลิตร เม็ดเลือดขาวลิมโฟไซท์ เหลือร้อยละ17.5 ค่าเฉลี่ยของเม็ดเลือดขาว ซีดี4 ลดลง 157.7 เซลล์ต่อไมโครลิตร แต่ร้อยละของเม็ดเลือดขาว ซีดี4 ไม่ลดลง พบผู้ป่วย 4 รายมีการเพิ่มขึ้นของปริมาณไวรัสเอชไอวี โดยผู้ป่วย 2 รายไม่ได้รับยาต้านไวรัส และผู้ป่วยอีก 2 รายได้รับยาต้านไวรัสนานกว่า 1 ปี*

สรุป: *การใช้จำนวนเม็ดเลือดขาวซีดี4 อย่างเดียวไม่เหมาะสมที่จะเป็นตัวชี้บ่งการทำนายภาวะภูมิคุ้มกันในผู้ป่วยมะเร็งที่ติดเชื้อเอชไอวี ระหว่างการฉายรังสี*