Acute Adverse Effects of Radiation Therapy on HIV-positive Patients in Japan: Study of 31 Cases at Tokyo Metropolitan Komagome Hospital

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HIV/Radiation therapy/Acute adverse effect.

Recently, the number of human immunodeficiency virus (HIV)-positive patients has increased in Japan. HIV-positive patients are at a higher risk of cancer than the general population. This paper retrospectively reports the acute adverse effects of radiation therapy on HIV-positive patients who were treated at Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital (TMCICK). Thirty-one cases involving 24 HIV-positive cancer patients who were treated at TMCICK from January 1997 to March 2009 were included in this study. All acute adverse effects of radiation therapy were examined during, and one month after, the last radiation therapy session. Acute adverse effects were classified according to the site of radiation therapy treatment and analyzed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Grade 3 acute adverse effects were seen in 17% of cases, and Grade 2 toxicities were found in 23% of patients. Damage to the skin and mucosa, including stomatitis or diarrhea, tended to occur after low-dose radiation therapy; however, no severe acute adverse effects were seen in other organs, such as the brain, lung, and bone. Acute adverse effects tended to occur earlier in HIV-positive patients and became severe more frequently than in the general population. In particular, disorders of the mucosa, such as those of the oral cavity, pharynx, and intestine, tended to occur rapidly. It was shown that radiation therapy is safe when treatment is performed carefully and that it is a very useful treatment for cancer in HIV-positive patients.

INTRODUCTION

Recently, the number of the human immunodeficiency virus (HIV)-positive patients has increased in Japan.¹) Highly active antiretroviral therapy (HAART) has been widely used to treat HIV-positive patients throughout the world since around 1997.²³⁴) The incidence and mortality rates of acquired immunodeficiency syndrome (AIDS) have fallen markedly in association with the use of HAART, and the survival time of current HIV-positive patients is expected to be longer than those of previous generations of HIV-positive patients.²³⁵⁶⁷⁸⁹¹⁰¹¹)

HIV-positive patients are at a greater risk of cancer than the general population.²⁻⁶) In both the pre-HAART and post-HAART eras, cancer has been one of the major causes of death in HIV-positive patients.²³) HAART has greatly decreased the number of deaths attributable to infectious disease so the proportion of deaths attributable to cancer has been increasing.²) Cancer in HIV-positive patients is classified as AIDS-definitive cancer (ADC) or non-AIDS-definitive cancer (NADC). ADC includes Kaposi’s sarcoma, primary central nerve system lymphoma (PCNSL), and cervical cancer. According to registry-, sex-, age-, and period-standardized incidence ratios (SIR), HIV-positive patients have a significantly higher risk of developing ADC than the general population. In a cohort study of Swiss patients, the SIR of Kaposi’s sarcoma was 192, that of non-Hodgkin lymphoma was 76.4, and that of cervical cancer was 8.²) Other cancers were classified as NADC. HIV-positive patients have a significantly higher risk of developing anal cancer, Hodgkin’s disease, hepatocellular carcinoma, oral/lip/pharynx cancer, lung cancer, and skin cancer without melanoma, and these cancers are classified as NADC.²⁻⁶)

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Cancer in HIV-positive patients tends to be more severe and/or is less often cured than in the general population.\textsuperscript{9)} Successful treatment of cancer in HIV-positive patients would improve the survival rate of this patient population, so it is important to improve the cancer treatment given to HIV-positive patients.

Radiation therapy is one of the main therapies for cancer. In Japan, approximately 25\% of all cancer patients are treated by radiation therapy, so it is inevitable that the number of HIV-positive patients receiving radiation therapy will increase; however, it has been reported that the frequency of adverse effects of radiation therapy is higher in HIV-positive patients than in the general population.\textsuperscript{12–19)} Many reports on late adverse effects (mainly late adverse effects of treatment for anal cancer in the United States) have been published; however, there have been few reports on other topics, for example, from Asia or on acute adverse effects. Reports on the adverse effects of radiation therapy for other cancers are also limited. Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (TMCICK) was established as an infectious disease special hospital at 1879. In 1975, this hospital became a cancer and infectious disease center. Hence, we have been taking care of HIV-positive patients since 1985 and have a great deal of experience of radiation therapy for several kinds of cancer involving various sites on HIV-positive patients treated at TMCICK.

\textbf{METHODS}

Between January 1997 and March 2009, 31 cases involving 24 HIV-positive cancer patients who were treated with radiation therapy at TMCICK were included in this study. The patients were treated with radiation, chemoradiation, and/or surgery plus adjuvant chemoradiation. All acute adverse effects of radiation therapy were examined during, and one month after, the last radiation therapy session. Acute adverse effects were classified according to the site of the radiation therapy treatment and analyzed. Analyses were performed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 of the National Cancer Institute of the United States of America. As secondary endpoints, the percentage of patients who completed the prescribed radiation therapy and the early response rates were evaluated.

\textbf{RESULTS}

\textbf{Patient characteristics}

Thirty-one cases involving 24 HIV-positive cancer patients were evaluated. The patients’ characteristics are summarized in Table 1. Twenty-three patients (96\%) were male, and all patients received HAART. The maximum radiation dose per fraction was 25 Gy, which was the dose used in intraoperative radiation therapy (IORT). Two IORT cases were included in this report. The total dose for the non-IORT cases was between 7.2 Gy and 71.2 Gy. The minimum dose per fraction of 1.1 Gy and the maximum total radiation dose of 71.3 Gy were administered to the same patient, who was treated with the hyperfractionated radiation therapy method for cancer of the external acoustic meatus.

The primary cancer sites are summarized in Table 2. Twenty cases involved AIDS-definitive cancer (ADC), such as Kaposi’s sarcoma, CNS lymphoma, and cervical cancer. Eleven cases involved non-AIDS-definitive cancer (NADC) including anal cancer, oropharyngeal cancer, lung cancer, and pancreatic cancer, etc.

The treatment sites are summarized in Table 3. The skin was the most common site, with almost all cases being Kaposi’s sarcoma, followed by the oral cavity and pharynx. Brain cases included one case of metastasis from lung cancer, and lung cases included one case of metastasis from oropharyngeal cancer. This classification was used in this report to evaluate acute adverse effects.

\begin{table}[h]
\centering
\caption{Patient characteristics}
\begin{tabular}{|l|l|}
\hline
\textbf{Characteristics} & \textbf{Cases} \\
\hline
\textbf{Age (years)} & 51 (29–70) \\
\textbf{Sex} & \\
\textbf{Male} & 30 \\
\textbf{Female} & 1 \\
\textbf{CD4+ lymphocytes (μl)} & 82 (11–561) \\
\textbf{Radiation dose/fr. (Gy)} & 2 (1.1–25) \\
\textbf{Radiation total dose (Gy)} & 30 (7.2–71.3) \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Primary cancer sites}
\begin{tabular}{|l|l|}
\hline
\textbf{Primary cancer} & \textbf{Cases} \\
\hline
AIDS definitive cancer & 20 \\
Kaposi’s sarcoma & 15 \\
CNS lymphoma & 4 \\
Cervical cancer & 1 \\
Non-AIDS definitive cancer & 11 \\
Anal cancer & 2 \\
Lung cancer & 2 \\
Oropharyngeal cancer & 2 \\
Pancreatic cancer & 2 \\
Multiple myeloma & 2 \\
SCC in oral cavity & 1 \\
External acoustic meatus ca. & 1 \\
\hline
\end{tabular}
\end{table}
Skin
The skin was the most common treatment site, and 12 cases were treated with radiation therapy. Only one case involved external acoustic meatus cancer, and the others involved Kaposi’s sarcoma (Table 4). No Grade 3–4 acute adverse effects were seen in this report, but Grade 2 dermatitis was seen in 33% of patients, and Grade 1 dermatitis was seen in 17% of patients, although almost all patients (11 cases) were treated with radiation therapy involving a total dose of less than 36 Gy. Radiation dermatitis tended to occur in association with lower dose radiation therapy in HIV-positive patients.

Oral cavity and pharynx
There were 6 cases in which the oral cavity was treated, and there was 1 case in which the oropharynx was treated (Table 5). At this site, the acute adverse effects observed in the HIV-positive patients tended to be more severe and to

Table 3. Treatment sites

<table>
<thead>
<tr>
<th>Treatment sites</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>12</td>
</tr>
<tr>
<td>Oral cavity and Pharynx</td>
<td>6</td>
</tr>
<tr>
<td>Abdomen</td>
<td>5</td>
</tr>
<tr>
<td>Brain</td>
<td>5</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. Acute adverse effects of skin irradiation

<table>
<thead>
<tr>
<th>Treatment cancer</th>
<th>Total dose (Gy)</th>
<th>Dose/fraction (Gy)</th>
<th>Adverse effects</th>
<th>CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex. acoustic meatus</td>
<td>71.3*</td>
<td>1.15*</td>
<td>Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>36</td>
<td>3</td>
<td>Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>36</td>
<td>3</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>36</td>
<td>2</td>
<td>Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>30</td>
<td>3</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>30</td>
<td>3</td>
<td>Dermatitis</td>
<td>1</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>30</td>
<td>3</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>30</td>
<td>2</td>
<td>Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>30</td>
<td>2</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>25</td>
<td>2.5</td>
<td>none</td>
<td>0</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>20</td>
<td>2.5</td>
<td>none</td>
<td>0</td>
</tr>
</tbody>
</table>

* Hyperfractionation method (2 fractions per day)

Table 5. Acute adverse effects of oral cavity and pharynx irradiation

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Total dose (Gy)</th>
<th>Dose/fraction (Gy)</th>
<th>Adverse effects</th>
<th>CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>66**</td>
<td>1.1**</td>
<td>Mucositis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hoarseness</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dry mouth</td>
<td>1</td>
</tr>
<tr>
<td>SCC in oral cavity</td>
<td>40</td>
<td>2</td>
<td>Stomatitis</td>
<td>3</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>36</td>
<td>3</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>30</td>
<td>2</td>
<td>Stomatitis</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>30</td>
<td>2</td>
<td>Stomatitis</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>2</td>
<td>Stomatitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Taste alteration</td>
<td>2</td>
</tr>
</tbody>
</table>

** Hyperfractionation method (2 fractions per day)
occur earlier than those in the general population. Grade 2 or 3 mucositis was seen in 5 cases (83%), and 4 mucositis cases occurred before a total dose of 20 Gy had been delivered. In the general population, the first mucosal reaction can be observed after a total dose of 10 Gy has been administered, a deepening erythema is visible after 20 Gy irradiation, and severe mucositis will develop after 30 Gy.20) Hence, radiation mucositis tends to occur earlier in HIV-positive patients than in the general population.

Abdomen
Five patients were treated with radiation therapy for cancer of the abdomen. One patient with pancreatic cancer was treated with EBRT plus IORT, and 1 patient with cervical cancer was treated with EBRT plus high dose rate (HDR) brachytherapy. Diarrhea and mucositis around the anus were seen in 2 cases each, but neither of these adverse effects was severe. One patient with pancreatic cancer could not complete the prescribed dose radiation therapy because of pancytopenia. This patient was treated with a combination of radiation therapy and chemotherapy (gemcitabine), so this drug must have been at least partly responsible for the pancytopenia that developed in this patient.

Brain
Five patients were treated for brain malignancy. The only acute adverse effect at this site was hair loss (2 cases), which did not persist. The acute adverse brain effects observed in the HIV-positive patients were as severe as those seen in the general population.

Lungs
Two patients were included in this category. One case of Grade 2 pneumothorax was seen 1 week after the completion of radiation therapy. Radiation pneumonitis was not seen in any HIV-positive patient.

Bone
Only one case was included in this category. This patient was treated with IORT, and no EBRT was performed. No significant acute adverse effects were seen in this case.

Hematologic toxicity
Hematologic toxicity was only observed in 1 case, which displayed Grade 3 leukocytopenia and thrombocytopenia. This patient had pancreatic cancer, and gemcitabine was administered concurrently with radiation therapy, so the above acute adverse effects might have been derived from either (or both) treatment(s).

The change in CD4 lymphocyte count was not associated with radiation therapy. The number of patients whose CD4 lymphocyte count was under 200 /μl was 20 before radiation therapy and 1 after radiation therapy.

Treatment response
Twenty-nine patients (94%) completed the prescribed radiation therapy. Both partial responses (PR) and complete responses (CR) were defined as “Response”. The response rate of the HIV-positive patients with Kaposi’s sarcoma to radiation therapy was 93%.

DISCUSSION
It is considered that normal tissue in HIV-positive patients is sensitive to radiation therapy, and both acute and late adverse effects tend to be severe in this patient group. The acute adverse effects of radiation therapy disappear after therapy, so radiation oncologists tend to make light of acute adverse effects; however, the percentage of patients completing the prescribed dose and the treatment response rate are decreased because of severe adverse effects. We therefore reported the acute adverse effects, the percentage of patients completing the prescribed dose, and the treatment response rate to radiation therapy of HIV-positive patients.

In this report, acute adverse effects tended to occur earlier in the HIV-positive patients and more frequently became severe than in the general population. In particular, disorders of the mucosa, such as those of the oral cavity, pharynx, and intestine, tended to occur more rapidly. Mucositis in the oral cavity and pharynx occurred before a total dose of 20 Gy irradiation had been delivered, the earliest case was observed after 12 Gy had been delivered, and became very severe; however, no Grade 4 or higher adverse effects occurred, and the percentage of patients completing the total prescribed radiation dose was very high. Of the two patients that did not complete their dose schedule, one suffered a worsening of their performance status, and the other did not finish the course because of hematologic toxicity. This patient was concurrently treated with gemcitabine, so radiation therapy can not be held solely responsible for this acute adverse effect. In other words, it can be said that no acute adverse effect that was caused by radiation therapy alone prevented radiation therapy.

The CD4 lymphocyte counts of HIV-positive patients are decreased. When a patient’s CD4 lymphocyte count falls below 200 /μl, many kinds of HIV-related disease, such as malignancies and opportunistic infection, can occur. In this study, CD4 lymphocyte count was not associated with radiation therapy. The reason for this phenomenon might be derived from the timing of the start of HAART therapy. Many patients started treatment with HAART therapy at the same time as radiation therapy. Hence, CD4 lymphocyte count tended to increase among the patients of this study.

The interactions between radiation therapy and HAART have not been discussed in the literature. For example, zidovudine appears to be myelosuppressive.21) Hence, this drug needs to be avoided if HIV-positive patients are administered radiation therapy to large areas of their bone marrow.
or myelosuppressive chemotherapeutics, such as cisplatin and alkylators. Some HAART drugs, such as didanosine, stavudine, and zalcitabine, are associated with neuropathy. Hence, these drugs need to be avoided if HIV-positive patients are administered radiation therapy to an extensive proportion of their nerves or central nervous system. There were no such cases in this study; hence, we have never had this trouble.

No strategy for radiation treatment of HIV-positive patients has been established. However, the acute and late adverse effects seen in this patient group tended to be severe; hence, radiation treatment must be performed as carefully as possible. In this study, the total radiation dose and dose per fraction of radiation therapy for HIV-positive patients tended to be less than those used for the general population. In general, the total dose and dose per fraction administered to HIV-positive patients in this study were approximately 90% of those used for the general population although the percentages differ according to the type of cancer. The radiation therapy field was also set so that it was as small as possible. As a result, a high proportion of patients completed the prescribed dose. Although we restricted the radiation dose and field, the early response rate was high, and the results were promising.

In conclusion, it was shown that radiation therapy is safe when treatments are performed carefully and that it is a very useful treatment for cancer in HIV-positive patients.

REFERENCES