Radiation Pneumonitis Following Twice-daily Radiotherapy with Concurrent Carboplatin and Paclitaxel in Patients with Stage III Non-small-cell Lung Cancer

Hiroki Kobayashi¹, Takashi Uno¹,*, Koichi Isobe¹, Naoyuki Ueno¹, Miho Watanabe¹, Rintaro Harada¹, Yuichi Takiguchi², Koichiro Tatsumi² and Hisao Ito¹

¹Department of Radiology, Graduate School of Medicine, Chiba University and ²Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan

*For reprints and all correspondence: Takashi Uno, Department of Radiology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuou-ku, Chiba-City, Chiba 260-8670, Japan. E-mail: unotakas@faculty.chiba-u.jp

Received September 26, 2009; accepted December 13, 2009

Objective: To examine the effects of dose–volume factors on the development of radiation pneumonitis in patients with non-small-cell lung cancer who received twice-daily radiotherapy concurrently with carboplatin and paclitaxel chemotherapy.

Methods: Radiotherapy consisted of twice-daily fractionation of 1.2 Gy, to a total dose of 60 Gy. Weekly carboplatin and paclitaxel were used as a concurrent chemotherapy. Effects of radiotherapy parameters on the development of radiation pneumonitis were retrospectively analyzed.

Results: Fourteen of 37 patients developed Grade 2 or worse (≥G2) radiation pneumonitis. Grade 2 or worse radiation pneumonitis occurred in all 5 patients with V5 ≥40%, all 4 patients with V10 ≥35%, all 4 patients with V13 ≥32%, 9 of 14 patients with V20 ≥24% and 8 of 11 patients with V30 ≥22%, whereas 9 of 32 patients with V5 <40%, 10 of 33 patients with V10 <35%, 10 of 33 patients with V13 <32%, 5 of 23 patients with V20 <24% and 6 of 26 patients with V30 <22%, with respective P values of 0.0045, 0.015, 0.015, 0.015 and 0.008. Eight of 11 patients with a mean lung dose of >14 Gy developed ≥G2 radiation pneumonitis in contrast to 6 of 26 patients with a mean lung dose of <14 Gy (P = 0.008).

Conclusions: Several cut-off values in the Vdose and the mean lung dose differentiating probabilities of developing ≥G2 radiation pneumonitis were identified in this combination therapy.

Key words: non-small-cell lung cancer — radiation pneumonitis — radiotherapy — dose–volume histogram

INTRODUCTION

Recent standard care for locally advanced non-small-cell lung cancer (NSCLC) is a concurrent platinum derivative-based doublet chemotherapy and radiotherapy (1,2). However, some patients with NSCLC who received radiotherapy suffer moderate-to-severe radiation pneumonitis (RP). Reported clinical risk factors for RP are poor performance status, preexisting chronic obstructive pulmonary disease, smoking history, low pulmonary function test, use of chemotherapy, and radiotherapy parameters such as high total dose and/or dose per fraction (3–11). Recently, by using three-dimensional (3D) treatment planning data, several investigators have demonstrated that dose–volume factors such as the percentage of lung volume that received a specific dose or more (Vdose) and the mean lung dose (MLD) had significant effect on the development of RP. Graham et al. (12) clearly showed the association between V20 and Radiation Therapy Oncology Group (RTOG) Grade 2 or worse (≥G2) RP. Kwa et al. (13) reported the relationship between MLD and development of Southwest Oncology Group (SWOG) ≥G2 RP. Although differences in the grading system of RP used in each study make it difficult to interpret these results, it seems that current radiation oncologists perform 3D treatment planning of radiotherapy paying attention to these parameters.

Effects of altered fractionation schedule on the development of RP are still controversial. A recent systematic review...
pointed out that even though most studies showed an association between radiotherapy parameters and risk of RP, overall accuracy, sensitivity and specificity were generally poor (14). The value of radiotherapy parameters may differ from those in conventional once-daily treatment due to differences in total dose, fractionation size and overall treatment time. The use of concurrent chemoradiotherapy and contents of chemotherapy regimen may be the further confounding factors. Combined carboplatin and paclitaxel is one of the standard treatment regimen for inoperable NSCLC (15,16). From 2001, in this institution, patients with locally advanced NSCLC have been treated with concurrent twice-daily radiotherapy and carboplatin/paclitaxel chemotherapy. In the present study, effects of radiotherapy parameters on the development of RP in this combination therapy were retrospectively analyzed.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the records of 37 patients with locally advanced NSCLC consecutively treated with concurrent twice-daily radiotherapy and carboplatin/paclitaxel chemotherapy between August 2001 and November 2005. The study population included 27 patients participated in a Phase I study performed at Chiba University Hospital, results of which have not yet been published, and additional 10 patients. The protocol of the study was approved by the institutional review board of Chiba University Hospital. The study was undertaken to establish the recommended dose of weekly paclitaxel (primary endpoint) in the setting of fixed dose of weekly carboplatin (AUC = 2.5 mg/ml min) for five cycles and concurrent twice-daily radiotherapy for patients with locally advanced NSCLC, with secondary endpoints of toxicities and response rate of the treatment. Patients with the following eligibility criteria were included in the study: 75 years or younger with Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; histologically or cytologically proven NSCLC; unresectable clinical stage IIIA or IIIB with measurable lesions on computed tomography (CT) but malignant effusion; no prior therapy; expected survival of more than 3 months; no previous or simultaneous malignancies; and written informed consent. Adequate organ functions were required: leukocyte count ≥4000/mm³; neutrophil count ≥2000/mm³; platelet count ≥100 000/mm³; hemoglobin ≥10.0 g/dl; GOT/GPT <80 IU/ml; creatinine ≤1.5 mg/dl; creatinine clearance ≥50 ml/min; and PaO₂ ≥70 torr. The initial evaluation included a complete history, physical examination, laboratory studies including complete blood cell count and chemistry profiles, chest radiography, CT of the thorax and upper abdomen, bone scintigraphy, and brain scan of CT or magnetic resonance imaging. Unresectable stage III disease was due mainly to multiple and/or bulky mediastinal lymph nodes on CT. Patients with superior sulcus tumor were not included in the study. Dose level of paclitaxel (mg/m²) was set at 0 (level 1), 20 (level 2), 40 (level 3), 60 (level 4) and 80 (level 5), with an actuarial dose of 0 (level 1), 20 (level 2), 40 (level 3) and 50 (level 4). Dose-limiting toxicities (DLTs) were Grade 4 neutropenia or leukocytopenia, febrile neutropenia, Grade 4 thrombocytopenia, Grade 2 pulmonary toxicity, Grade 3 esophagitis or treatment delay exceeding 1 week because of adverse events including the criteria to postpone treatment (leukocyte count <3000/mm³, platelet count <75 000/mm³ or fever ≥38°C at the day of chemotherapy administration). Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The patients who suspended the treatment and had not recovered from adverse effects within 2 weeks had stopped the protocol treatment. The number of patients allocated to each dose level was three in level 1, three in level 2, six in level 3 and six in level 4. DLTs were occurred in one (esophagitis) of six patients treated with level 3 (40 mg/m²) and three (esophagitis in one and treatment delay in two) of six patients treated with level 4 (50 mg/m²) dose. After that, further 12 patients were treated using level 3 dose to confirm the feasibility of the dose level. Thus, the study population of this retrospective study included three patients treated with level 2 (20 mg/m²), 6 + 12 patients with level 3 (40 mg/m²) and six patients with level 4 (50 mg/m²) from the Phase I study and additional 10 patients treated using level 3 dose but out of the clinical study, resulting 37 patients in total. Three patients, allocated to level 1 and never received paclitaxel, were not included. All 10 patients treated out of the study met the above-mentioned eligibility criteria of the Phase I study except ECOG performance status. There were four patients with ECOG performance status of 2. The study was in accordance with the Declaration of Helsinki (2001).

Radiotherapy

For all patients, radiation therapy was delivered using a linear accelerator with a 10 MV photon beam and all patients underwent 3D treatment planning. Patients were positioned on the couch of the CT simulator (AcQSIM, Picker PQ2000 CT, Philips Medical Systems, Andover, MA, USA) in a supine position. CT images were acquired in spiral mode using 1.5 pitch and 3 mm slice thickness during quiet respiration with no attempt at breath holding or obtaining the scan during any particular phase of respiration. A virtual simulation was performed based on the full 3D-CT anatomical data that were obtained. The treatment planning and dose distribution calculation with tissue heterogeneity correction were performed using a 3D treatment planning system (FOCUS version 3.2.1 or Xio version 4.1, CMS, St Louis, MO, USA). Because the Clarkson dose calculation algorithm appears to be less precise for use within tissue—air interfaces, all planning in the present study was based on the Superposition algorithm. Radiation therapy targets were defined according to the International Commission on Radiation Units and Measurements Report Nos 50 and 62.
The gross tumor volume (GTV) was defined as all detectable tumors and lymph nodes with a short-axis diameter $>$1 cm observed on CT scans. The clinical target volume included the GTV and prophylactic nodal area with 1 cm margin. A further margin is then given to allow for set-up error and organ motion in order to create the planning target volume. As a result, the original irradiated volume included the GTVs with a margin of 2 cm which account for subclinical disease extension, organ motion, set-up errors and dose uncertainties around multi-leaf collimator edges. If supraclavicular lymph nodes were involved, only the involved side was included. The typical beam arrangements were initial AP–PA opposed fields followed by off-cord oblique fields excluding uninvolved nodal area after 40.8 Gy. Each beam was individually conformed to the target volume using a multi-leaf collimator. The prescribed isocenter dose was 60 Gy at 1.2 Gy per fraction twice-daily, 10 times per week, with a minimum 6 h interfraction interval. When the criteria to postpone chemotherapy were met, radiotherapy was also suspended.

ASSESSMENTS AND ANALYSES

After the completion of treatment, patients usually attended the outpatient clinic every 2–4 weeks for up to 12 months and every 1–3 months thereafter if the patient’s general status continued to remain stable. A diagnosis of RP was made on the basis of clinical symptoms such as cough, shortness of breath and fever, with chest radiography and CT findings in the absence of any other likely cause during the follow-up period. RP was graded retrospectively according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 as follows: Grade 1 pneumonitis was asymptomatic and diagnosed by radiographic findings only; Grade 2 pneumonitis was symptomatic but did not interfere with daily activities; Grade 3 pneumonitis was symptomatic and interfered with daily activities or required administration of oxygen to the patient; Grade 4 pneumonitis required assisted ventilation for the patient; and Grade 5 pneumonitis was fatal. Effects of several risk factors on development of RP were examined. Risk factors included in the present study were dose–volume parameters of radiotherapy and patient-related factors such as gender, age ($<$70 vs. $>$70), location of the tumor (upper lobe vs. middle or lower lobe) and performance status (0–1 vs. 2). Dose–volume parameters analyzed were percentage of lung volume that received a specific dose (Gy) or more ($V_{\text{dose}}$: V5, V10, V13, V20, V30, V35, V40) and MLD. The MLD was defined as the average dose of the CT-defined total lung volume. Total lung volume was defined as the both lungs together minus GTV. The lungs were considered together as a single-paired organ. Lung contours were obtained automatically by CT threshold and the GTV within the lung was excluded automatically. Fisher’s exact test was used to compare proportions, and Mann–Whitney U test was used to compare continuous variables between groups. A partitioning technique was used to detect potential significant cut-off values for dividing the patient population into two subgroups based on continuous dose–volume factors (MLD and $V_{\text{dose}}$). The cut-off value identified for each factor was the one minimizing the P value in each exact test with at least 10% of patients in each subgroup. The tumor responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Actuarial survival curves were calculated by the Kaplan–Meier method.

RESULTS

Patient’s characteristics are shown in Table 1. Twenty-eight required treatment break with a median of 8 days (range, 2–18) due mainly to leukopenia. However, 32 patients completed a planned radiotherapy of 60 Gy. Five patients who stopped the treatment had received a total dose of 45.6–56.4 Gy (median, 49.2). Thirty-four patients received five courses of weekly chemotherapy, three received four courses. Tumor responses after chemoradiotherapy were partial response in 22, stable disease in 12 and progressive disease (PD) in 3. All patients with PD had appearance of new lesions without progression of primary lesions. A median follow-up for all patients was 25.2 months (range, 5.3–65.3). The first site of relapse was primary site in 13 patients, distant site in 14 patients and both sites in 3 patients. One patient died of cancer within 6 months after

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>44–75 (median 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 70$</td>
<td>31</td>
</tr>
<tr>
<td>$&gt;70$</td>
<td>6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
</tr>
<tr>
<td>PS</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>15</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>2</td>
</tr>
<tr>
<td>Clinical disease stage</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>10</td>
</tr>
<tr>
<td>IIIB</td>
<td>27</td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
</tr>
<tr>
<td>Upper lobe</td>
<td>21</td>
</tr>
<tr>
<td>Middle or lower lobe</td>
<td>16</td>
</tr>
</tbody>
</table>

PS, Eastern Cooperative Oncology Group performance status.
the treatment. The median progression-free survival and overall survival were 8.7 and 25.2 months, respectively. The overall survival at 2 years was 51.4%.

During the follow-up period, a total of 31 patients experienced RP; Grade 1 in 17, Grade 2 in 12, Grade 3 in 1 and Grade 4 in 1. Although most patients experienced some degree of RP, Grade 3 or worse RP was observed in only two (Grade 3 and Grade 4 each in one). Fourteen patients developed ≥G2 RP. Cumulative incidence of ≥G2 RP at 6 months was 38%. Because one patient who died of cancer at 5.3 months had experienced Grade 3 RP at 2.3 months after the treatment, this patient was included in all analyses for RP. None of the patient-related factors such as gender, age and performance status significantly influenced on the development of ≥G2 RP (Table 2). Mean values of Vdose and MLD are shown in Table 3. For the entire study group, the mean value of V5, V10, V13, V20, V30, V35 and V40 was 32.8%, 27.8%, 26.0%, 22.7%, 19.0%, 17.3% and 15.2%, respectively. The mean value of MLD was 12 Gy. For all dose–volume parameters concerned, there was nonsignificant trend that the mean value in patients with ≥G2 RP was higher than that in the remainders. The cut-off values identified for dose–volume parameters to divide the patient population into two subgroups, differentiating probabilities of developing ≥G2 RP, are shown in Table 4. Grade 2 or worse RP occurred in all 5 patients with V5 >40%, all 4 patients with V10 >35%, all 4 patients with V13 >32%, 9 of 14 patients with V20 >24% and 8 of 11 patients with V30 >22%, whereas 9 of 32 patients with V5 <40%, 10 of 33 patients with V10 <35%, 10 of 33 patients with V13 <32%, 5 of 23 patients with V20 <24% and 6 of 26 patients with V30 <22%, with respective P values of 0.0045, 0.015, 0.015, 0.015 and 0.008. Eight of 11 patients with an MLD of >14 Gy developed ≥G2 RP in contrast to 6 of 26 patients with an MLD of <14 Gy (P = 0.008).

**DISCUSSION**

RP is a relatively common adverse event of radiotherapy for lung cancer. The reported incidence of RP ranges from 10% to 40% (9,12,13,17–20), with variation among reports because of inconsistencies in the criteria used to define RP, heterogeneity in patient populations and differences in treatment regimens and radiotherapy techniques. Grade 2 RP is relatively mild toxicity and seems not to be clinically serious. However, it is sometimes clinically observed that not a small fraction of patients who developed Grade 3 RP experience preceding Grade 2 RP for at least several days. This suggests that patients who suffer Grade 2 RP have a potential to develop Grade 3 RP. Thus, we consider that Grade 2 RP can be a surrogate indicator for more severe RP and compared two groups of RP G0–1 vs. ≥G2 in this study.

The influence of altered fractionation on lung toxicity, when compared with conventional fractionation has not been well examined and seems to be controversial. In a setting of the intergroup study, there was no difference in the incidence of RP between the twice-daily fractionation group and a...
conventional once-daily group (21). By following up their Phase III study comparing the different fractionation schedule, Schild et al. (22) reported that there was no difference in the incidence of RP between split-course twice-daily radiotherapy of 48 Gy in 32 fractions and 50.4 Gy in 28 fractions. Roach et al. (10), on the other hand, presented the advantage of twice-daily fractionation concerning lung toxicity. They found that hypofractionation using fraction size >2.67 Gy was the most significant factor for the increased risk of RP. In the study evaluating the therapeutic benefit of continuous hyperfractionated accelerated radiotherapy (CHART) for NSCLC, Saunders et al. (23) showed that symptomatic RP was more frequently observed in the conventional fractionation group (10% vs. 19%). Jenkins et al. (24) also reported that CHART appeared to have superior therapeutic index in relation to acute RP than that of conventionally fractionated schedule. It seems, however, that differences in total dose, fractionation size and overall treatment time, as well as regimen of combined therapy, may be the confounding factor in this issue. In the present study, 28 patients required unplanned treatment break with a median of 8 days, despite a planned total treatment time of 5 weeks using twice-daily fractionation of 1.2 Gy. Thus, this single-arm study with a small patient number has limitations in evaluating the influence of twice-daily fractionation on lung toxicity.

Platinum-based chemotherapeutic doublets have produced survival benefits for patients with locally advanced non-small cell lung cancer. In the present study, all patients received combined carboplatin and paclitaxel concurrently with radiotherapy. Recently, this combination regimen is frequently used as a standard regimen for NSCLC (15,16). Several studies have now reported pulmonary toxicities in this regimen concurrently with definitive radiotherapy. Choy et al. (25) reported that an incidence of RTOG Grade 3 or worse RP after concurrent weekly paclitaxel/carboplatin and hyperfractionated radiation therapy for locally advanced NSCLC was 16.7%. Wang et al. (26) showed that the actuarial incidence of CTCAE ver. 3.0 Grade 3 or worse RP was 22% at 6 months where 155 of 223 patients received this two-drug combination. Belani et al. (15) reported that 15 of 92 patients developed CTC ver. 2.0 Grade 3 or worse RP among patients who received concurrent carboplatin/paclitaxel and radiotherapy followed by chemotherapy. In their sequential arm, where carboplatin/paclitaxel was followed by radiotherapy alone, only 6 of 90 patients had Grade 3 or worse RP. Our results indicate that several cut-off values in the \( V_{dose} \) and MLD can be a useful surrogate for the development of \( \geq G2 \) RP in this combination therapy. The incidence of \( \geq G2 \) RP can be acceptable if 3D radiotherapy parameters are favorable.

Many studies have reported that higher V20 value is associated with the incidence and grade of RP. However, in the setting of concurrent chemoradiation, it is reported that lower \( V_{dose} \) can be the threshold for RP when compared with radiotherapy alone (14). Schallenkamp et al. (27), mainly using concurrent carboplatin/paclitaxel and radiotherapy, demonstrated that a rate of \( \geq G2 \) RP to be significantly related to V10 and V13, and concluded that radiotherapy should be planned with caution when using techniques delivering doses of 10–15 Gy to large lung volumes. Wang et al. (26) showed a relationship between the development of RP and a wide range of \( V_{dose} (V5–V65) \), of which V5 is the most significant factor associated with RP. We identified that there are cut-off values in V5 and V13 differentiating probabilities of developing \( \geq G2 \) RP. Initial AP–PA opposed fields were followed by off-cord oblique fields after 40.8 Gy in this study. Thus, newly irradiated lung volume in the oblique fields receiving <20 Gy might have contributed to V5 and V13. It should be emphasized that every effort should be made to exclude normal lung tissue as much as possible not only at the start of radiotherapy but when off-cord oblique fields are planned. Clinical significance of an initial small field without irradiating elective nodal area for NSCLC is still under investigation and beyond the scope of the present study.

**Funding**

This study was supported by Grants-in-Aid for Cancer Research No. 21-8-8 from the Ministry of Health, Labor, and Welfare of Japan.

**Conflict of interest statement**

None declared.

**References**


