A Case of Acute Exacerbation of Idiopathic Pulmonary Fibrosis After Proton Beam Therapy for Non-small Cell Lung Cancer

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There have been no reports describing acute exacerbations of idiopathic pulmonary fibrosis after particle radiotherapy for non-small cell lung cancer. The present study describes the case of a 76-year-old Japanese man with squamous cell carcinoma of the lung that relapsed in the left upper lobe 1 year after right upper lobectomy. He had been treated with oral prednisolone 20 mg/day every 2 days for idiopathic pulmonary fibrosis, and the relapsed lung cancer was treated by proton beam therapy, which was expected to cause the least adverse effects on the idiopathic pulmonary fibrosis. Fifteen days after the initiation of proton beam therapy, the idiopathic pulmonary fibrosis exacerbated, centered on the left upper lobe, for which intensive steroid therapy was given. About 3 months later, the acute exacerbation of idiopathic pulmonary fibrosis had improved, and the relapsed lung cancer became undetectable. Clinicians should be aware that an acute exacerbation of idiopathic pulmonary fibrosis may occur even in proton beam therapy, although proton beam therapy appears to be an effective treatment option for patients with idiopathic pulmonary fibrosis.

Key words: acute exacerbation — idiopathic pulmonary fibrosis — non-small cell lung cancer — proton beam therapy

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonia and is known to be associated with an independently increased risk of lung cancer (1). Although the clinical course is usually chronic and slowly progressive, some patients experience rapid deterioration during the course of IPF, and this deterioration is a substantial cause of death in patients with IPF (2). Acute deterioration of IPF may occur secondary to infections, pulmonary embolism, pneumothorax and heart failure, but it may also occur without an identifiable cause or secondary to iatrogenic procedures, which is termed an acute exacerbation (AE) of IPF (3). Since cancer therapy including surgery, chemotherapy and conventional radiotherapy can cause a life-threatening AE of IPF, the treatment of lung cancer in patients with IPF is a difficult task for clinicians.

Proton beam therapy can theoretically produce a superior dose distribution to the target using the sharp distal falloff of the Bragg peaks produced by these techniques than that produced by photon irradiation (4, 5). Compared with the pulmonary damage caused by stereotactic radiotherapy for the treatment of Stage I lung cancer (6–8), the incidence and
severity are expected to be markedly lower and safer in IPF patients, because the small-irradiated volume decreases the adverse effects on the lung (9).

The present case highlights AE of IPF after proton beam therapy for non-small cell lung cancer (NSCLC) in a patient with IPF. Prior to the present case, there were no reports of patients who experienced AE of IPF after particle radiotherapy.

CASE REPORT

A 76-year-old Japanese man who had smoked 112 pack-years was admitted to our hospital in October 2010, 18 days after the initiation of proton beam therapy, because of dyspnea. One year before the initiation of proton beam therapy, squamous cell carcinoma of the lung was diagnosed, and right upper lobectomy was performed. The lung squamous cell carcinoma was pathologically characterized as T1N2M0, Stage IIIA according to the TNM classification of the International Union Against Cancer (10). In addition to lung cancer, pathological examination showed honeycomb lung (Fig. 1). The patient had no previous history of diseases associated with honeycomb lung. Based on his history, clinical examination and histopathology, he was diagnosed as having IPF. Three days after surgery, he developed AE of IPF and received intensive steroid therapy. Ultimately, the IPF was controlled by oral steroid therapy with prednisolone 20 mg every 2 days. He was not given adjuvant chemotherapy after surgery. Follow-up computed tomography (CT) examination 2 months before the initiation of proton beam therapy demonstrated a mass in the left upper lobe (Fig. 2A). On pathological examination of biopsy specimens, the diagnosis was a relapse of lung squamous cell carcinoma in the left upper lobe. Because he had IPF, he received protonbeam therapy as an alternative to chemotherapy or conventional radiotherapy, both of which have been reported to lead to AE of IPF. The total dose of 66 gray equivalents was delivered in 10 fractions at the isocenter of the planning target volume using a 150 MeV proton beam (Fig. 2B). Fifteen days after the initiation of proton beam therapy, he completed proton beam therapy without developing any respiratory symptoms. However, on the very day of the completion of the proton beam therapy, he emergently presented with dyspnea without fever or increased sputum.

Arterial blood gas analysis on admission showed hypoxia (pCO$_2$, 44.1 mm Hg; pO$_2$, 29 mm Hg; base excess, 2.4; bicarbonate [HCO$_3$], 27.9 mmol/l; pH, 7.414) on room air. Laboratory testing showed increased serum levels of C-reactive protein (4.98 mg/dl), lactate dehydrogenase (319 IU/l) and sialylated carbohydrate antigen KL-6 (1194 U/ml). The number of white blood cells had increased to 9400/μl (neutrophils 95.8, eosinophils 0.5, basophils 0.3, monocytes 1.3, lymphocytes 2.1%). The serum beta-glucan level was within normal limits, and he tested negative for Streptococcus pneumoniae and Legionella pneumophila antigen in urine and two sets of blood cultures. A thin-section CT (TSCT) showed consolidation with fibrotic changes in the left upper lobe, ground-glass opacities, reticulation, traction bronchiectases, microcystic honeycomb and volume loss in both lungs (Fig. 3A and B). AE of IPF was thought to be the main cause of the acute respiratory failure based on the clinical course, laboratory tests and radiological findings. Therefore, he was given intensive steroid therapy (1 g of methylprednisolone on three consecutive days) and then oral prednisolone (1 mg/kg). His symptoms gradually improved. Follow-up CT 4 months after the initiation of proton beam therapy revealed disappearing ground-glass opacities and consolidation, with fibrotic changes in the left upper lobe (Fig. 4). Thirteen months after the initiation of proton beam therapy, there was no relapse of lung cancer, and deterioration of IPF was treated with prednisolone 12.5 mg/day.

DISCUSSION

Particle radiotherapy is a promising modality because of its excellent dose localization and high biological effect on tumors. This excellent dose localization is especially important for IPF, which may be exacerbated by iatrogenic procedures. The prevalence and mortality of AE of concomitant IP, which is diffuse parenchymal lung disease and is diagnosed by histological or radiological features such as ground-glass opacity or reticular shadow, induced by cancer treatment in patients with lung cancer described in the literature are summarized in Table 1 (11–18). In the patients with concomitant IP, 62–100% of patients had IPF. Unfortunately, AE is generally associated with an increased risk of poor outcome, although the mortality rate ranges from 25 to 100%. In a Phase I/II trial of carbon-ion

Figure 1. Photomicrograph of the surgical specimen of the lung shows a heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibrosis and honeycomb change. The fibrotic zones are partly composed of proliferating fibroblasts (so-called ‘fibroblastic foci’, arrow) (hematoxylin and eosin stain; scale bar, 500 μm).
radiotherapy for Stage I NSCLC, 5 of 81 patients had concomitant IPF, and AE of IPF did not occur, although 3 of 81 patients developed Grade III radiation pneumonitis (17) according to the Radiation Therapy Oncology Group (RTOG, acute) and RTOG/European Organization for Research and Treatment of Cancer (EORTC, late) classification (19). In a recent study, 80 patients with Stage I NSCLC, which included 7 patients with concomitant IP, were treated with particle therapy including proton therapy and carbon-ion therapy, but no patients developed AE of IP after the particle therapy (12). Therefore, there were no reports of patients who experienced AE of IPF after particle radiotherapy, prior to the present case.

Infection is the most important factor in the differential diagnosis of acute deterioration of IPF, because many patients with IPF are treated with corticosteroids either with or without cytotoxic drugs. In the present case, the patient tested negative on all of the microbiological studies performed. On TSCT, ground-glass opacities, reticulation, traction bronchiectasis, microcystic honeycomb and volume loss were observed, and these findings were consistent with AE of IPF. In addition, these lung lesions are thought to differ from radiation pneumonitis, which includes at least the irradiated lung (20), since the lung lesions in the present case were not centered on the exposure field of proton beam therapy and spread to another lobe. Most notably, the present patient experienced AE of IPF 15 days after the initiation of proton beam therapy, and this onset time is earlier than the 3–5 months when most cases of symptomatic Grade 2 or 3 radiation pneumonitis cases are reported to occur after the start of irradiation with particle radiotherapy (12).
outcome. AE is generally associated with an increased risk of poor time, it is important for clinicians to be aware that an AE patients than other cancer therapy. However, at the same increasing frequency for NSCLC in patients with IPF, because the incidence and severity of pulmonary damage experience, proton beam therapy appears to be an effect-

In the present case, cancer relapse has been controlled by proton beam therapy and the patient has survived 1.3 years after the initiation of proton beam therapy. This survival period seems to be longer than expected, because the mean survival of patients with IPF and lung cancer was reported to be 2.3 years after the diagnosis of IPF and 1.6 years after that of cancer (21). Based on our experience, proton beam therapy appears to be an effective treatment option for patients with IPF, although careful attention needs to be paid to the occurrence of AE of IPF.

Proton beam therapy is expected to be performed with increasing frequency for NSCLC in patients with IPF, because the incidence and severity of pulmonary damage are expected to be markedly lower and safer in IPF patients than other cancer therapy. However, at the same time, it is important for clinicians to be aware that an AE of IPF may occur even in proton beam therapy, because AE is generally associated with an increased risk of poor outcome.

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Conflict of interest statement

None declared.

Table 1. Summary of the prevalence and mortality of acute exacerbation of concomitant interstitial pneumonia in patients with lung cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Number of patients with lung cancer</th>
<th>Number of patients with lung cancer and IP (%)</th>
<th>Number of patients who experienced AE of IP (%)</th>
<th>Number of patients who died of deterioration of IP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koizumi et al.</td>
<td>Surgery</td>
<td>1103</td>
<td>47 (4.3)</td>
<td>7 (15)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Kanzaki et al.</td>
<td>Surgery</td>
<td>758</td>
<td>40 (5.3)</td>
<td>12 (30)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Okamoto et al.</td>
<td>Surgery</td>
<td>101</td>
<td>20 (20)</td>
<td>4 (20)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Chiyotani et al.</td>
<td>Surgery</td>
<td>931</td>
<td>36 (3.9)</td>
<td>9 (25)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Kenmotsu et al.</td>
<td>Chemosurgery</td>
<td>NR</td>
<td>109</td>
<td>24 (22)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Minegishi et al.</td>
<td>Radiotherapy</td>
<td>NR</td>
<td>6</td>
<td>1 (17)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Miyamoto et al.</td>
<td>Particle radiotherapy</td>
<td>81</td>
<td>5 (6.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Iwata et al.</td>
<td>Particle radiotherapy</td>
<td>80</td>
<td>7 (8.8)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

IP, interstitial pneumonia; AE, acute exacerbation; NR, not reported.

References

17. Koizumi et al. Surgical treatment of lung cancer combined with interstitial pneumonia: the effect of surgical approach on


