"Lung cancer against cisplatin lipiodol suspension (CLS) 的经皮的局注療法"

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Introduction

Cisplatin lipiodol suspension (CLS: cisplatin lipiodol suspension) has a slowly releasing tendency of cisplatin. Fukushima et al1) reported that cisplatin was gradually released from CLS in vitro. Previously, we2) reported experimentally that percutaneous injection of CLS into normal lung of rabbits caused regional infiltrates, immature fibrosis, bronchiolitis and sporadic infarction in the limited lung tissue. Intra bronchial or intrathoracic leaks of CLS disappeared immediately and provoked little damage to the bronchus or pleura. Despite the fatal dose of cisplatin (2~6 mg/kg), seven of eight rabbits showed increase in body weight. The experimental animal study suggested that intratumor CLS injection therapy for human lung cancer would be safe and worthy of trying. This study evaluates the safety and feasibility of intratumor CLS injection therapy for human lung cancer.

Patients and methods

Two of three patients were inoperable and radiation therapy (2 cases) and mild systemic chemotherapy (1 case) were added. Patients received percutaneous intratumor CLS injection therapy with 21 or 22 gage needle (PEIT needle or Cathelin's needle) under fluoroscopic or CT guidance. CLS was slowly and carefully injected into tumor parenchyma under fluoroscopic monitor (Fig. 1) in order to avoid intrathoracic, intrabronchial or intravascular leak-
age. Mild hydration (1～1.5 L), metoclopramide and hydrocortisone were used to protect renal or alimentary adverse effects of cisplatin. At each therapeutic procedure, as CLS was injected slowly and directly into the tumor, it diffused within tumor parenchyma, intrabronchial space or transitional zone between tumor and surrounding lung tissue. A small quantity of CLS leakage into thoracic space was noted in case 1. The CLS amount administered was 1～4 ml/procedure (cisplatin: 20～80 mg/procedure).

Clinical features and results of 3 patients are summarized in Table 1. The clinical stage of the first patient was stage IIIA (T3N2M0, Fig. 2) and he was considered inoperable because of poor pulmonary function. He received 6 times of CLS injection therapy (cisplatin: 270 mg in all) and low dose megavoltage X-ray irradia-

<table>
<thead>
<tr>
<th>patients</th>
<th>pathology</th>
<th>tumor size(cm)</th>
<th>total CDDP volume(mg)</th>
<th>reduction rate(%)</th>
<th>combined treatments</th>
<th>complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1 82y(M)</td>
<td>squamous cell ca.</td>
<td>11×8</td>
<td>270 mg(6 times)</td>
<td>54%</td>
<td>Linac 40Gy</td>
<td>cough</td>
</tr>
<tr>
<td>No. 2 65y(M)</td>
<td>poorly diff. ca.</td>
<td>8×7.5</td>
<td>60 mg(1 time)</td>
<td>0%</td>
<td>none</td>
<td>mild fever</td>
</tr>
<tr>
<td>No. 3 75y(M)</td>
<td>large cell ca.</td>
<td>5.5×4</td>
<td>30 mg(1 time)</td>
<td>90%</td>
<td>Linac 40Gy</td>
<td>WBC</td>
</tr>
</tbody>
</table>

tion (total dose: 40.2 Gy/34 days). The treatment was discontinued after 2 months, and 1 month later the patient was died from concurring interstitial pneumonitis. The second patient had a large tumor in left upper lobe (stage IV, T3N1M1), and was considered to be at poor risk because of severe lung emphysema. The primary tumor was punctured under CT guidance by double needle method, and 3 ml of CLS (cisplatin: 60 mg) was injected into the tumor parenchyma. No additional treatment was performed. The third patient refused the operation. Therefore combined therapy of intratumor injection therapy of CLS (1.5 ml: cisplatin 30 mg) with mild irradiation therapy (40.4 Gy) and mild systemic chemotherapy (4 courses of intravenous carboplatin: 150 mg and oral etoposide: 150 mg) was performed in this patient.

Results
In the first patient, good tumor reduction was achieved (reduction rate: 54%). Follow up CT revealed CLS was transferred to the hilar region. One month later the patient died from secondary interstitial pneumonitis. Softex X-ray examination of autopsied lung demonstrated scattered distribution of CLS in the periph-

Fig. 3 Examinations of autopsied lung of case 1
a: Softex X-ray of the lung (sliced axially in about 3 mm thickness) shows dense accumulation of CLS in the posterior periphery of the tumor and around the tumor.
b: Scheme of distribution of tumor necrotic portion (●●●●) and viable portion (□□□□) in the axially section. CLS leakage around the tumor provoked fibrotic change of the limited area of lung tissue (|||||).
ery of the tumor (Fig. 3a).

Histological examination demonstrated marked tumor necrosis rate with small amount of viable tumor cells in the peripheral area (Fig. 3b and 4). The lung showed organizing state of the diffuse alveolar damage characterized with fibroblasts proliferation mainly in the interstitium and focally within air space.

Follow up CT (8 days after) of the second patient showed mild increase of CT density of pretracheal lymph node, which was considered CLS migration to the mediastinal lymph node (Fig. 5).

Concerning the mediastinal lymph node, CT of the next day demonstrated mild CLS accumulation in the pretracheal lymph node of the third patient (Fig. 6).

Moreover the tumor demonstrated a remarkable shrinkage and had only a CLS lake (Fig. 6c).

Regarding to the adverse effects, mild fever and leucocytosis were noted in two cases and disappeared in two or three days (case 2, 3). Reactive pleural effusion (case 1) and slight sense of discomfort at the puncture site was noted in one case (case 3). Cough was noted in one case (case 1) for a few days, which was thought to be induced by intrabronchial leakage of CLS. Neither alimentary symptom nor renal toxicity was noted. All side effects such as fever, leucocytosis and sense of discomfort at the puncture site were mild and transient. As to the major complication, the second trial of the third patient gave rise to a cardiac tamponade (Fig. 7) and circulatory shock because of pulmonary artery injury by needle tip. Resuscitation and drainage of pericardial bloody effusion for about 40 ml was performed. Anterior chest pain and secondary atrial fibrillation were accompanied during a few days. One week after
almost all of the pericardial effusion and accompanied symptoms were disappeared. As a result, good responses of tumor reduction rate were achieved in two cases. CT demonstrated lipiodol accumulation in pretracheal lymph nodes in two cases and showed lipiodol transference to the hilar region in the other.

Discussion
Controlling of lymph node metastasis has ever been one of a great concern for surgeons or radiation oncologists who treat lung cancer, however further improvement would be necessary to control sufficiently it. Unfortunately, despite good control of the local lesion, occult lymph node metastasis may often lead to recurrence.

Previously we reported CLS movement to mediastinal lymph nodes in 2 of 9 rabbits. Although metastasis was not proved in pathological study in our clinical series, 2 of 3 cases demonstrated CLS accumulation in mediastinal lymph node. On that ground, intratumor injection therapy might have a potentiality to treat or protect lymph node metastasis directly through lymphatic system which is exactly a metastatic route from the lung cancer. Okada et al proved bleomycin transfer to the metastatic lymph node from subpleural lymph channel in surgical cases. Takahashi et al reported a case of marked therapeutic effects on regional lymph node metastases by local administration of fat emulsion containing anticancer agents. However problems awaiting solution would be insufficient transference of cisplatin to the metastatic lymph node in general or complete lymph channel block by bulky lymph node metastasis.

Concerning intratumor injection therapy of lung cancer, Holmes et al reported that percutaneous intratumor injection therapy of BCG had produced tumor necrosis. Kitamura, Suzuki et al and Fujisawa et al reported transbronchial injection of multiple anti-cancer drugs, OK-432 and ethanol by fiberscope,
respectively. Matsumoto injected cisplatin solution percutaneously and reduction in tumor size was noted.

To control sufficiently the primary lung tumor, our intratumor injection therapy may have a limited value and there seemed to be a technical difficulty to sprinkle CLS densely into the whole of the tumor. Nevertheless, good tumor responses (reduction rate in size and necrosis rate) were achieved in two of three cases (case 1, 2).

Despite the lack of immunological study, cytomegaloviral infection would be considered as the most probable cause of the diffuse alveolar damage of the first patient because the patient did not have high dose oxygen inhalation or severe circulatory shock in the course.

Sonnenberg reported complications of CT-guided lung biopsy were pneumothorax (40%), hemoptysis (3%) and hemothorax. In Seibel’s series, the complication rate were pneumothorax (7.5%), hemoptysis (1.4%) and shoulder pain (1.6%). Cardiac tamponade is a major and critical complication which should be avoided with maximum caution. Thereafter we designed a simple needle stopper device protecting the over-pass of the needle through tumor to perform much more safely the procedure.

Our previous animal experiment and this clinical study are suggesting that systemic toxicity of cisplatin administered intratumor would be reduced much more when compared to intravenous administration of cisplatin. Fukushima et al. reported cisplatin was gradually released from CLS in vitro (11.8%/24 hr by paddle method). This slowly releasing tendency of cisplatin from CLS might contribute to reducing systemic toxicity.

This study suggest that the intratumor CLS injection therapy of lung cancer is easily tolerable and technically simple. Consequently intratumor injection therapy may be worthy of trying for lung cancer as an additional treatment. Moreover this method might have a potentiality to become one of the valuable therapies for controlling or prevention of regional lymph node metastasis in the future. Complication of bleeding due to needle traversing great vessels should be avoided with great caution.

The benefits of this therapy have not yet been demonstrated clearly, but our preliminary results would indicate that clinical trials with the method are feasible.

References


