肺癌に対する cisplatin lipiodol suspension (CLS) の
経皮的局注療法小野原信一・中條政敬・宮路紀昭・阿辺山和浩・吉満 彰・荻田幹夫・
平木嘉幸・小山隆夫^{*1)}、早瀬ヨネ子^{*2)}、本屋敏郎・中村和男^{*3)}*Percutaneous intratumor injection therapy of cisplatin lipiodol suspension (CLS) for human lung cancer*

肺癌の3症例に対して cisplatin lipiodol suspension (以下、CLS) の経皮的な腫瘍内局注療法を実施した。

症例1 (扁平上皮癌) には、総量 260 mg の cisplatin を6回にわけて局注し、40.2 Gy のマイルドな放射線治療も併用した。症例2 (低分化癌) には、CLS 3 ml (cisplatin 60 mg) の単回単独治療を実施した。症例3 (大細胞癌) には CLS 1.5 ml (cisplatin 30 mg) を局注したあと、軽い全身化学療法と放射線療法を追加した。

その結果、3例中2例において良好な腫瘍縮小効果が得られた。また、リンパ節への lipiodol の移行については、2例で気管前リンパ節、残りの1例で肺門部への lipiodol の集積が CT にて確認できた。

副作用については、発熱、白血球増多、穿刺部の違和感などがみられたものの、すべて軽微でかつ一過性であった。ただ穿刺手技の点では、症例3の2回目施行時に針先で肺動脈を傷つけ、心タンポナーデを引き起こした。

以上、肺癌の経皮的局注療法は、副作用が少なく、集学的治療法の一つとして有用と思われた。さらに本療法は、肺癌の領域リンパ節転移に対して、今後有力な治療法の一つになる可能性が示唆された。

なお、穿刺時、大血管損傷による出血を起こさないよう最大限の注意を払って防止すべきである。

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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-

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Table 1 List of patients

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

y : years. (M) : male. ca. : carcinoma. diff. : differentiated. CDDP : cisplatin. chemo : chemotherapy.
WBC : leucocytosis

Fig. 1 X-ray during the procedure(case 1)
Scattered CLS in tumor parenchyma is noted around the needle tip(arrow). Small amount of CLS leakage into bronchus(arrow heads) is also visualized.

Fig. 2 Chest-X ray at the beginning of CLS injection therapy(case 1)
A large snowman type tumor is shown in the right lung. Spotty accumulation of CLS is sporadically noted in the tumor.

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 irradiation.

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 (stippled) and viable portion (solid black) in the axially section. CLS leakage around the tumor provoked fibrotic change of the limited area of lung tissue (vertical lines).

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. 4 Microscopic examination of the tumor (case 1, HE, $\times 100$)

Almost all the tumor cells and tumor parenchymal cells undergo cellular necrosis around the lipidol lakes (arrows). In the other site, a few cells near the parenchymal vessels are still survived.

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

Fig. 5 The course of CT findings (case 2)

- a : CT of case 2 performed one day after CLS injection.
- b : Eight days after the CLS injection, increase of pretracheal lymph node density (arrow), suggesting CLS accumulation, is noted.

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

Fig. 6 The course of CT findings in case 3

- a : Dumbbell type tumor (arrows) is noted in front of pulmonary arterial trunk. Arrow head indicates the pretracheal lymph node.
- b : Next day after CLS injection, CT demonstrates dense accumulation of CLS in the center of the tumor. Moreover slight deposit of CLS is revealed in pretracheal lymph node (arrow head).
- c : Seventy days after CLS injection, marked shrinkage of the tumor is demonstrated, with a dense CLS lake (arrow). CT density of the pretracheal lymph node (arrow head) decreased to the pretherapeutic density.

almost all of the pericardial effusion and accompanied symptoms were disappeared.

As a result, good responses of tumor reduc-

tion 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 we²⁾ 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 al³⁾ proved bleomycin transfer to the metastatic lymph node from subpleural lymph channel in surgical cases. Takahashi et al⁴⁾ 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 al⁵⁾ reported that percutaneous intratumor injection therapy of BCG had produced tumor necrosis. Kitamura⁶⁾, Suzuki et al⁷⁾ and Fujisawa et al⁸⁾ reported transbronchial injection of multiple anti-cancer drugs, OK-432 and ethanol by fiberscope,

Fig. 7 Cardiac tamponade on CT at 24 hours after injection(case 3)

Pericardial bloody effusion with high spotty densities of CLS and reactive pleural effusion are shown.

respectively. Matsumoto⁹⁾ 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, cytomegalo viral 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.

Sonnenberg¹⁰⁾ reported complications of CT-guided lung biopsy were pneumothorax(40%), hemoptysis(3%)and hemothorax. In Seibel's series¹¹⁾, 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 experiment²⁾ 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 al¹⁾ 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.

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