A case of advanced lung cancer treated by surgery followed by adjuvant combination therapy of gefitinib and interleukin-2 lymphokine-activated killer cell immunotherapy

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Abstract

A smoker, 55-year-old male with a small nodule in left S⁵ on computed tomographic (CT) scanning of chest was diagnosed with pulmonary adenocarcinoma (cT1N0M0, c-stage IA). However, the CT scanning revealed that several small nodules on pleural surface might suspect a pleural dissemination, that is, IV-staged advanced lung cancer. The patient desired for receiving an aggressive multimodality containing of surgery, immunotherapy, and gefitinib treatment. After thoracotomy, the small pleural nodules were intraoperatively diagnosed with pleural dissemination by pathological examination. However, there was no malignant pleural effusion and intraoperative cytological examination of intrathoracic lavage resulted in a negative finding. Because of clinical N2-negative disease without malignant pleural effusion, left upper lobectomy with mediastinal lymph nodes dissection was preceded. The postoperative pathological examination disclosed pulmonary adenocarcinoma with mixed subtypes (pT1N2M1a, p-stage IV) and with micropapillary pattern. A detection test of epidermal growth factor receptor (EGFR) gene mutation revealed a positive result (L858R). As a systemic therapy, a combination chemotherapy of gemcitabine and carboplatin was performed in 2 cycles for the remained pleural dissemination. The patient received combination therapy of gefitinib and interleukin-2 lymphokine-activated killer cell immunotherapy in 6 cycles. A CT scanning of chest displayed disappearances of the remained pleural dissemination. There had been uneventful for 25 months. On the third postoperative year, a stereotactic radiotherapy surgery was performed for small three brain metastases. He had been healthy and received the gefitinib treatment for 45 months without any regrowing of the irradiated cerebral metastases and the treated pleural dissemination. The combination therapy of gefitinib and immunotherapy in the postoperative early phase would take advantage of extending the patient's progression-free survival, and also in case of the selected population of the advanced lung cancer harboring a EGFR mutation-positive.

Key Words: surgery, gefitinib, immunotherapy, micropapillary, advanced lung cancer

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Introduction

Adjuvant therapy with anticancer drugs or radiation may inhibit tumor cell growth but simultaneously suppress host immune mechanisms^{1,2)} and indirectly induce cancer cells to recur or metastasize to distant organs. Considering the possible dual effects of adjuvant chemotherapy or radiotherapy, Kimura H et al.³⁾ tried to restore host immunity by adoptively transferring immune lymphocytes and interleukin (IL)-2 after adjuvant therapy. Adoptive immunotherapy with IL-2 and lymphokine-activated killer (LAK) cells combined with chemotherapy or radiotherapy improved the survival of patients after surgical resection of primary lung carcinoma³⁾. We

report a case of surgery followed by combination therapy of gefitinib (IRESSATM, AstraZeneca, Osaka, Japan) and immunotherapy for the advanced lung cancer (pT1N2M1a, p-stage IV, EGFR mutation-positive, adenocarcinoma with micropapillary pattern).

Case report

A smoker, 55-year-old male was pointed out of an abnormal shadow on X-ray film and of a small nodule in left S⁵ on computed tomographic (CT) scanning of chest by medical examination, however, which nodule had been tightly followed up as an old inflammatory scar. The twenty months later, the pulmonary nodule had increased in size, fluorodeoxyglucose positron emission tomography showed an abnormal accumulation. In December, 2007, he was admitted to our hospital and diagnosed with pulmonary adenocarcinoma by trans-bronchial lung biopsy from left B⁵ bronchus (cT1N0M0,

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c-stage IA). The level of carcinoembryonal antigen (CEA) was within normal limits (4.7 ng/ml). A CT scanning of chest displayed 22 mm of nodule in left S⁵ and no mediastinal lymphadenopathy (Fig. 1a). However, several small nodules (Fig. 1a) were revealed on pleural surface without pleural effusion, which findings might suspect a pleural dissemination, that is, IV-staged advanced lung cancer. The patient desired for receiving an aggressive multimodality therapy containing of standard surgical treatment and immunotherapy combined with gefitinib for the advanced primary cancer.

After thoracotomy, the small pleural nodules were intraoperatively diagnosed with pleural dissemination (M1a) by a pathological examination (Fig. 1b), however, malignant pleural effusion had not been recognized. An intraoperative cytology of intrathoracic lavage showed a negative result of malignancy. Because of the clinical N2-negative disease without malignant pleural effusion, left upper lobectomy with mediastinal lymph nodes dissection was preceded. As a result, the postoperative pathological examination disclosed adenocarcinoma with mixed subtypes of the lung (p3, D2, E0, PM0, pT1N2M1a, p-stage IV), which showed micropapillary pattern (Fig. 2a, 2b). The dissected lymph nodes were confirmed as metastasis in station 4, 5, 6, 7, 10, and 11. A detection test⁽⁴⁾ of EGFR gene mutation showed a positive result (L858R).

As a systemic treatment for the remained pleural dissemination, adjuvant chemotherapy of gemcitabine and carboplatin was performed in 2 cycles. As second-line adjuvant therapy, an oral administration of gefitinib (IRESSATM, AstraZeneca, Osaka, Japan) was started in April, 2008. After the administration of gefitinib, facial dermatitis was recognized but the patient did not need its rash management. In May, 2009, the patient received a lymphokine-activated killer (LAK) cell immunotherapy, which modality was performed in 6 cycles in another hospital (Fig. 3). LAK cells were produced from peripheral blood lymphocytes and consist mainly of activated NK cells. This immunotherapy has been described in detail elsewhere^(5, 6). There were no serious side effects such as fever on the day after administration of LAK cells. During the combination therapy of gefitinib and immunotherapy, there were no side effects suggestive of viral or bacterial infection caused by LAK cells and were no worsening of skin rash caused by gefitinib treatment. There had been uneventful during the combination therapy of immunotherapy and gefitinib. A CT follow-up scanning of chest displayed shrinkages or disappearances of the pleural disseminated lesions (Fig. 4a, 4b). On the 25th postoperative month, local recurrence and distant metastasis had not been detected, the disseminated lesions had obtained a long stable disease. On the third postoperative year, three small cerebral metastases had been found in caudate nucleus (Fig. 5a), thalamus,

and frontal lobe. Because the patient rejected to receive whole brain radiotherapy, a stereotactic radiological surgery had been performed for three metastatic lesions, respectively. He had been healthy with a good quality of life and could maintain the treatment of gefitinib for 45 months without regrowing of the irradiated brain metastases (Fig. 5b) and the treated pleural disseminated lesions.

Discussion

Overall outcome from standard tri-modality therapy of surgery, chemotherapy, and radiotherapy for lung cancer remains poor. As the fourth modality, immunotherapy could have an important role to play in the treatment of lung cancer. Initially, IL-2 LAK adoptive immunotherapy was regarded as a powerful and ideal therapy effective for patients in any condition with any kind of malignant diseases^(7, 8). Kimura et al.⁽⁶⁾ used adoptive immunotherapy in 82 patients following curative resection. The patients were randomized to receive IL-2 and LAKs following two course of combination chemotherapy (cisplatin, vindesine, and mitomycin) or chemotherapy alone. The 5- and 7-year survival rates of the chemo-immunotherapy group and chemotherapy group were 58.2% and 31.5%, respectively in stage II and IIIA patients. This difference was statistically significant ($P=0.0038$). In patients undergoing non-curative resection, Kimura et al.⁽⁵⁾ reported a survival benefit for the immunotherapy arm (IL-2 and LAK) following randomization of 105 patients to chemotherapy, radiotherapy or immunotherapy. The 7-year survival rate was greater in the immunotherapy group compared with the chemotherapy and chemo-radiotherapy groups (39.1%, 12.7%, $P<0.01$). In a phase III randomized study⁽³⁾, adoptive immunotherapy with IL-2 and LAK cells combined with chemotherapy or radiotherapy improved the survival of patients after surgical resection of primary lung carcinoma, which was compared with control standard therapy. In this case, the reason for the selection of immunotherapy was depended on the patient's desire as the forth modality.

On the other hand, on the treatment of gefitinib, EGFR mutation examination is widespread at academic medical centers and in some local clinics in community practice. The American Society of Clinical Oncology (ASCO) 2009 Guideline Update on stage IV NSCLC addresses the use of EGFR-TKIs in the second- and third-line settings⁽⁹⁾. One large phase III trial (the Iressa Pan-Asia Study [IPASS] trial)⁽¹⁰⁻¹²⁾, three smaller phase III randomized controlled trials using progression-free survival as the primary end point⁽¹³⁻¹⁵⁾, and one small phase III trial with overall survival as the primary endpoint⁽¹⁶⁾, all involving first-line EGFR-TKIs and chemotherapy doublets, form the basis of the provisional clinical opinion. That is, on the basis of the results of five phase III

Fig. 1 a. Computed tomographic (CT) scanning of chest showing a lung cancer (left S⁵, 22 mm) (bold arrow) and suspected intrathoracic dissemination (M1a) (thin arrows).
b. Intraoperative photo. The pleural surface of left lower lobe showing a dissemination, which was diagnosed with adenocarcinoma (M1a, IV-stage). An intraoperative cytology of intrathoracic lavage revealed a negative finding.

Fig. 2. Postoperative pathology.
a. In the tumor tissue in left S⁵, cancer cells proliferated in papillary, acinar and bronchioalveolar pattern with desmoplastic stroma. Micropapillary pattern was associated in part. Lymphatic and vascular permeation was also seen. Adenocarcinoma of the mixed subtypes (papillary, acinar, bronchioalveolar type) was considered.
b. Apart from the tumor, a cancer nodule was found, probably showing dissemination (green arrows).

Fig. 3. The time course of treatment schedule.
Adjuvant chemotherapy of gemcitabine and carboplatin was performed in 2 cycles after surgery. Adjuvant interleukin-2 lymphokine-activated killer cell immunotherapy (IL-2 LAK) had been performed in 6 cycles for 6 months. Simultaneously, adjuvant administration of gefitinib treatment has been performed for more than 3 years.

Fig. 4. A CT scanning of chest.

- a: Preoperative lower lobe before adjuvant therapy of gefitinib and immunotherapy. Pleural dissemination was displayed (arrows).
- b: Postoperative lower lobe after adjuvant therapy of gefitinib and immunotherapy. The remained pleural dissemination had been partly unclear or disappeared.

Fig. 5. The most largest cerebral metastasis detected by postoperative magnetic resonance imaging of brain.

- a: Pre-stereotactic radiological surgery (in Feb., 2010). The small cerebral metastasis was found in caudate nucleus (arrow).
- b: Post-stereotactic radiological surgery (in Nov., 2011). The irradiated small metastatic lesion has not been re-growing and showed radiologic necrosis with edema (arrow).

randomized controlled trials, patients with NSCLC who are being considered for the first-line therapy with an EGFR-TKI (patient who have not previously received chemotherapy or an EGFR-TKI) should have their tumor tested for EGFR mutations to determine whether an EGFR-TKI or chemotherapy is the appropriate first-line therapy¹⁷⁾.

The role of gefitinib in first-line therapy for patients with known EGFR mutations was confirmed in the randomized Phase III Iressa Pan-Asia Study (IPASS)¹⁰⁾. Gefitinib group demonstrated superior progression-free survival than carboplatin-paclitaxel group (HR: 0.74; 95% CI: 0.65 – 0.85; $P < 0.0001$) in the overall population. Most importantly, the PFS of the subgroup of patients with EGFR mutations was significantly better than that of the overall population who received gefitinib alone (HR: 0.48; 95% CI: 0.36 – 0.64; $p < 0.0001$). Patients without EGFR mutations had detrimental effects from treatment with first-line gefitinib (HR: 2.86; 95% CI: 2.05 – 3.86; $p < 0.0001$). Our case harbored a EGFR-mutation and could continue more than 3 years without any adverse events.

A micropapillary pattern is defined as a pattern showing micropapillary structures without a fibrovascular core. It is well known that the presence of a micropapillary pattern leads to a poorer prognosis in lung adenocarcinoma¹⁸⁻²³⁾. This adenocarcinoma frequently metastasizes to lymph nodes, shows pleural invasion and follows an aggressive clinical course^{18, 21, 23)}. However, little is known about the mechanisms involved in micropapillary-pattern-associated lymph node metastasis. It is still unclear how small micropapillary clusters of carcinoma cells present in tumoral alveolar spaces invade lymphatics and lead to increased lymph node metastasis. Our case showed the micropapillary pattern and resulted in advanced cancer such as multiple dissemination and lymph nodal metastasis in multistation. Generally, the prognosis of the cancers with micropapillary pattern had been known to be poor, however, in this case of advanced lung cancer, combination therapy of gefitinib and immunotherapy might enable the patient to have more than 3 years of PFS.

In our case, preoperatively, the lung cancer was suspected with stage IV disease with pleural dissemination by chest CT scanning. However, the patient desired for receiving an aggressive multimodality therapy containing of standard surgical treatment, chemotherapy, molecular-targeted therapy, and immunotherapy for the advanced primary cancer. The reason why we performed standard lobectomy was caused by clinical N2-negative disease without malignant pleural effusion and also by the discrepancy of intraoperative cytological negative result of intrathoracic lavage and the pathological positive result of dissemination. In this case, as an operative procedure, generally, a partial resection or a simple

lobectomy should be selected in considering of the curability of the advanced cancer and of the postoperative pulmonary function. However, the patient was young age and a degree of the decreased quality of life could be permitted and he expected to the possibility of the benefit from the adjuvant combination therapy, that is, adjuvant immunotherapy and molecular-targeted therapy, for the disseminated disease. Lobectomy with lymph nodal dissection was the first step to reduce the volume of cancer cells of primary tumor and the mediastinal lymph nodal metastasis as possible. The intrathoracic residual disseminated lesions and the suspected lymphatic and/or distant micrometastases were the next targets of this adjuvant chemotherapy, gefitinib, and LAK therapy. There are some merits derived from administering chemotherapy before immunotherapy, which might also contribute to reducing tumor volume of dissemination or to damaging the residual tumor cells. As a multimodality therapy, immunotherapy in conjunction with adjuvant molecular-targeted therapy of gefitinib was added to improve the patient's postsurgical survival. After cytotoxic chemotherapy, immunosuppressive agents or procedures, such as anticancer drugs, are also toxic to host immune cells and may well be effective in eliminating or inhibiting suppressor cells or suppressive factors that inhibit the function of killer cells³⁾. It is also conceivable that the Fas antigen induced by chemotherapy may be recognized by LAK cells and induce apoptosis of tumor cells^{24, 25)}. To prevent a recurrence, LAK immunotherapy would play a role of recovering and enhancement of the suppressive host-immune system in the post-chemotherapy period.

This patient is alive 45 months after surgery and immunochemotherapy. It can be considered as long survivor in advanced non-small cell lung cancer. The 5-year overall survival of pathological stage IV for the proposed International Association for the Study of Lung Cancer (IASLC) stage grouping was reported to be 13% and median survival time (MST) was 17 months²⁶⁾. On descriptors of distant metastasis (M descriptors), M1a subgroup includes patients with either pleural dissemination or contralateral pulmonary nodules and an M1b subgroup with distant metastases, the 5-year survival of M1a (pleural effusion) was 6% and MST was 10 months²⁶⁾. This patient is uncommon long survivor by comparison with previous survival data of advanced or non-small lung cancer based on clinical trial with dissemination and distant metastasis.

Lastly, extraordinarily, this patient was an advanced case with staged IV, dissemination, lymph nodal metastases in multistation, and micropapillary pattern. However, an aggressive multimodality therapy of surgery, immunotherapy, gefitinib enabled the patient to maintain a more than 3 years of good quality of life, in spite of carrying with brain metastasis.

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