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Successful Treatment of a Patient with Synchronous Advanced Non-small Cell Lung Cancer and Acute Myeloid Leukemia by a Combination of Gefitinib, Low-dose Cytarabine and Aclarubicin

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Abstract. *There are few reports describing simultaneous occurrence of acute leukemia and lung cancer. We describe here an 83-year-old woman who simultaneously developed advanced adenocarcinoma of the lung and acute myeloid leukemia. She could not receive intensive chemotherapy due to poor performance status. This patient was treated with a combination of gefitinib, low-dose cytarabine and aclarubicin. This combination could be safely administered in the elderly patient with poor performance status and was effective for both lung cancer and acute myeloid leukemia.*

The incidence of lung cancer is increasing worldwide and the proportion of elderly patients affected is high in Western countries and Japan (1). Similarly, the incidence of acute leukemia increases with increasing age (2). However, simultaneous occurrence of lung cancer and acute leukemia has been rarely reported, even in elderly populations.

For the treatment of advanced non-small cell lung cancer (NSCLC), the American Society of Clinical Oncology recommends systemic chemotherapy for patients with performance status (PS) of 0 - 1, and at most 2 (4). Vinorelbine monotherapy has been considered the treatment of choice for elderly patients with advanced NSCLC in Europe (3), however, the standard treatment has not yet been established. Gefitinib, the tyrosine kinase inhibitor of epidermal growth factor receptor, has anti-tumor activity in advanced NSCLC (5, 6), and was effective even in elderly patients with poor PS (7, 8). On the other hand, for elderly patients with acute myeloid leukemia (AML), conventional combinations of anthracycline (daunorubicin or idarubicin) and cytarabine have frequently been used (9), however, the standard treatment for patients aged 75 years or older has not been established (10). In Japan, a combination of low-dose cytarabine and aclarubicin was reported to be useful in previously untreated elderly (65 - 82 years old) patients with AML (11).

A frail, elderly patient with advanced adenocarcinoma of the lung and AML, who was successfully treated with a combination of gefitinib, low-dose cytarabine and aclarubicin, is presented.

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Case Report

An 83-year-old Japanese woman complaining of dyspnea was admitted to a community hospital on July 22, 2003. She was treated with antibiotics and diuretics, however, her respiratory condition became worse. She was referred to our hospital on August 21, 2003. She had never smoked. Her temperature was 36.4˚C and blood pressure was 105/90 mmHg. Her PS, defined by the Eastern Cooperative Oncology Group criteria, was 3. Pulmonary auscultation revealed a respiratory sound with wheeze and fine crackles. A chest radiograph showed patchy density on the left upper lung field, and reticular opacities and septal lines on both lung fields. Computed tomography (CT) scans of the chest revealed patchy consolidation on the left S^3b, thickening of the peribronchovascular interstitum

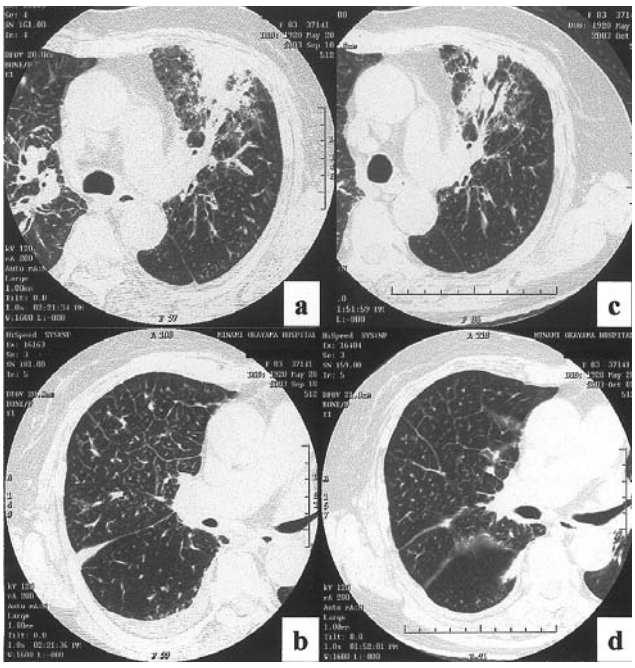

Figure 1. *Chest CT films showing patchy consolidation on left S^{3}b, thickening of the peribronchovascular interstitum surrounding vessels and bronchi, and peribronchial cuffing and interlobular septal thickening in the peripheral lung lesions (a, b: September 10, 2003); decrease of primary lesion and improvement of peribronchovascular interstitial and interlobular septal thickening (c, d: October 1, 2003).*

surrounding vessels and bronchi, and peribronchial cuffing (Figure 1a) and interlobular septal thickening in the peripheral lung lesions (Figure 1b). Laboratory data showed mild anemia (hemoglobin 11.2 g/dL) and leucocytosis (10,200 /μL) with 67.5% neutrophils, 17.2% lymphocytes, 13.3% monocytes, 1.9% eosinophils and 0.1% basophils. C-reactive protein was elevated (2.19 mg/dL). Liver and renal function and electrolysis were normal. The serum CEA level was elevated to 16.3 ng/mL. Arterial blood gas analysis on room air showed hypoxia (PaO_2=55.5torr, $PaCO_2$=39.2torr, and pH=7.438). The electrocardiogram and two-dimensional echocardiogram findings were normal. Fiberoptic bronchoscopy revealed slightly edematous and faintly whitened bronchial mucosa. Histological assessment of the transbronchially biopsied samples from the left B^{3}b and spur between the left upper lobe and lower lobe bronchus showed a proliferation of atypical cells along the alveolar walls. The patient was given a diagnosis of adenocarcinoma of the lung: stage IV disease (T2N0M1) with lymphangitis carcinomatosa.

On September 11, the white blood cell count was elevated to 26,600 /μL with 61.0% monocytes. A bone marrow examination showed a nucleated cell count of

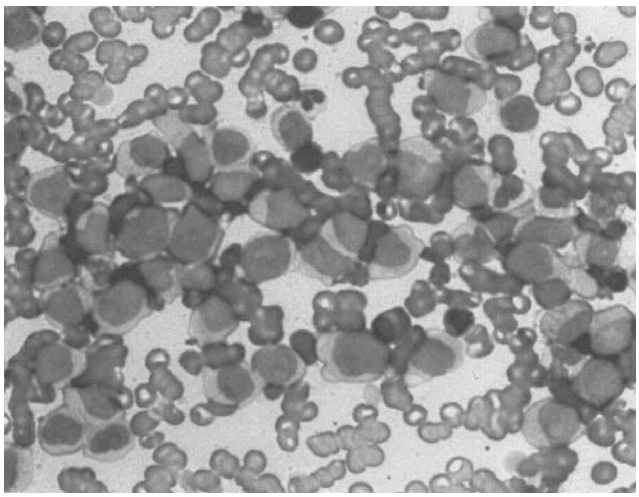

Figure 2. *A bone marrow aspirate from the sternum showing leukemic blasts.*

22x10^4/μL with 63.4% of leukemic cells consisting of myeloblasts and monoblasts (Figure 2). Leukemic cells were positive for either the specific chloracetate esterase or the non-specific α-naphthyl butylate esterase stain, and were partly positive for myeloperoxidase stain. According to these findings, she was given a diagnosis of acute myelomonocytic leukemia. Her PS deteriorated to 4 because she was confined to bed with oxygen supplementation.

The patient received gefitinib (250 mg) once daily from September 13, followed by low-dose cytarabine (10 mg/m^2, subcutaneous injection every 12 hours) for 7 days from September 16. Dyspnea improved on September 22. CT scans of the chest showed regression of the primary lesion and improvement of the peribronchovascular interstitial and interlobular septal thickening (Figure 1c, d). The serum CEA level decreased to 6.7 ng/mL. The white blood cell count was reduced to 3,200 /μL on September 25, but was rapidly elevated to 42,800 /μL on October 6. A second course of low-dose cytarabine was administered from October 6 and aclarubicin (14 mg/m^2, bolus infusion, days 1-4) was given from October 15. Leukemic cells disappeared from the peripheral blood on October 27. However, because no further response in lung cancer was observed, gefitinib administration was stopped on October 28. The patient was then treated with amrubicin (14 mg/m^2, bolus injection, days 1-3) from November 12. Although no regression of lung cancer was obtained, her respiratory condition did not become worse. Bone marrow examination showed a decrease of leukemic cells (6.4%) on November 27. Her PS improved to 2 when she was discharged with oxygen supplementation on December 6. The lung cancer and AML did not progress

without chemotherapy until March 2004. However, the patient passed away on April 19 because of rapid AML progression.

Discussion

Secondary leukemia after treatment for solid tumor including lung cancer has occasionally been described (12, 13). However, the simultaneous occurrence of acute leukemia and solid tumor is considered to be very rare. To the best of our knowledge, there has been only one case report describing the simultaneous occurrence of AML and breast cancer (14). The cause of secondary leukemia is considered to be leukemogenic effects of topoisomerase II inhibitors or alkylating agents and abnormalities of chromosomes such as 11q23 (the locus of the MLL gene) (12, 13). However, no association between gene abnormality and inherent susceptibility for leukemia could be made in this case because cytogenetic analysis could not be performed.

Although chemotherapy for NSCLC is not recommended for patients with poor PS (4), gefitinib showed some activity in such cases (7, 8, 15). Because gefitinib seems to be highly effective for non-smoking women with adenocarcinoma (6), we expected that gefitinib might be effective for this frail patient. Actually, gefitinib was effective and she obtained tumor regression and symptom-relief. Accordingly, gefitinib as initial therapy for advanced NSCLC patients who have poor PS or double cancers may be recommended. However, we should carefully follow-up the patients because interstitial lung disease during gefitinib treatment tends to occur frequently in patients with poor PS (17). Recently, patients with epidermal growth factor receptor gene mutations in the tumors were reported to have good response to gefitinib (18, 19). Therefore, investigation of the mutations may identify those patients who will benefit from treatment with gefitinib, even in patients with poor PS.

When patients aged ≥80 years with AML were treated with dounorubicin alone or in combination with low-dose cytarabine, complete response occurred in 36% with PS ≤2 and 20% with PS >2 and the median survival time was only 3 - 4 weeks (16). In a Japanese report, 45% of the previously untreated elderly patients (≥65 years old) with AML achieved complete response by a combination of low-dose cytarabine and aclarubicin (11). Accordingly, this patient was treated with low-dose cytarabine and aclarubicin and considerably benefited from the chemotherapy. Since this patient could receive gefitinib and chemotherapy for the leukemia simultaneously, she was probably able to survive longer than expected.

In conclusion, we successfully treated a frail patient with lung cancer and AML with a combination of gefitinib, low-dose cytarabine and aclarubicin. This combination may be recommended to elderly patients who develop AML and solid tumor simultaneously.

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