

Amrubicin Monotherapy for Patients with Small-Cell Lung Carcinoma Complicated with Chronic Renal and Heart Failure

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Abstract

An 82-year-old female presented to our institution with mild dyspnea. Her medical history included effort angina pectoris, which was treated with stent placement in the coronary artery at the age of 78, and congestive heart failure, which was improved by oxygen inhalation and administration of diuretic agents. Chest radiography revealed evidence of swollen lymph nodes at the level of the left pulmonary hilar lesion. Contrast-enhanced chest computed tomography revealed a mass at the pulmonary hilar lesion site extending into the left pulmonary artery and left lower pulmonary vein, swollen lymph nodes proximal to the left pulmonary hilar lesion and bilateral mediastinum, and pleural dissemination. Bronchoscopy revealed almost total occlusion of the left upper bronchial trunk. Biopsied specimen confirmed the diagnosis of small-cell lung carcinoma (SCLC). Although the standard chemotherapy regimen for extended SCLC is a combination therapy of cisplatin (CDDP) and etoposide (ETP), that regimen was considered intolerable for the patient because of chronic heart and renal failure. Therefore, the regimen of amrubicin hydrochloride (AMR) monotherapy was decided. After the first cycle of chemotherapy, the tumor was remarkably reduced. Despite mild digestive symptoms, including nausea and loss of appetite, and mild myelosuppression, the patient was well tolerated with AMR monotherapy. The patient has been kept partial response during the fifth cycle of chemotherapy until the patient developed pneumonia.

Keywords: Amrubicin monotherapy; Small-cell lung carcinoma; Chronic heart failure; Chronic renal failure

Introduction

The standard chemotherapy regimen for extended small-cell lung carcinoma (SCLC) is a combination of cisplatin (CDDP) and etoposide (ETP). However, CDDP is unsuitable for use in elderly patient or those with chronic renal heart failure. In such cases, amrubicin hydrochloride (AMR) may be considered as an alternative to CDDP. Although AMR is known to be metabolized in the liver, the efficacy of AMR for treatment of SCLC is unknown.

AMR, an anticancer agent belonging to the anthracycline family, was developed in Japan. In a phase II study of AMR for untreated, extended SCLC, a response rate (RR) of 76% and mean survival time (MST) of 11.7 months were reported. In this study, we report the case of a female patient with SCLC complicated with chronic renal and heart failure treated with AMR.

Case Presentation

An 82-year-old female presented to our institution with mild dyspnea. Her medical history included effort angina pectoris, which was treated with stent placement in the coronary artery at the age of 78, and congestive heart failure, which was improved by oxygen inhalation and administration of diuretic agents. No alcohol or tobacco use was recorded. On admission, her blood pressure was 130/51 mm Hg, heart rate was 81 beats/min, body temperature was 36.4°C, and oxygen saturation was 95% on room air. Inspection of the palpebral conjunctiva revealed evidence of mild anemia. No evidence of abnormal heart murmurs and no rales or other lung sounds were found on auscultation. Physical examination revealed no cyanosis, but edema was observed in both legs. Blood chemistry analyses revealed the following, normal white blood cell counts (6500/ μ l); mild anemia (red blood cell counts, 302×10^4 / μ l; hemoglobin, 10.4 g/dl); normal C-reactive protein levels (0.17 mg/dl); mild hypoalbuminemia (3.9 g/dl); elevated creatinine levels (1.27 mg/dl); elevated 6500 per μ l blood urea nitrogen levels (27.3 IU/l); decreased estimated glomerular

filtration rate (31.2 ml/min/1.73m²); slightly elevated brain natriuretic peptide (45.6 pg/ml); and evidence of coagulation dysfunction (fibrin/fibrinogen degradation products, 1.5 μ g/ml). In tumor marker analyses, neuron specific enolase (NSE) and progastrin-releasing peptide (ProGRP) levels were elevated to 134 ng/ml (normal levels, <10 ng/ml) and 1930 pg/ml (normal levels, <81 pg/ml), respectively. Chest radiography revealed a normal cardiothoracic ratio of 47%. Evidence of swollen lymph nodes at the level of the left pulmonary hilar lesion or old inflammatory changes in the middle lung field was found (Figure 1A). Contrast-enhanced chest computed tomography (CT) revealed a mass at the left pulmonary hilar lesion site extending into the left pulmonary artery and left lower pulmonary vein, swollen lymph nodes proximal to the left pulmonary hilar lesion and bilateral mediastinum, and pleural dissemination (Figure 1B). Transthoracic echocardiography revealed a slightly reduced ejection fraction of 58.9% with hypo kinetic movement in the septum of the posterior and lateral walls, E/A ratio of 0.48 which indicated the presence of diastolic heart failure, and a 61×52 mm solid mass at the carina of the left pulmonary artery (Figure 1C). Bronchoscopy revealed almost total occlusion of the left upper bronchial trunk (Figure 2A). Analysis of the biopsied specimen revealed small and seemingly naked cells (Figure 2B). Thus, the diagnosis of SCLC was confirmed.

Considering the patient's age and underlying medical condition (chronic heart and renal failure), a regimen including CDDP was

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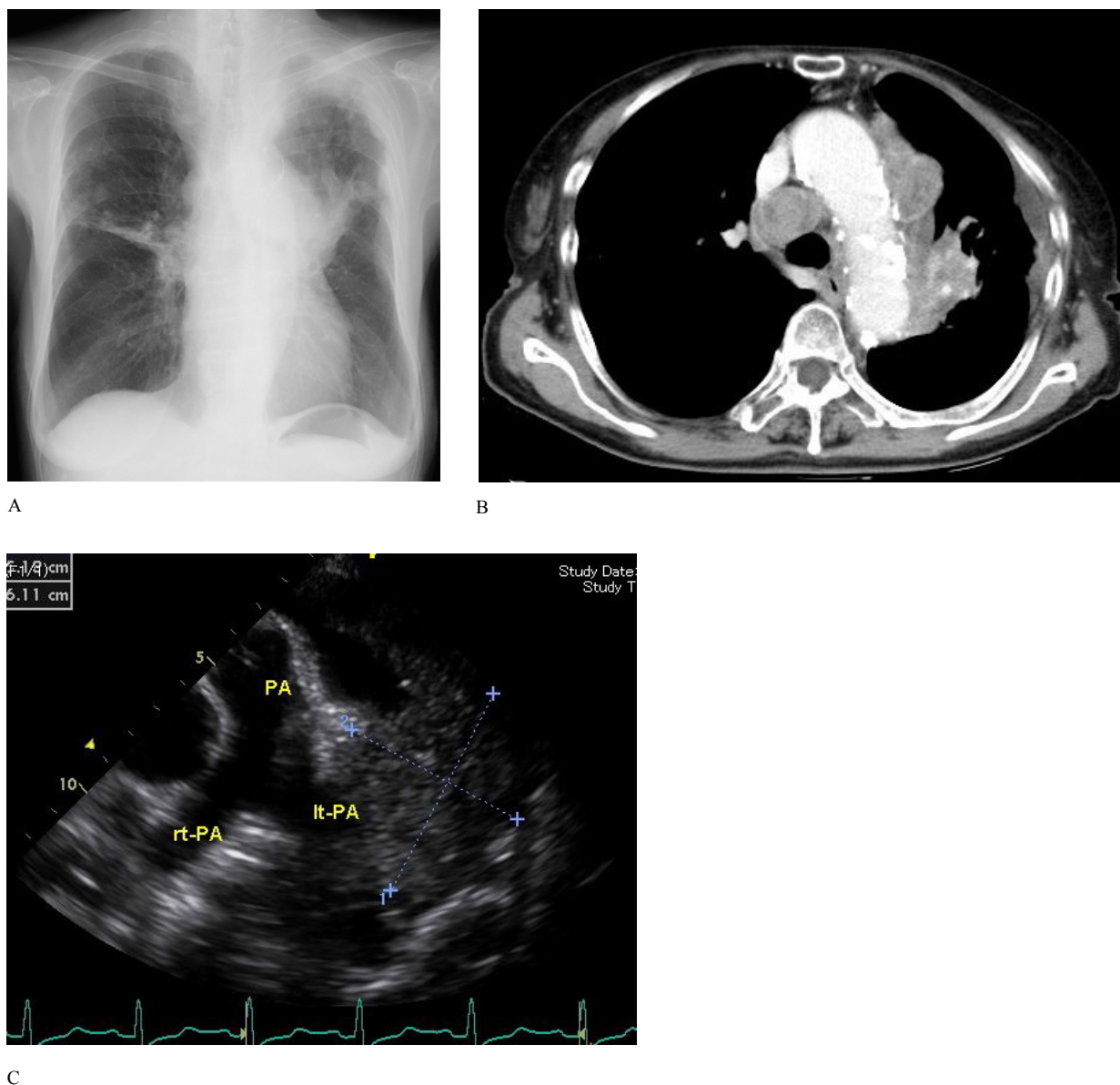


Figure 1: Chest radiography revealed a normal cardiothoracic ratio of 47%. Evidence of swollen lymph nodes at the level of the left pulmonary hilar lesion or old inflammatory changes in the middle lung field was found (A). Contrast-enhanced chest computed tomography (CT) revealed a mass at the left pulmonary hilar lesion site extending into the left pulmonary artery and left lower pulmonary vein, swollen lymph nodes proximal to the left pulmonary hilar lesion and bilateral mediastinum, and pleural dissemination (B). Transthoracic echocardiography revealed a 61×52 mm solid mass at the carina of the left pulmonary artery (C).

considered intolerable because its regimen required large amount of fluid infusion. AMR monotherapy was considered safe for the patient's age and medical condition. Therefore, a chemotherapy protocol of AMR 40 mg/m² for 3 days every 4 weeks was planned. In initiating the chemotherapy, the patient was provided with informed consent. Two days after initiation of the first cycle of chemotherapy, the patient complained of chest pain. A 12-lead electrocardiography revealed no remarkable changes. However, chest radiography revealed atelectasis of the left upper lung field, probably caused by cancer progression or sputum retention. Conservative treatment resulted in improvement in condition and chest pain disappeared. Eleven days after initiation of chemotherapy, white blood cell counts and hemoglobin concentration decreased to 1100 per μ l and 7.2 g/dl, respectively. However, C-reactive protein levels increased to 10.0 mg/dl. Myelosuppression due to

treatment with AMR, which was equivalent to a Grade 3 side effect, may have caused this. Granulocyte-colony stimulating factor drugs and red blood cell transfusion were administered for treatment of myelosuppression. Antibiotic agents were intravenously administered for low-grade fever due to a possible bacterial infection. Digestive symptoms developed, including nausea and loss of appetite that was equivalent to a Grade 2 side effect. Thereafter, the patient's general condition gradually improved. After the second cycle of chemotherapy, AMR dose was reduced to 35 mg/m² for 3 days every 4 weeks to alleviate myelosuppression. Eleven days after initiation of the second cycle of chemotherapy, white blood cell counts and hemoglobin concentrations were reduced to 3100/ μ l and 7.2 g/dl, respectively, and C-reactive protein levels were slightly elevated (2.3 mg/dl). During the second to fourth cycles, no digestive symptoms were reported. After the fourth

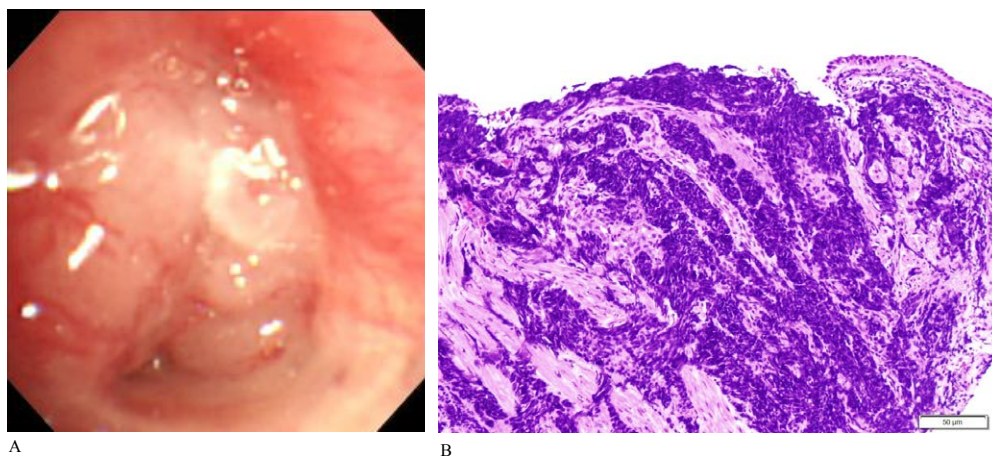


Figure 2: Bronchoscopy revealed almost total occlusion of the left upper bronchial trunk (A). Analysis of the biopsied specimen revealed small and seemingly naked cells (B).

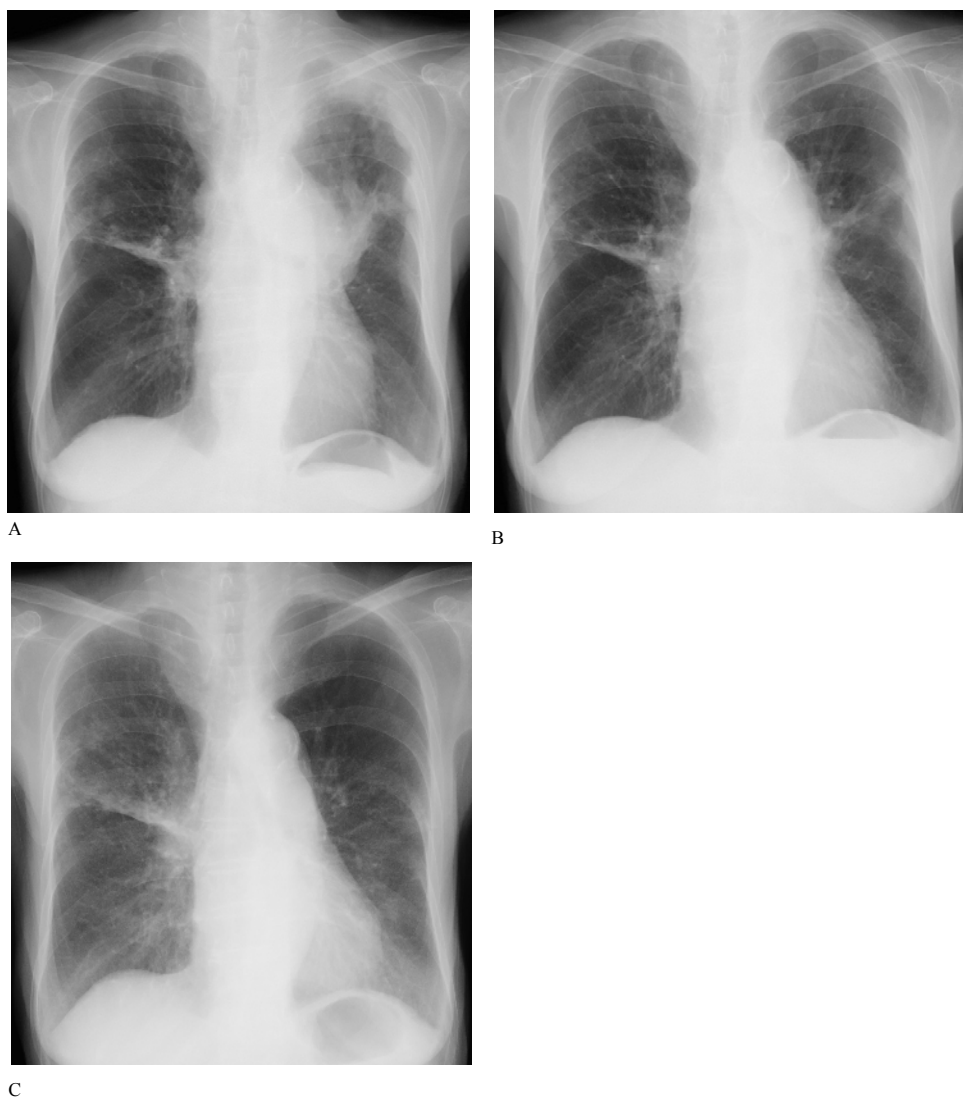


Figure 3: The change of chest radiography is shown. A mass in the left lung field is apparently reduced. (A: Before chemotherapy, B: After the first course of chemotherapy, C: After the fourth course of chemotherapy).

cycle of chemotherapy, thoracic radiography and contrast-enhanced CT were performed. The lymph nodes proximal to the left pulmonary hilar lesion and bilateral mediastinum had largely resolved, and pleural dissemination ameliorated (Figure 3C and 4C). The change of chest radiography and contrast-enhanced chest CT is shown in Figure 3 and 4. Levels of tumor markers (including NSE and ProGRP) markedly reduced. After the fifth cycle of chemotherapy, high-grade fever and severe dyspnea developed. Chest radiography revealed reticulonodular infiltrates in both lung fields. The diagnosis of pneumonia was confirmed, and the patient was treated with antibacterial drugs and oxygen inhalation. Unfortunately, the patient died of pneumonia.

Discussion

AMR is an anticancer agent belonging to the anthracycline family that was developed in Japan. AMR is a derivative of doxorubicin. It exerts antitumor effects by inhibiting type II topoisomerase. Strong antitumor effects of AMR for SCLC cancer were reported at a meeting of the American Society of Clinical Oncology in 1998. Since then, the use of AMR has increased. AMR is considered to be a promising second-line chemotherapy drug for patients with relapsed SCLC. In high-risk cases, AMR is used as a first-line chemotherapy drug. In a phase II study for SCLC comparing combination therapy with CDDP plus ETP as well as with CDDP plus irinotecan [1], the results were as follows, RR 84% vs. 66%, MST 12.8 vs. 9.4 months, and 2-year survival rate 19.5% vs. 5.2%, respectively. In a phase II study of AMR monotherapy for untreated [2], extended SCLC, RR was reported to be 76% and MST 11.7 months.

Thus, the results of AMR monotherapy were not inferior to those of the multidrug chemotherapy. Combination therapy of AMR plus CDDP yielded better results, in a phase I/II study of combination therapy with AMR (60 mg/m²) plus CDDP (40 mg/m²) [3]. In that study, RR was 87.8% and MST was 13.6 months. In a study of AMR monotherapy (40 mg/m² for 3 days every 3 weeks) for relapsed SCLC [4], the rate of sensitive relapse was 52% and that of resistant relapse was 50%. MST in cases of sensitive relapse was 11.5 months and MST in cases of resistant relapse was 10.3 months. In a study of AMR monotherapy (45 mg/m² for 3 days every 3 weeks) for relapsed SCLC after initial treatment with CDDP [5], RR was 53% and MST was 8.8 months.

For estimating the appropriate dose of AMR in patients with SCLS, a phase II trial was performed comparing the efficiency and efficacy of AMR at a dose of 40 mg/m² and a dose of 35 mg/m² [6]. The latter dose was not inferior to AMR at a dose of 40 mg/m², and hematological toxicity was low. In the case reported here, during the first cycle of chemotherapy (AMR 40 mg/m²), hematological toxicity and digestive symptoms, including nausea and loss of appetite were evident. After the second cycle, a reduction in the dose of AMR to 35 mg/m² alleviated the side effects while maintaining partial response prior to the development of pneumonia.

The patients with history of coronary artery disease or congestive heart failure are considered unsuitable in phase II trial of AMR monotherapy for SCLS because of its cardiac toxicity. However, if selected properly, some cases can be treated safely and effectively

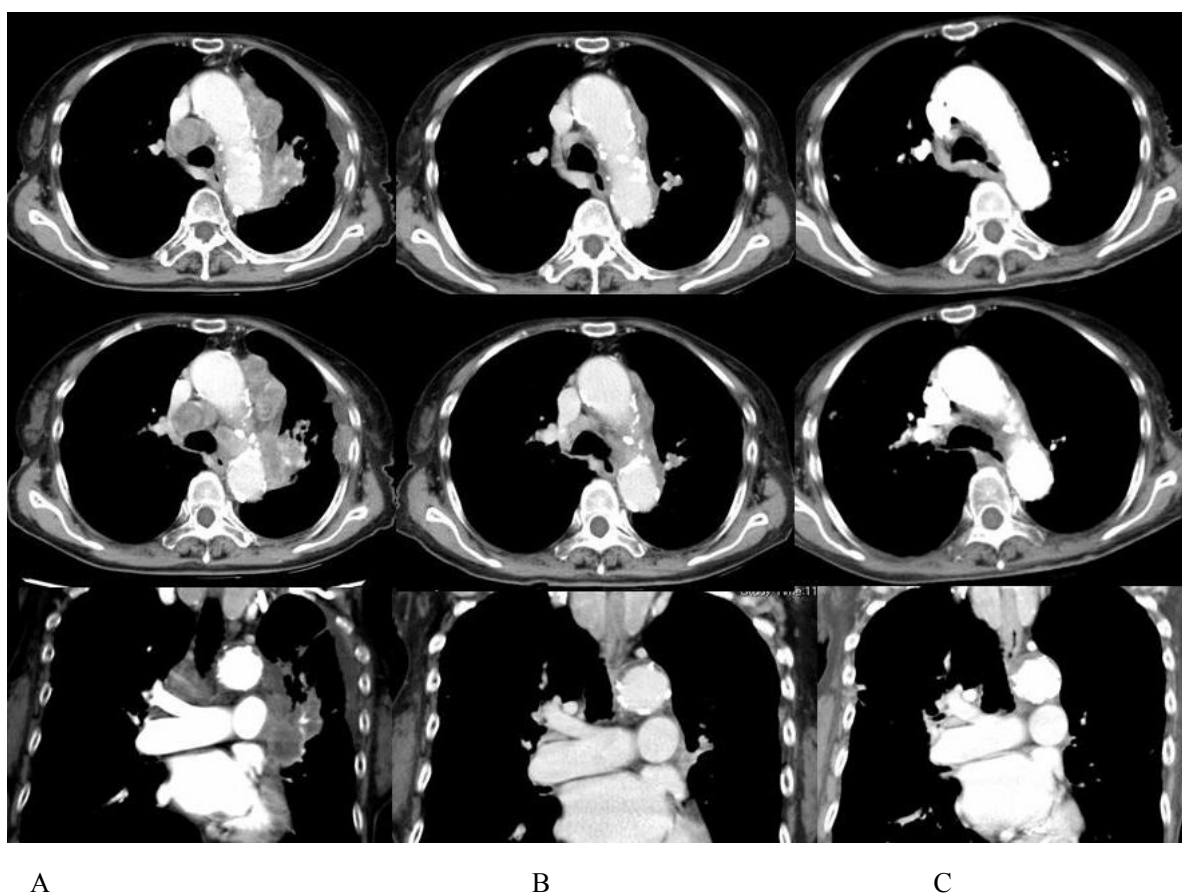


Figure 4: The change of contrast-enhanced chest computed tomography is shown. A mass in the left lung field is apparently reduced. (A: Before chemotherapy, B: After the first course of chemotherapy, C: After the fourth course of chemotherapy).

despite the history of coronary artery disease or congestive heart failure.

Conclusion

We experienced a case of SCLC in an elderly female patient complicated by chronic renal and heart failure treated using AMR monotherapy. In this case, hematological toxicity (Grade 3) and digestive symptoms (Grade 2) were ameliorated by dose reduction of AMR from 40 mg/m² to 35 mg/m². Further evidence of the efficacy of AMR monotherapy for untreated SCLC is required. Despite the history of coronary artery disease or congestive heart failure, it is suggested that there may be cases which are treated safely and effectively.

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