Long-term Complete Response in a Patient with Disseminated Pulmonary Pleomorphic Carcinoma Induced by Cisplatin and Gemcitabine

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Abstract

A 47-year-old man was referred to our department due to multiple metastases in the lungs and liver with pleural dissemination six weeks after undergoing curative surgery for lung pleomorphic carcinoma. He received two regimens of chemotherapy, both of which resulted in disease progression. Considering his good general condition, he was treated with cisplatin plus gemcitabine (GP). The metastatic lesions exhibited a complete response after six courses of GP, and the patient has remained free from recurrence for over six years. An immunohistochemical analysis revealed that the tumor was highly expressive of gemcitabine transporter human equilibrative nucleoside transporter 1, thus suggesting a high sensitivity to gemcitabine.

Key words: pleomorphic carcinoma, gemcitabine, hENT1, complete response

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Introduction

Pulmonary pleomorphic carcinoma is defined as poorly differentiated adenocarcinoma, squamous cell carcinoma or large cell carcinoma, containing a component of spindle or giant cells with a sarcomatoid tumor component of at least 10% (1). This entity is rarely encountered, comprising only 0.3% of all pulmonary malignancies (2). Although only a limited number of reports are available due to the rarity of this condition, most reports have described pulmonary pleomorphic carcinoma as being an aggressive tumor that is often refractory to treatment with an accordingly dismal prognosis among types of non-small cell lung carcinoma (NSCLC) (3, 4).

We herein report a case of disseminated pulmonary pleomorphic carcinoma in which a complete response (CR) was finally achieved using cisplatin plus gemcitabine (GP) as third-line chemotherapy. The patient has remained free from recurrence for more than six years after completing the chemotherapy regimen. To the best of our knowledge, this represents the first report of metastatic pleomorphic carcinoma in which the patient achieved a durable complete response with cytotoxic chemotherapy that may be indicative of a “cure.”

Case Report

A 47-year-old man with a 50-pack-year smoking history presented with hemoptysis. Chest radiography and computed tomography (CT) showed an irregular mass measuring 50 mm in diameter in the upper lobe of the right lung. The...
tumor was initially diagnosed as squamous cell carcinoma based on a bronchial biopsy and categorized as T2N0M0, clinical stage IB (AJCC version 6). The patient underwent right upper lobectomy with mediastinal dissection. The resected tumor had increased in size to 88 mm in diameter with significant central necrosis and hemorrhage.

Microscopically, the tumor cells comprised poorly differentiated squamous cell carcinoma cells with multinucleated neoplastic giant cells (>10%), showing vascular and chest wall invasion. An immunohistochemical examination revealed that the tumor cells were positive for AE1/AE3 (pan-cytokeratin, CK) and CK7, weakly positive for carcinoembryonic antigen (CEA), neuron-specific enolase (10%) and synaptophysin (1%) and negative for CK20, thyroid transcription factor-1, surfactant protein-A, vimentin and chromogranin A. The tumor cells also showed a strong molecular immunology borstel-1 (MIB-1) proliferation index (82.6%). These microscopic characteristics were diagnostic of pleomorphic carcinoma with giant cells, squamous differentiation and neuroendocrine differentiation (Fig. 1) of pathological stage IIB (p-T3N0).

Only six weeks after surgery, multiple metastases were detected in the right lower lobe, right pleura and liver on follow-up CT of the chest and abdomen. The unusually rapid relapse of the tumor led us to review the results of chest CT before surgery. We found that at least one lung metastasis had been present in the right lower lobe prior to surgery, indicating that stage IV disease existed preoperatively. The patient was enrolled in a phase II clinical trial of combination therapy with S-1 and irinotecan for advanced NSCLC (5) and started the first-line chemotherapy; however, the tumor progressed within just one course of treatment. The patient then received standard platinum doublet chemotherapy with carboplatin and paclitaxel that again resulted in progressive disease within just one course, with rapid growth of lung metastasis, pleura dissemination and hepatic metastasis.

Considering the patient’s young age, good major organ function and good performance status, we prescribed cisplatin (80 mg/m², day 1) plus gemcitabine (1,000 mg/m², day 1 and 8) every three weeks as the third-line chemotherapy. Surprisingly, the lung and pleural metastases began to shrink within one week. The metastatic lesions continued to shrink. A partial response (PR) was judged to be present after two courses of GP, and CR was finally determined after six courses of therapy. As of the time of writing, the patient remains free from recurrence, more than six years after completing the chemotherapy regimen, with no subsequent treatment [Fig. 2A, D and G before GP; B, E and H after six courses of GP; C, F and I five years after GP; representative lesions are shown (arrows)].

We searched for molecular reasons for why the tumor responded so well to the third-line GP. Molecular analyses of the surgically resected specimen revealed that the tumor was negative for known activating epidermal growth factor receptor (EGFR) mutations, K-ras mutations and anaplastic lymphoma kinase gene rearrangements. Immunohistochemical analyses showed that the tumor was highly expressive of human equilibrative nucleoside transporter 1 (hENT1), the major transporter of gemcitabine, in the cell membrane (Fig. 3) (6).

**Discussion**

The tumor in the present case showed an aggressive clinical course until the administration of the third-line chemotherapy, with rapid growth from onset to surgery, followed by the emergence of lung metastases by the time of surgery, rapid growth of multiple lung metastases, rapid pleural dissemination, the rapid emergence of liver metastases soon after surgery and multidrug resistance to the first- and second-line chemotherapy regimens, which included carboplatin, paclitaxel, irinotecan and S-1. The pathological characteristics of the surgical specimen revealed intratumoral hemorrhaging and necrotic changes, with a very high MIB-1 proliferation index, all of which indicated the aggressive clini-
While pleomorphic carcinoma has been deemed a tumor with a poor prognosis, several reports have described pleomorphic carcinomas that responded to cytotoxic chemotherapy containing platinum plus gemcitabine (7-10). For example, Hong et al. reported two cases of PR and two cases of stable disease among eight patients with pleomorphic carcinoma treated with platinum plus gemcitabine (11). Kaira et al. also reported one case of PR achieved with second-line carboplatin plus gemcitabine (8). However, no reports have specifically mentioned the expression status of hENT1 in cases of pleomorphic carcinoma and the relationship of this parameter to chemosensitivity or survival. hENT1 is a major nucleoside transporter responsible for gemcitabine uptake into cells (11). An increased expression of hENT1 has been reported to be a determinant of gemcitabine sensitivity in patients with NSCLC, pancreatic cancer and mantle cell lymphoma (6, 12, 13). In patients with pancreatic cancer treated with gemcitabine, those with a high hENT1 expression have been reported to exhibit significantly longer overall survival than those with a low hENT1 expression (11, 12). These results suggest that hENT1 is a favorable predictive biomarker of gemcitabine treatment. Despite the aggressive clinical, pathological and molecular characteristics of the pleomorphic carcinoma observed in the present case, the expression of hENT1 appeared to have a significant impact on the durable response of the tumor to GP and, accordingly, the long-term disease-free survival.

The authors state that they have no Conflict of Interest (COI).
References