Interstitial Pneumonia Possibly Due to a Novel Anticancer Drug, TS-1: First Case Report

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A newly approved oral fluoropyrimidine, TS-1, is a dihydropyrimide dehydrogenase (DPD)-inhibiting fluoropyrimidine (DIF) drug. We describe a case of interstitial pneumonia probably caused by TS-1. A peripheral blood lymphocytes stimulating test (DLST) with TS-1 demonstrated a substantial positive reaction. So far only three cases of TS-1-induced interstitial pneumonia have been reported but the relationship between interstitial pneumonia and TS-1 was demonstrated only in this case. Considering that interstitial pneumonia has also been reported with 5-FU, it is necessary in the future to clarify which component of this drug is directly related to interstitial pneumonia.

Key words: interstitial pneumonia – anticancer drug – TS-1

INTRODUCTION

Drug-induced interstitial pneumonia is one of the serious adverse reactions which can be induced by various drugs. We often experience great difficulty in diagnosing and treating interstitial pneumonia which occurs during anticancer chemotherapy as it is attributable not only to the tumor but also to other causes such as infection. We recently encountered a case of drug-induced interstitial pneumonia which was attributable to TS-1, an oral anticancer drug which has recently been used as a dihydropyrimide dehydrogenase (DPD)-inhibiting fluoropyrimidine (DIF).

CASE REPORT

A 70-year-old man was referred to our hospital for the first time on November 23, 1999 with the chief complaint of anorexia. He was treated with sodium ropabazole and rebamipide and later with ranitidine hydrochloride. On December 6, 1999, an advanced gastric cancer (Bormann III type; poorly differentiated adenocarcinoma) was found by endoscopy and also multiple metastases to the liver and intra-abdominal lymph nodes by abdominal computed tomography (CT). He was diagnosed as having inoperable advanced disease and was given TS-1 (100 mg/day), an anticancer drug, orally from December 25, 1999 to January 21, 2000. Hematological data at the beginning of the treatment showed leukocytosis (WBC 14,900/µl) and anemia (Hb 9.7 g/dl). In biochemistry, GOT showed a slightly high level (47 U/l), but other data were within the normal range. He had no obvious clinical symptoms during the treatment. However, he noticed a gradual increase in exertional dyspnea from around January 20. On January 29, X-ray film showed interstitial shadows in both lung fields and fine crackles were audible on auscultation. On January 31, as arterial blood gas analysis revealed hypoxemia (PaO₂ 79 Torr; PaCO₂ 34.5 Torr) and treatment with prednisolone (20 mg/day) was started. On February 3, the chest X-ray film showed aggravation of interstitial pneumonia and he was hospitalized on February 7.

At the time, he was febrile (36.9°C) and physical examination revealed no particular changes, except for fine crackles in both lower lung fields. Hematological data showed a shift to the left of nuclear cells (leukocyte count 11,700/µl, neutrophil count 80.1%). In biochemistry, although increased lactate dehydrogenase, alkaline phosphatase and γ-glutamyl transpeptidase were observed, Klebsvonden Lungen-6 (KL-6) was within the normal range (333 U/ml). Pulmonary function tests indicated restrictive ventilatory defect and diffusing capacity disturbance (VC, 52.6%; DLco, 67.8%). Chest X-ray films showed interstitial shadows mainly in the middle to lower lung fields on both sides (Figure 1a). Chest CT revealed ground

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glass-like shadows mainly in the dorsal mid to lower lung fields on both sides (Figure 1b).

After admission, he was treated continuously with oral prednisolone (30 mg/day). On February 10, bronchoscopy was performed, but no abnormalities were observed in the visible range. Bronchoalveolar lavage (BAL) was carried out from the left lingula and transbronchial lung biopsy (TBLB) was performed from the left lower lobe and lingula. The BAL fluid was free from bacteria. TBLB specimens showed fibrous thickening in the alveolar septum, nuclear swelling in the alveolar epithelium and intra-alveolar histiocyte infiltration (Fig. 2). BAL showed an increasing number of leukocytes and lymphocytes count (14.67%). On February 14, a peripheral blood lymphocytes stimulating test (DLST) with TS-1 was performed. The measurement result was 3365 c.p.m. compared with 229 c.p.m. for the control, showing a strong positive reaction. The data obtained from DLST with the bronchoalveolar lavage could not be analyzed because of an insufficient number of lymphocytes. Based on the above findings, TS-1-induced interstitial pneumonia was suspected. After steroid pulse therapy was started on day 9 of hospitalization, the subjective symptoms improved considerably and the interstitial shadows observed on the chest X-ray films and chest CT were resolved. He continued to take oral steroid and was discharged from the hospital. He continued the treatment on an outpatient basis, but on March 4, 2000 he died of progression of gastric cancer. An autopsy could not be performed.

DISCUSSION

TS-1 is a drug containing three components, tegafur, an oral anticancer drug which is a prodrug of 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP) and monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate (Oxo) (1,2). CDHP inhibits the decomposition of 5-FU, whereby it maintains a high concentration of 5-FU in blood. Oxo inhibits the phosphorylation of 5-FU, whereby it attenuates the toxic effects of 5-FU on the gastrointestinal tract. TS-1 has been approved only for gastric cancer, but clinical studies in patients with lung cancer, etc., are ongoing (3). It has been reported that interstitial pneumonia caused by anticancer drugs or immunosuppressants accounts for 50.3% of all cases of drug-induced interstitial pneumonia reported thus far in Japan (4,5). 5-FU is widely and frequently used, but 5-FU-induced interstitial pneumonia has very rarely been reported.

As for interstitial pneumonia induced by TS-1, a prodrug of 5-FU, only three cases, including our patient, have been
reported so far. One of them was a patient with lung cancer with a medical history of idiopathic interstitial pneumonia. In this case, aggravation of interstitial pneumonia was observed 1 week after the start of treatment with TS-1. The other two patients were given TS-1 to treat gastric cancer (unpublished observations). In one of them, anticancer chemotherapy with cisplatin was given before the treatment with TS-1 and interstitial pneumonia was already present after treatment with cisplatin (data from Taiho Pharmaceutical). However, as interstitial pneumonia was aggravated after the start of treatment with TS-1, TS-1 was discontinued 1 week after the start of treatment. The definite causal relationship between aggravation of interstitial pneumonia and TS-1 is still unknown in this case. Among the three cases, DLST was performed only in the present case. Therefore, the relationship between interstitial pneumonia and TS-1 was more clearly shown in this case. Considering that interstitial pneumonia has also been reported with 5-FU, it is necessary in the future to clarify which component of the drug is directly related to interstitial pneumonia.

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References