An Autopsy Case of Acute Pulmonary Toxicity Associated with Gemcitabine

Ko Maniwa, Eisaku Tanaka, Tetsuro Inoue, Terufumi Kato, Minoru Sakuramoto, Masayoshi Minakuchi, Yuji Maeda, Satoshi Noma*, Yoichiro Kobashi** and Yoshio Taguchi

Abstract

Acute respiratory distress syndrome (ARDS) developed following intravenous gemcitabine monotherapy in a 75-year-old man with non-small cell lung cancer. The total dose of gemcitabine was 1,500 mg, and the latent period from starting gemcitabine to pulmonary toxicity was three days. The chest radiographs and high resolution computed tomographic scan revealed bilateral ground-glass opacity. He died on the fourteenth post-chemotherapeutic day due to respiratory failure. Postmortem examination of the lung revealed mixed exudative and fibrotic stages of diffuse alveolar damage. Pulmonary toxicity from gemcitabine can be acute and fatal. (Internal Medicine 42: 1022-1025, 2003)

Key words: gemcitabine, lung cancer, corticosteroids, diffuse alveolar damage

Case Report

A 75-year-old man with a 2 pack-per-day smoking history was admitted to our hospital on October 5, 2000, because of persistent cough and bloody sputum for over three months. The chest radiograph and CT film showed a giant mass with a cavity in the right lung lower lobe, and multiple small nodules in both of the lungs without apparent interstitial pneumonia (Figs. 1, 2). Oxygen saturation was 97%. Examination of the lung revealed mixed exudative and fibrotic stages of diffuse alveolar damage. Pulmonary toxicity from gemcitabine can be acute and fatal. (Internal Medicine 42: 1022-1025, 2003)

Key words: gemcitabine, lung cancer, corticosteroids, diffuse alveolar damage

Introduction

Gemcitabine (2’, 2’-difluoro-2’-deoxycytidine) is a new nucleoside analog that is used for the treatment of non-small cell lung cancer, pancreatic cancer, urothelial cancer, breast cancer and ovarian cancer. Though it is thought that gemcitabine is relatively safe, various pulmonary toxicities have been reported (1-7). We report the autopsy of a non-small cell lung cancer patient who died because of acute respiratory distress syndrome (ARDS) 14 days after administration of gemcitabine.

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From the Department of Respiratory Medicine, *Department of Radiology and **Department of Pathology, Tenri Hospital, Nara
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Reprint requests should be addressed to Dr. Ko Maniwa, the Department of Respiratory Medicine, Tenri Hospital, 200 Mishima, Tenri, Nara 632-8552
Figure 1. A chest radiograph on admission, showing a giant mass with a cavity in the right lung lower lobe, and multiple small nodules in both of the lungs.

Figure 2. A chest CT film on admission shows no apparent interstitial pneumonia in the lung, though the presence of emphysema, the partial volume effect of the tumor and some shadows mimick interstitial changes.

Figure 3. A chest radiograph on Day 3, showing dense infiltration mainly in the right upper lobe.

Figure 4. A chest radiograph on Day 8, showing diffuse ground-glass shadow on both lung fields and a giant mass (primary lesion) with a cavity in the right lower field.
Figure 5. A high resolution computed tomographic scan of the lung revealed bilateral perihilar ground-glass opacity.

Figure 6. Photomicrograph of autopsy specimen from right upper lung lobe, showing interstitial infiltrates and hyaline membrane formation. These findings were compatible with diffuse alveolar damage (HE stain, ×20 and bottom left ×100).

Table 1. Severe Cases of Gemcitabine-induced Pulmonary Toxicity: Review of the Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Disease</th>
<th>Number of doses before onset of symptoms</th>
<th>The latent period from the first use</th>
<th>Response to corticosteroids</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pavlakis (1)/1997</td>
<td>48</td>
<td>male</td>
<td>large cell lung carcinoma post left pneumonectomy</td>
<td>6 (1,250 mg/m²)</td>
<td>43 days</td>
<td>poor</td>
<td>death diffuse alveolar damage (postmortem)</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>female</td>
<td>ovarian carcinoma</td>
<td>8 (1,250 mg/m²)</td>
<td>78 days</td>
<td>good</td>
<td>recover died of primary disease after 6 months death</td>
</tr>
<tr>
<td>Takada (5)/1998</td>
<td>72</td>
<td>male</td>
<td>squamous cell lung carcinoma squamous cell lung carcinoma post left pneumonectomy</td>
<td>3 (1,000 mg/m²)</td>
<td>23 days*</td>
<td>poor</td>
<td>death diffuse alveolar damage (postmortem)</td>
</tr>
<tr>
<td>Marruchella (3)/1998</td>
<td>68</td>
<td>male</td>
<td>lung carcinoma</td>
<td>6 (1,250 mg/m²)</td>
<td>42 days</td>
<td>poor</td>
<td>death diffuse alveolar damage (postmortem)</td>
</tr>
<tr>
<td>Vander (2)/1998</td>
<td>60</td>
<td>female</td>
<td>lung adenocarcinoma</td>
<td>5 (1,000 mg/m²)</td>
<td>30 days</td>
<td>good</td>
<td>recover</td>
</tr>
<tr>
<td>Rosado (6)/2002</td>
<td>85</td>
<td>male</td>
<td>lung adenocarcinoma</td>
<td>4 (1,000 mg/m²)</td>
<td>27 days</td>
<td>moderate</td>
<td>death died of sepsis death</td>
</tr>
<tr>
<td>Gupta (7)/2002</td>
<td>71</td>
<td>male</td>
<td>non-small cell lung carcinoma</td>
<td>6 (1,000 mg/m²)</td>
<td>58 days*</td>
<td>poor</td>
<td>recover</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>male</td>
<td>non-small cell lung carcinoma</td>
<td>6 (1,000 mg/m²)</td>
<td>56 days*</td>
<td>good</td>
<td>recover</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>male</td>
<td>ureteral cancer</td>
<td>9 (1,000 mg/m² – 750 mg/m²)</td>
<td>84 days*</td>
<td>good</td>
<td>recover</td>
</tr>
<tr>
<td>Maniwa (our case)</td>
<td>75</td>
<td>male</td>
<td>lung adenocarcinoma</td>
<td>1 (1,000 mg/m²)</td>
<td>3 days</td>
<td>poor</td>
<td>death diffuse alveolar damage and DIC (postmortem)</td>
</tr>
</tbody>
</table>

*not specified exactly.
died of respiratory failure on day 14. Both of the lungs at autopsy were heavy and congestive, and microscopic examination of the lungs revealed hyaline membrane formation, compatible with diffuse alveolar damage (Fig. 6). In addition, multiple microscopic fibroid thromboses were observed in arterioles and capillaries of the lungs, liver, kidney. These findings were compatible with disseminated intravascular coagulation (DIC). No pathogens were detected in cultures of blood and lung specimens obtained at autopsy.

**Discussion**

Various pulmonary toxicities of gemcitabine have been reported. Transient dyspnea is reported to occur within hours after its administration in about 8–10% of patients (1, 2). This transient dyspnea is often associated with bronchospasm and is usually a self-limiting event. Severe dyspnea associated with gemcitabine occurred in 3–5% of the patients (1, 3). Most of these cases could be cured by withdrawing gemcitabine, and/or by administration of diuretics and corticosteroids. Another recent report evaluated that in the clinical database the incidence rates of dyspnea and the other serious pulmonary toxicities associated with gemcitabine were 0.45% and 0.27% (4). According to an analysis of published reports (1–7), several cases including the present case have resulted in a fatal outcome (Table 1). Other reported autopsy findings revealed diffuse alveolar damage that was consistent with ARDS. The incidence rate of ARDS associated with gemcitabine is reported to be 0.002% (4). The number of doses of gemcitabine before the onset of symptoms that induced pulmonary toxicity was on average 5.4, and the latent period from starting gemcitabine to developing pulmonary toxicity was 44.4 days (3–84 days). Neither prior chemotherapy nor radiation therapy was performed on our patient, and the latent period from the initial administration of gemcitabine was three days. Compared to other reports in the literature, our case constitutes the briefest onset of fatal pulmonary toxicity after starting gemcitabine.

The diagnosis of drug-induced lung disease is made by exclusion of other potential causes, including congestive heart failure, infections, auto-immune disease, or lymphangitic carcinomatosis. At the beginning the clinical course of our patient was consistent with nosocomial pneumonia, so he was given some antibiotics. But his condition deteriorated in spite of the large amount of additional corticosteroids for ARDS. No pathogens were detected in cultures of sputum and blood obtained during the lifetime of our patient, or from blood and lung specimens obtained at autopsy. Invasion of carcinoma on the field of ground-glass opacity on the chest radiograph and CT films was ruled out at autopsy. Thus, the present case is probably gemcitabine-induced ARDS, pathologically diffuse alveolar damage and DIC, all of which occurred acutely following the initial administration of gemcitabine.

**Conclusion**

We present a case of fatal pulmonary toxicity that developed following intravenous gemcitabine monotherapy for non-small cell lung cancer. Although most of the pulmonary toxicities associated with gemcitabine are transient and mild, they can occur acutely and can be fatal.

**References**