

Gemcitabine-related pulmonary toxicity

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Summary

Background: Gemcitabine is an increasingly used and generally well tolerated anticancer drug. Rarely, it leads to potentially fatal pulmonary toxicity.

Case descriptions and results: We describe the clinical features of 5 patients with gemcitabine-related pulmonary toxicity. Due to early diagnosis,

prompt discontinuation of the drug, and treatment with steroids, toxicity was reversible in all cases.

Conclusion: Early recognition of gemcitabine-related pulmonary toxicity is mandatory.

Key words: gemcitabine; pulmonary toxicity

Introduction

Gemcitabine was introduced into clinical practice in 1989. This purine analogue anti-metabolite has a broad range of activity. It is used alone or in combination chemotherapy in non-small cell lung cancer (NSCLC), pancreatic cancer, cancer of the bladder, ovary, breast etc. Generally, it has a very favourable toxicity profile, which permits its use in elderly and less fit patients [1, 2]. Myelosuppression is the major dose-limiting toxicity. Nausea and vomiting are rare. Pulmonary

toxicity was first described in 1997 [3] and is increasingly recognised [4, 5]. It usually occurs after months of treatment, manifests with dyspnoea and interstitial infiltrates, responds to steroids, and is reversible when the drug is discontinued. We report a series of 5 patients with gemcitabine-related pulmonary toxicity. Due to early diagnosis, prompt steroid treatment, and discontinuation of the offending drug, toxicity resolved in all of them.

Case descriptions

Case 1

A 69-year-old male patient with recurrence of oesophageal squamous cell carcinoma after previous treatment with cisplatin and 5-fluorouracil. Second line treatment with weekly single agent gemcitabine was started in 03/00

(table 1). Four months later the patient presented with severe dyspnoea, orthopnoea, and peripheral oedema. Chest X-ray revealed new bilateral reticulo-nodular infiltrates predominantly in the lower lobes and bilateral pleural effusions (figure 1a). Pulmonary function tests showed a

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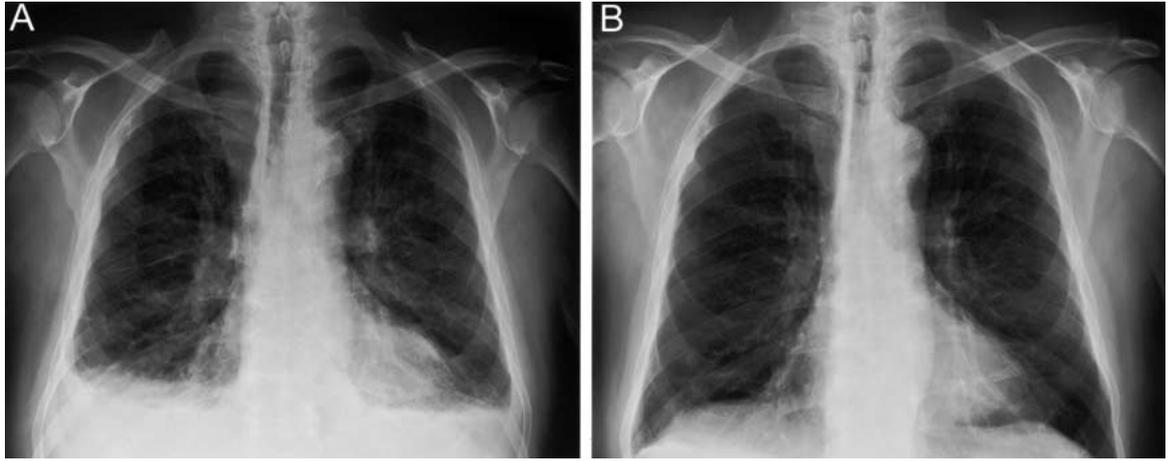
Table 1

Patient and selected disease characteristics.

Patient	cancer	thoracic tumour involvement	prior thoracic irradiation	gemcitabine		symptoms	investigations		treatment
				total dose (g/m ²)	cycles		echo	CT-scan	
66♂	oesophagus	mediastinum	no	12.9	13	dyspnoea, oedema	yes	no	steroids
78♂	NSCLC	lung, mediastinum	no	16.5	14	dyspnoea, oedema	yes	no	steroids, diuretics
69♀	NSCLC	lung, mediastinum	yes	12.0	10	dyspnoea, cough	no	yes	steroids
70♀	adeno-carcinoma	lung, mediastinum	no	8.0	8	dyspnoea, oedema	yes	yes	steroids, heparin, antibiotics
64♂	pancreas	none	no	7.8	8	dyspnoea, cough, oedema	no	yes	none

Figure 1

A: Chest X-ray of case 1 showing bilateral predominantly reticulo-nodular interstitial infiltrates, increased density of the bronchovascular bundle and bilateral pleural effusions. B: Almost complete resolution of the radiographic abnormalities.

**Figure 2**

A, B: Chest X-ray of case 2 showing bilateral reticulo-nodular interstitial infiltrates, also visible on the lateral chest radiograph. Known previous right upper lobe resection. C and D: Regression of the bilateral infiltrates.

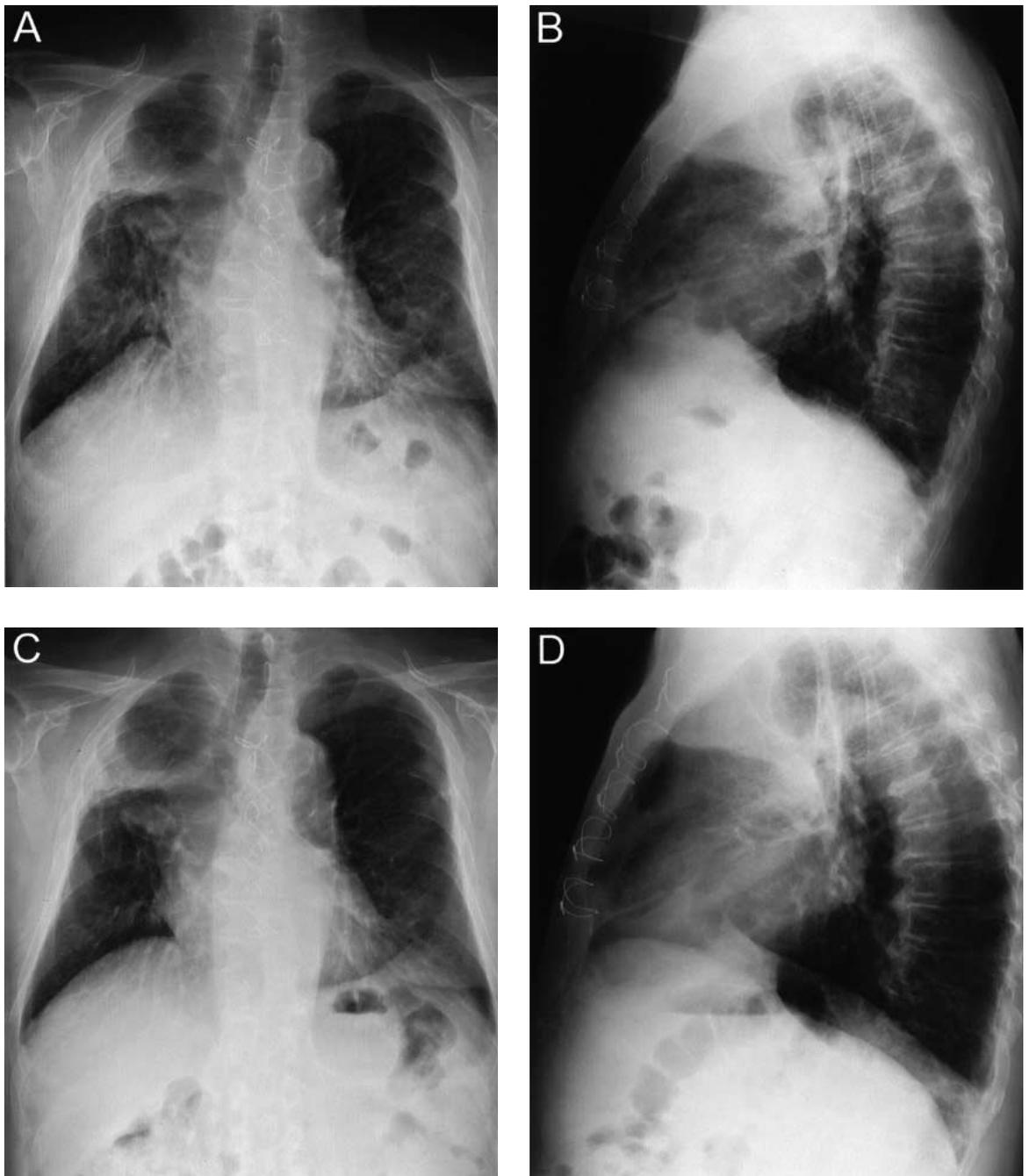
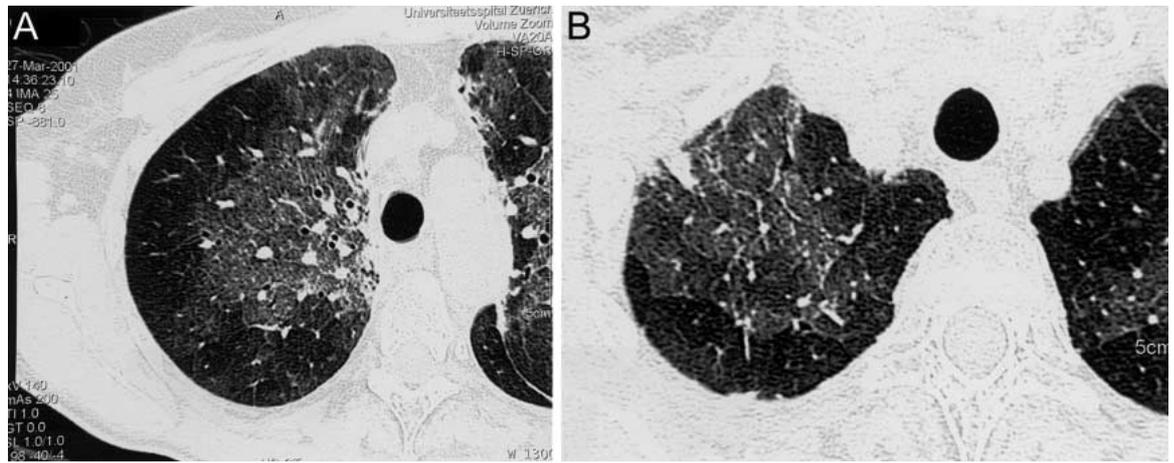


Figure 3

A: High-resolution computed tomography of case 3 showing a mixed pattern of reticular centrilobular infiltrates and ground-glass opacities.
B: Mosaic perfusion pattern.



severe restrictive ventilatory defect and reduced diffusion capacity. Steroids were started on the same day at a dose of 100 mg prednisone daily. There was prompt clinical improvement. One week later the chest X-ray showed almost complete resolution of the infiltrates (figure 1b). Steroids were tapered slowly over one month. The patient had progressive disease in 12/00 and died in 8/01.

Case 2

This 78-year-old male patient had a wedge-resection of a T2 NSCLC of the right upper lobe in 05/97. In 11/00 a large local recurrence in the right upper lobe and bilateral mediastinal lymph node metastases were diagnosed. Treatment with weekly intravenous gemcitabine was started (table 1). In 03/01 he presented with severe dyspnoea, peripheral oedema, and a 5 kg weight gain. Chest X-ray showed new bilateral reticulo-nodular interstitial infiltrates, predominantly in the lower lobes, and no pleural effusion (figure 2a, b). Gemcitabine was discontinued, the patient received steroids (100 mg prednisolone daily) and the dose of diuretics was increased. One week later chest X-ray showed regression of the infiltrates (figure 2c, d) and dyspnoea improved while steroids were tapered over one month. Without further therapy the patient remained clinically stable up to 10/01.

Case 3

A 68-year-old female patient was referred in 10/99 for adenocarcinoma of the lung and mediastinal lymph node metastases considered inoperable. She was treated with mediastinal radiation (56 Gray) until 1/00. In 8/00 CT-scan showed regression of the mediastinal metastases but new multiple bilateral pulmonary nodules, presumably representing metastases. In 1/01 gemcitabine monotherapy was started for progressive disease (table 1). In 03/01 a CT-scan showed minor regression of the metastases. The patient developed slowly increasing dyspnoea on exertion and chemotherapy was discontinued. One week later the patient had to be admitted for dyspnoea at rest, chills, severe cough, and chest pain on deep inspiration. Blood gas analysis showed an increased arterio-alveolar gradient P(A-a) of 50 mm Hg. Chest X-ray and CT-scan showed no evidence of pulmonary embolism, unchanged tumour manifestations but new extensive bilateral infiltrates of both reticular and ground glass appearance on high-resolution images (figure 3a) as well as a mosaic perfusion pattern (figure 3b) and new small bilateral pleural

effusions. Treatment with prednisone 100 mg daily and oxygen was initiated. After 3 days, her dyspnoea had improved substantially. Two weeks later chest CT-scan showed almost complete resolution of the combined reticular and ground glass infiltrates as well as resolution of pleural effusions. Dyspnoea subsided and steroids were discontinued another two weeks later. In 8/01 the disease progressed and treatment with vinorelbine was started.

Case 4

A 70-year-old female patient was referred in 09/01 for newly diagnosed malignant pleural effusion and mediastinal lymph node metastasis from adenocarcinoma of unknown origin. Therapy with gemcitabine was started (table 1). Two months later she developed progressive fatigue, dyspnoea at rest and peripheral oedema. A CT-scan showed bilateral patchy infiltrates of reticular and ground glass character in the upper lobes, a single subsegmental pulmonary embolism, and decreased size of mediastinal lymph node metastasis. The small embolism was unlikely to be the only cause of the very severe dyspnoea. Therefore, the additional diagnosis of gemcitabine toxicity was considered likely. The patient was treated with heparin, prednisone 100 mg daily and antibiotics. Dyspnoea improved substantially within a few days. Steroids were tapered over one month. Chest X-ray showed a marked regression of interstitial infiltrates. The patient was started on docetaxel.

Case 5

A 64-year-old male patient was referred for relapsed pancreatic cancer. He had undergone a Whipple procedure in 7/98 for T3N1 adenocarcinoma of the pancreatic head. In 1/01 he was diagnosed with enlarged coeliac lymph nodes interpreted as local relapse. He was started on weekly gemcitabine (table 1). After two months a chest X-ray was performed because of increasing cough, which showed new bilateral reticular infiltrates. A chest CT-scan confirmed the reticulo-nodular infiltrates located predominantly in the anterior parts of the upper lobes. Gemcitabine-related pulmonary toxicity was considered a likely diagnosis, and the drug was discontinued. No steroids were given since the patient had only moderate dyspnoea and cough. The pulmonary complaints subsided completely and pulmonary infiltrates regressed in 06/01. In 09/01 the patient developed liver metastases and died of rapid tumour progression.

Discussion

We describe 5 patients with a presumed diagnosis of gemcitabine-related pulmonary toxicity. As is the case with other examples of drug-related pulmonary toxicity, the diagnosis remains one of exclusion. In the first 4 cases the diagnosis is very probable, while in case 5 the diagnosis is possible. These patients developed increasing dyspnoea, cough, and peripheral oedema while on treatment with gemcitabine. They were found to have bilateral, predominantly reticulo-nodular interstitial lung infiltrates as described in the literature [6]. Other possible causes of dyspnoea and lung infiltrates (cardiac insufficiency, pulmonary embolism, pneumonia, carcinomatous lymphangitis) were excluded in each case by the appropriate tests. Peripheral oedema is a well known side effect of gemcitabine, occurring in 20% of patients [1]. It is thought to be related to increased vascular permeability, a mechanism which may contribute to the pulmonary toxicity of gemcitabine. Clinically, these patients showed improvement of pulmonary symptoms within a few days of gemcitabine being discontinued and steroids being given.

In drug-related pulmonary toxicity, several patterns of pulmonary response have been recognised [7]. These include the more acute hypersensitivity infiltrate, the non-cardiogenic pulmonary oedema, the more chronic interstitial pneumonitis/fibrosis, and pleural effusions. These pulmonary responses to different drugs are by no means mutually exclusive. An acute response may evolve into chronic changes. Among anticancer agents, bleomycin and methotrexate are associated with hypersensitivity infiltrates, interstitial fibrosis, and/or pleural effusions [7]. Cytarabine, interleukin-2, all-trans-retinoic acid, and gemcitabine can cause noncardiogenic pulmonary oedema [8]. Case 3 fulfills the criteria for noncardiogenic pulmonary oedema, which are the combination of hypoxaemia, bilateral ground-glass opacities (figure 3), and no evidence of congestive heart failure. In all cases, the predominant radiographic pattern on conventional chest X-ray were reticulo-nodular interstitial infiltrates, which are quite uncommon

in drug-induced lung disease. From the high-resolution computed chest tomography in case 3 showing a centrilobular pattern with mosaic perfusion it can be concluded that the reticulonodular densities on conventional chest radiograph are primarily due to thickening of the peribronchovascular interstitium by interstitial pulmonary oedema. This is underscored by the presence of a markedly increased density of the bronchovascular bundle in case 1. All radiographic abnormalities were reversible.

The frequency of gemcitabine-related pulmonary toxicity has been estimated to be 0.7–13% in retrospective analyses. During the period of one and a half years in which we observed the above 5 cases, we estimate to have treated 100 cancer patients with gemcitabine. This would yield a frequency of pulmonary toxicity of 4%. Usually, pulmonary toxicity develops after weeks or months of treatment with gemcitabine [3] but it has also been described after a single dose of gemcitabine [5, 9]

Preventing a severe course of the syndrome depends on its early recognition. If gemcitabine is not discontinued, pulmonary toxicity may be fatal [3]. Obviously, patients with prior resection of lung parenchyma and/or lung irradiation have less pulmonary functional reserve. They seem to be at increased risk.

In conclusion, gemcitabine-related pulmonary toxicity is an increasingly recognised and potentially fatal syndrome. Clinicians should have a high index of suspicion in order to ensure early diagnosis.

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