Gemcitabine and atrial fibrillation: a rare manifestation of chemotherapy toxicity

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Gemcitabine is a purine analog with known activity in many solid tumors, namely lung, breast, pancreatic, genitourinary and head/neck cancers. Cardiac toxicity is a rare event and only one report previously described atrial fibrillation (AF) as a consequence of gemcitabine infusion. We report two cases of women suffering from lung cancer who were treated with gemcitabine. Both patients were admitted to hospital for paroxysmal AF occurring 12–24 h after the infusion of the drug. In the first case a sinus rhythm was spontaneously repristinated when AF occurred for the first time, while the second episode required an anti-arrhythmic drug to interrupt the dysrhythmia. In the second case, the patient had to be treated with digitalis glycoside to control the ventricular response without attaining a sinus rhythm. We could not recognize any other precipitating factor beyond the infusion of gemcitabine as a cause for the arrhythmia. Both cases were treated with gemcitabine for lung cancer and we observed the appearance of AF less than 24 h after drug administration. We assume that 2′,2′-difluorodeoxyuridine, an active metabolite of gemcitabine, could be responsible for the toxic effect. We conclude that AF is an unusual, but potentially dangerous, side-effect of gemcitabine infusion. The arrhythmia should be suspected whenever patients complain of dyspnea and palpitations beginning 12–24 h after treatment. In these cases, the treatment of AF consists of anti-arrhythmic drugs in order to repristinate a sinus rhythm or control the heart rate. *Anti-Cancer Drugs* **17:359–361 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine) is an anti-metabolite frequently utilized in the treatment of many solid tumors. Gemcitabine is a pyrimidine analog with a dual mechanism of action. When it flows into the cell it is activated by deoxycytidine kinase resulting in the formation of intermediate compounds, such as gemcitabine diphosphate and triphosphate [1,2]. The former is an inhibitor of the enzyme ribonucleotide reductase, implicated in the DNA repair process [1–3]. The latter is a possible substrate for DNA polymerase that can be utilized by the enzyme, leading to the arrest of nucleic acid synthesis [1–4].

The pharmacokinetics of gemcitabine depend on the rate of drug infusion, and age and sex of the patient. Men and younger patients eliminate the drug faster than women and elderly patients [5]. Gemcitabine does not bind to plasma proteins and is almost completely cleared from the kidney as deaminated gemcitabine. Only 10% is eliminated unmodified [1]. Gemcitabine is a well-tolerated drug when used as a single agent.

The most common and limiting toxicity for the standard dose (1200 mg/m^2 administered i.v. over 30 min on days 1–8 every 21 days) is myelosuppression. Other relatively uncommon side-effects are fever, pain, asthenia, abdominal pain, dyspnea, vomiting, anorexia, deep vein thrombosis, anal pruritus and hemolytic–uremic syndrome. Idiosyncratic reactions and hypertensive crises can occur rarely when the drug is used in a daily schedule. Patients presenting with dyspnea may have an acute respiratory distress syndrome [6] without evidence of left ventricular failure, whose onset usually begins at least 2 days after gemcitabine infusion [7]. Grade 3–4 cardiac toxicity (ventricular tachiarrhythmias and reduction in left ventricular ejection fraction) is reported in a small fraction of patients [8].

Case history

We report two cases of women suffering from non-small cell lung cancer (NSCLC) who developed paroxysmal atrial fibrillation (AF) after the infusion of gemcitabine.

The first case was a 72-year-old woman who presented with lung adenocarcinoma and metastatic spread in the right mandibula in December 2004. She was in good clinical condition without relevant comorbidity. The patient was treated with 6 weekly cycles of Docetaxel

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30 mg/m^2 i.v. Chemotherapy was well tolerated, but the patient went on progressive disease in 6 months. She then was treated with gemcitabine 1200 mg/m^2 days 1–8 every 21 days. Eighteen hours after the first infusion the patient referred increasing dyspnea and accelerated cardiac rhythm that regressed spontaneously in about 2 h. On day 8 (first cycle) she was visited and evaluated by a cardiologist who did not find any sign of cardiac toxicity. The electrocardiogram (ECG) was normal. Therapy was administered as scheduled and the patient was discharged on the same day. Again, 18 h later she complained of the same transitory symptoms of dyspnea and chest discomfort. A cardiologic evaluation on the next day was normal and the patient was judged suitable for continuing therapy.

The second cycle was followed by a similar, but prolonged, episode of palpitations and dyspnea that required urgent control in the Emergency Department. Physical evaluation demonstrated the presence of an altered cardiac rhythm. Blood pressure was normal. The ECG was consistent with paroxysmal AF with rapid ventricular response and the patient needed treatment with a class III anti-arrhythmic drug such as amiodarone 300 mg i.v. A sinus rhythm was repristinated in 2 h. During this episode biochemical and hematological values were normal, and no predisposing factors for AF could be identified. Chemotherapy was interrupted and the patient was treated with prophylactic oral amiodarone 200 mg daily. She did not refer any other cardiac problems. Two months later she developed a brain metastasis treated with whole-brain radiotherapy. Three months thereafter a stable sinus rhythm was maintained with oral amiodarone.

The second case was a 73-year-old woman, clinically fit, who was operated on for a colonic carcinoma (stage C2 according to Duke's modified Astler–Coller staging system) in January 2004, and treated with folinic acid and 5-fluorouracil adjuvant chemotherapy according to Machover's protocol regimen [9]. In March 2005 she presented with spinal cord metastasis at the D9 level that required vertebroplasty. During her stay in hospital a pulmonary mass was occasionally found on her chest X-ray. Computed tomography (CT) demonstrated the presence of a right hylar mass 4 cm in maximum diameter and monolateral lymphadenopathy. Fibrobronchoscopy confirmed the finding of a mass in the main right bronchial and FNBA demonstrated a cellular pattern suggestive of NSCLC. The patient was found to have asymptomatic pulmonary thromboembolism without cardiac failure or arrhythmia and was treated with low-molecular-weight heparin (LMWH). In April 2005 a CT scan could not demonstrate residual thrombi in the pulmonary artery and the patient started monochemotherapy with gemcitabine 1200 mg/m^2 days 1–8 every 21 days that was well tolerated for the first 2 cycles. Twelve hours after the third cycle the patient was admitted to hospital for dyspnea and palpitations. An ECG showed the presence of AF with rapid ventricular rhythm. The patient was in poor clinical condition; the cardiologists suggested treatment with digitalis glycoside that was started immediately. A stable sinus rhythm could not be achieved. The patient was discharged 5 days later in good hemodynamic control with compensated AF. Chemotherapy was definitely stopped.

Discussion

AF is a frequent arrhythmia occurring mainly in elderly people, associated with symptoms of dyspnea, palpitations and chest discomfort. It is a benign disease, but may be potentially fatal due to the risk of pulmonary or systemic embolism and cardiac failure. Three subtypes of AF are recognized: non-sustained, paroxysmal and chronic. Paroxysmal AF represents 25% of cases and can evolve to the chronic form in 12% of patients by 2 years [10]. It is associated with dyspnea, palpitations and cardiac failure. Both paroxysmal and chronic AF can be complicated by thromboembolic disease and stroke (5-fold increase for non-rheumatic AF) [7]. We report two cases of gemcitabine cardiac toxicity only rarely described previously. In the first case, AF resolved with anti-arrythmic therapy and had a very good clinical outcome. In the second case, the patient could be treated only with digitalis glycoside, less effective than amiodarone as an anti-arrhythmic drug, and AF persisted indefinitely 3 months after the episode. Both cases occurred less than 24 h from gemcitabine administration, and we suppose a strict correlation between the drug infusion and the arrhythmia. Gemcitabine metabolism leads to the formation of a deaminated compound [2′,2′-difluorodeoxyuridine (dFdU)] characterized by a half-life of approximately 18–24 h, i.e. longer than the gemcitabine half-life, the latter being rapidly cleared from plasma [8]. The causative role of dFdU in precipitating paroxysmal AF is strongly supported by the kinetics of the compound, and by the absence of other predisposing factors [4] such as hypertensive crisis, acute thromboembolism, electrolytic imbalance, salt and water retention, and impaired neurologic and endocrine functions [10]. To our knowledge only one study reported AF as a consequence of gemcitabine administration. In that case, the temporal relationship between the drug infusion and occurrence of arrhythmia was similar to our cases. About 12–24 h is supposed to be the risk interval for developing AF. Even in the absence of known risk factors AF should be immediately suspected in the case of breathlessness, palpitations or chest discomfort. Our second patient had asymptomatic pulmonary thromboembolism that resolved with LWMH before starting chemotherapy, so we believe that this should not be considered a risk factor for that patient. The occurrence of AF was reported in two more studies as a consequence of gemcitabine-based chemotherapy. It is noteworthy that most of the patients

in these studies were suffering from considerable cardiac comorbidities [11,12].

Other chemotherapeutic agents (anthracyclines, taxanes, 5-fluorouracil) can determine cardiac toxicity and be responsible for arrhythmias [13], but in these cases the most frequently reported toxicities are cardiac failure or ischemic cardiomyopathy [1].

It is not clear how chemotherapy can induce cardiac damage. Cisplatin, etoposide [14] and 5-fluorouracil [15] infusion can sometimes be related to the occurrence of AF, whereas dexamethasone, administered to our patients 30 min before gemcitabine, is not associated with this arrhythmia.

Chemotherapeutic agents can interfere with sinoatrial conduction, but the pathogenetic mechanism has yet to be determined. Either bradycardic or tachycardic activity, mediated by vagal hyperstimulation or sympathetic hypertone, not demonstrated in our patients, can lead to supraventricular arrhythmias. Even a sudden change in potassium or magnesium plasma concentration is frequently implicated in the pathogenesis of AF, but both our patients had normal electrolyte levels. We suppose that gemcitabine and specifically its deaminated metabolite dFdU could have a direct effect on the myocardial cell and the conduction system, evoking an overstimulation of the sinoatrial node [16] or a failure in the mechanisms of supraventricular conduction, but further studies are required to clarify this issue [1]. After treatment with gemcitabine-based chemotherapy, the occurrence of AF must be kept in mind every time the patient refers chest discomfort, and an ECG must be promptly performed in order to ascertain and eventually treat the arrhythmia. Patients suffering from cardiac comorbidities, such as ischemic heart disease or hypertension, should be carefully monitored.

References

1 Santini D, Tonini G, Abbate A, Di Cosimo S, Gravante G, Vincenti B, *et al.* Gemcitabine-induced atrial fibrillation: a hitherto unreported manifestation of drug toxicity. *Ann Oncol* 2000; **11**:479–481.

2 Plunkett W, Huang P, Xu YZ, Heinemann V, Grunewald R, Ghandi V. Gemcitabine: metabolism, mechanisms of action and self-potentiation. *Semin Oncol* 1995; **32**:3–10.

3 Plunkett W, Huang P, Gandhi V. Preclinical characteristics of gemcitabine. *Anticancer Drugs* 1995; **6**(**Suppl 6**):7–13.

4 Gianni L, Sessa C, Capri G, Grasselli G, Bianchi G, Vitali G. Farmaci chemioterapici. In: Bonadonna G, Robustelli Della Cuna G, Valagussa P (editors): *Medicina oncologica* 7. Milan: Masson; 2003. pp. 631–632.

5 Abbruzzese JL, Grunewald R, Weeks EA, Gravel D, Adams T, Nowak B, *et al.* A phase I clinical, plasma and cellular pharmacology study of gemcitabine. *J Clin Oncol* 1991; **9**:491–498.

6 Davidoff S, Shah RD, Arunabh T. Gemcitabine-induced respiratory failure associated with elevated erythrocyte sedimentation rate (ESR). *Respir Med* 2005. (Epub ahead of print)

7 Pavlakis N, Bell DR, Millward MJ, Levi JA. Fatal pulmonary toxicity resulting from treatment with gemcitabine. *Cancer* 1997; **80**:286–291.

8 Storniolo AM, Allerheiligen SR, Pearche HL. Preclinical, pharmacologic, and phase I studies of gemcitabine. *Semin Oncol* 1997; **24** (**Suppl 2**): S7-2–S7-7.

9 Machover D, Goldschmit E, Chollet P, Metzger G, Zittoun J, Marquet J, *et al.* Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol* 1985; **4**:685–696.

10 Narayan SM, Cain ME, Smith JM. Atrial fibrillation [seminar]. *Lancet* 1997; **350**:943–950.

11 Gridelli C, Cigolari S, Gallo C, Manzione L, Ianniello GP, Frontini L, *et al.* Activity and toxicity of gemcitabine and gemcitabine + vinorelbine in advanced non-small-cell lung cancer elderly patients. Phase II data from the Multicenter Italian Lung Cancer in the Elderly Study (MILES) randomized trial. *Lung Cancer* 2001; **31**:277–284.

12 Illiano A, Barletta E, De Marino V, Battiloro C, Barzelloni M, Scognamiglio F, *et al.* New triplet chemotherapy combination with carboplatin, paclitaxel and gemcitabine plus amifostine support in advanced non small cell lung cancer: a phase II study. *Anticancer Res* 2000; **20**:3999–4003.

13 Wood AJJ. Adverse reactions to drug. In: Fauci AS, Braunwald E, Kasper DL, Hanser JL, Longo DL, Jameson JL (editors): *Harrison's principles of internal medicine*, 14th edn. New York: McGraw-Hill; 1998; pp. 422–430.

14 Petrella V, Alciato P, Cantone PA, Fico D, Gagliardini R. High-frequency supraventricular arrhythmias induced by a cisplatin-etoposide combination. *Minerva Med* 1989; **80**:305–307.

15 Aziz Sa, Tramboo NA, Mohi-ud-Din K, Iqbal K, Jalal S, Ahmad M. Supraventricular arrhythmias: a complication of 5-fluorouracil therapy. *Clin Oncol (R Coll Radiol)* 1998; **10**:377–378.

16 Williams GH, Lilly LS, Seely EW. The heart in endocrine and nutrional disorders. In: Braunwald E (editor): *Heart disease*, 5th edn. Philadelphia: Saunders; 1995. pp. 1901–1903.