Thrombotic microangiopathy and digital necrosis: two unrecognized toxicities of gemcitabine

L. Vénat-Bouvet[a], K. Ly[b], J. C. Szelag[c], J. Martin[a], J. L. Labourey[a], D. Genet[a] and N. Tubiana-Mathieu[a]

We report one new case of hemolytic–uremic syndrome (HUS) and one case of digital necrosis after treatment with gemcitabine (Gemzar). Case 1, a 34-year-old man, was given first-line metastatic treatment with gemcitabine for a adenocarcinoma of the pancreas. After a cumulative dose of 10 000 mg/m^2 gemcitabine, the onset of subacute renal failure associated with hemolytic anemia of mechanical origin was observed. A diagnosis of probable gemcitabine-induced thrombotic microangiopathy was arrived at. Symptoms resolved after stopping the chemotherapy, in spite of the progression of the disease. Case 2, a 61-year-old man, was administered a combination of gemcitabine and a platinum salt as first-line metastatic treatment for carcinoma of the bladder urothelium. Following a cumulative dose of 10 000 mg/m^2 of gemcitabine, the patient suffered from bilateral peripheral vascular disease of somewhat acute onset with hemorrhagic lesions of the finger pads that became necrotic. The work-up was negative and a causal relationship was attributed to gemcitabine. The patient made good progress when given an i.v. infusion of Ilomedine (iloprost trometamol) and chemotherapy was withdrawn. We conclude that gemcitabine must be added to the list of drugs that cause HUS and necrotizing vasculitis. ***Anti-Cancer Drugs*** **14:829–832 © 2003 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2003, **14**:829–832

Keywords: digital necrosis, gemcitabine, hemolytic–uremic syndrome, thrombotic microangiopathy

[a]Service Oncologie Médicale, [b]Service Médecine Interne and [c]Service de Néphrologie, CHU Dupuytren, Limoges, France.

Correspondence to L. Vénat-Bouvet, Service Oncologie Médicale, CHU Dupuytren, 2 Avenue Martin Luther King, 87042 Limoges Cedex, France. Tel: +33 555056100; fax: +33 555056183; e-mail: laurence.venat@wanadoo.fr

Received 27 May 2003 **Revised form accepted** 3 September 2003

Introduction

Gemcitabine (Gemzar) is a pyrimidine nucleoside and an analog of cytarabine employed in the treatment of carcinoma of the lung, pancreas and urothelium. This new anticancer agent was granted an American Marketing Authorization in 1987 and a French Marketing Authorization in 1996; it is usually well tolerated. The major side-effects reported are myelotoxicity, skin rashes, 'flu-like-syndrome' (influenza-like syndrome, asthenia and malaise), hematuria and moderate proteinuria [1]. More recently, cases of thrombotic microangiopathy (TMA) [2–5] and two cases of necrotizing vasculitis [6,7] have been described. We report on one new case of hemolytic–uremic system (HUS) and one case of digital necrosis.

Case 1

A man, aged 34 years, was given first-line metastatic treatment with gemcitabine (weekly schedule of 1000 mg/m^2 for 7 weeks, then for 3 out of 4 weeks) for a well-differentiated progressive adenocarcinoma of the pancreas with an elevation in Ca19-9 and skeletal metastases occurring 19 months after the end of post-operative radiotherapy and chemotherapy. After a cumulative dose of 10 000 mg/m^2 of gemcitabine, the onset of subacute renal failure was noted with an elevation in creatinine to 180 μmol/l associated with proteinuria at 0.57 g/24 h, hemolytic anemia with hemoglobin at 8.5 g/dl, a sharp fall in haptoglobin, raised LDH at 835 U and positive schistocytes. White blood cell count was 5.5 $\times$ 10^9/l with neutrophils at 3 $\times$ 10^9/l and the platelet count 150 $\times$ 10^9/l. Hemostasis was normal. Clinically, a change was noted in the patient's general condition, with edema of the lower limbs and eyelids, hypertension, and bilateral pleural effusion. An ultrasound scan of the kidneys was normal. Symptoms became worse as gemcitabine therapy was continued up to a cumulative dose of 14 000 mg/m^2, and then rapidly improved when chemotherapy was discontinued and symptomatic treatment was administered. The diagnosis arrived at was that of probable thrombotic microangiopathy induced by gemcitabine. The patient is currently untreated, with a progressive disease in terms of clinical signs and markers. The signs of hemolysis, proteinuria and schistocytosis have receded, and the creatinine concentration is stable at 170 μmol/l.

Case 2

A man, aged 61 years, was given first-line metastatic treatment with a combination of gemcitabine and a platinum salt (Gemzar 1250 mg/m^2 days 1 and 8, and cisplatin 100 mg/m^2 at day 1 with day 1 = day 21) for

0959-4973 DOI: 10.1097/01.cad.0000098998.92896.01

urothelial carcinoma of the bladder spreading to the pelvic lymph nodes and skin less than 1 year after the end of conservative management with concomitant radiotherapy and chemotherapy. The patient received four cycles of chemotherapy, i.e. a cumulative dose of gemcitabine 10 000 mg/m^2, which produced a partial response in the skin and lymph nodes. Three days after the end of the third cycle, the patient suffered from bilateral peripheral vascular disease of somewhat acute onset consisting of painful paresthesia, acrocyanosis and hemorrhagic lesions of the finger pads which subsequently became necrotic at the tip of the index finger and the middle finger of both hands, and showed no improvement after i.v. infusions of buflomedil (Fonzylane) (Fig. 1). Apart from active smoking (70 package-years), the patient had no notable history of cardiovascular or thromboembolic disorders or diabetes. Capillaroscopy revealed numerous hemorrhagic lesions. Arterial Doppler ultrasound studies of the four extremities were normal. Immunologic tests revealed positive antinuclear factors at 1/10 240 with negative anti-double-stranded DNA without a low serum complement level. Tests for antihistone, antiphosphatidyl-ethanolamine, anticardiolipin, anti-β_2-glycoprotein and anti-ENA antibodies, and for cryoglobulin, cryofibrinogen and schistocytes were negative. Renal function was normal, there were no signs of hemolysis and hemostasis was normal.

The symptoms were attributed to gemcitabine, given the absence of any convincing argument in favor of induced lupus or another connective tissue disease. Symptoms resolved following i.v. infusion of Ilomedine and the cessation of chemotherapy; skin signs completely disappeared within 15 days, although an incomplete Raynaud's phenomenum persisted and was probably attributable to cisplatin. After six cycles of a new schedule of chemotherapy, diffuse progression in the lymph node and skin metastases occurred, outstripping therapeutic resources and leading to the death of the patient.

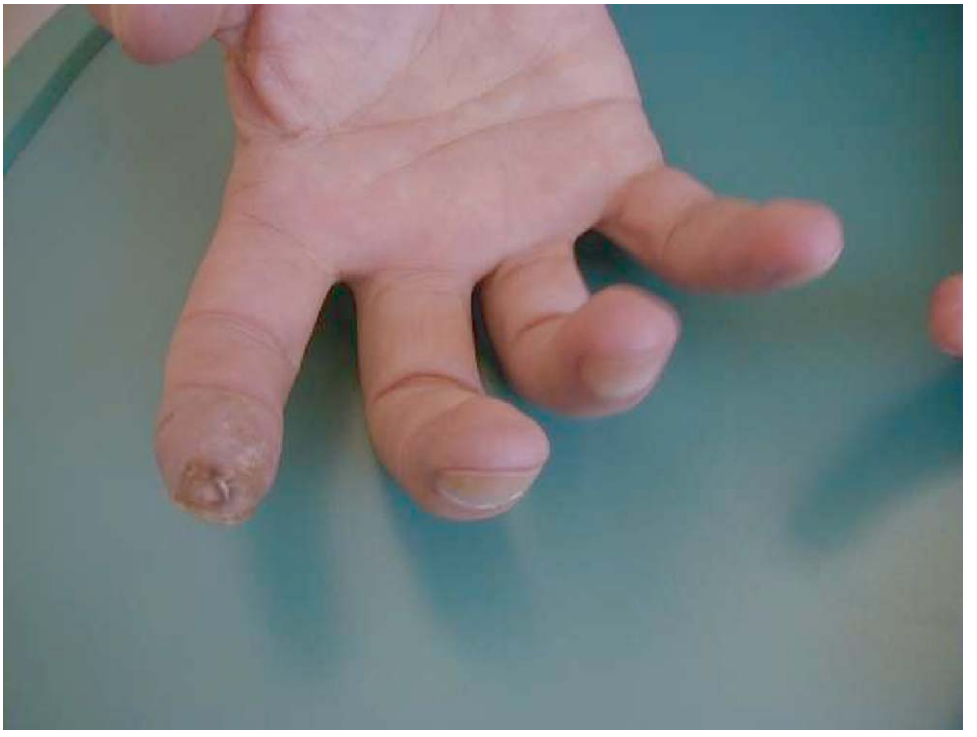
Discussion

Due to physiopathologic similarities, TMAs include HUS with predominant renal involvement and thrombotic thrombocytopenic purpura (TTP) or Moschcowitz's disease with neurological involvement [8]. HUS is characterized by acute or subacute renal failure of varying severity associated with non-immunologic mechanical hemolytic anemia: drop in haptoglobin, reticulocytosis, elevation in LDH, Coombs' test negative, schistocytes present and peripheral thrombocytopenia, even disseminated intravascular coagulation. All of these criteria were present in our patient, except for thrombocytopenia, which is not consistently present. From the physiopathologic point of view, thrombi form in the lumen of glomerular capillaries, accompanied by the adhesion of neutrophils, causing fragmentation of the erythrocytes and renal failure [2]. Our patient had none of the acknowledged causes of HUS (infectious diseases, systemic diseases, treatment with another anticancer agent, etc.). It is difficult to make an accurate evaluation of the incidence of TMAs associated with cancers. In one prospective study, Lohrmann *et al.* assessed the incidence of TMAs in patients with metastatic carcinomas at between 5 and 6% [9]. The histologic type most frequently associated with TMA is adenocarcinoma (88%), generally affecting the stomach, more rarely the lung or breast. The cancer is usually advanced and metastatic, and includes invasion of bone marrow in 60% of cases. Our patient had a progressive disease and skeletal metastases located in the pelvis without documented bone marrow invasion. Even if there are overlaps, TMAs of paraneoplastic origin look like TTP with definite thrombocytopenia and few renal signs; whereas TMAs secondary to therapy bear a closer resemblance to HUS with major renal signs, as in the case reported [10].

Mitomycin C gives rise to hemolytic anemia, HUS in 5–10% of patients undergoing treatment. Its toxicity becomes apparent after a cumulative dose exceeding 60 mg, with a mean onset of 11.5 months after the start of treatment [11]. The mortality rate is very high. TMAs induced by gemcitabine have been identified more recently. They usually involve advanced adenocarcinomas of the pancreas for which gemcitabine is the reference treatment [2–5,12]. It is difficult to explain the mechanisms called into play in chemotherapy-induced TMAs. In spite of the small number of cases described in the literature, it seems that the prognosis is favorable for gemcitabine-induced HUS and it rarely gives rise to irreversible renal failure. Treatment depends on the severity of the clinical feature. Symptomatic treatment may be all that is needed, as in the case of our patient, although repeated plasmapheresis may be necessary.

Gemcitabine is a nucleoside analog with a structure similar to that of cytarabine. This other antimetabolite is used in treating acute leukaemia and has been implicated in the onset of necrotizing vasculitis in two patients treated for acute non-lymphoblastic leukemia [13]. In both cases, skin biopsies documented necrotizing vasculitis devoid of leukemic cells. Banach *et al.* reported one case of necrotizing vasculitis affecting the extremities in a patient treated with gemcitabine for non-small cell lung carcinoma [6]. The antinuclear factor level was high (1/1280), as in the case of our patient, suggesting a physiopathologic mechanism of immunologic origin. An examination of skin lesions of drug-induced vasculitis using a direct immunofluorescence method suggests a mechanism involving the deposition of immune complexes [14]. The immunoallergic effects of gemcitabine

Fig. 1



Right second digit demonstrating distal necrosis.

are well recognized. Influenza-like syndrome is noted in 20% of cases with myalgia and rarely severe pulmonary toxicity with interstitial lung disease [15,16]. However, the physiopathologic mechanism involved is not understood. Voorburg *et al.* reported one other case of vasculitis due to gemcitabine with vascular purpura of the four limbs, and clinical and laboratory muscle involvement: this was confirmed by muscle biopsy which documented hypersensitivity vasculitis with fibrinoid necrosis [7]. Moreover, various cytotoxic drugs are implicated in the onset of Raynaud's phenomenum, such as bleomycin, vinblastine and, especially, cisplatin. Persistent distal ischemia may lead to ulceration or gangrene. Due to the hemorrhagic nature of our patient's lesions, a skin biopsy was not performed and we are therefore unable to actually attribute the digital necrotic lesions to gemcitabine or cisplatin. The treatment of drug-induced vasculitis usually consists of stopping the drug involved and using corticosteroids or even colchicine for the most severe cases [17,18]. In the case of our patient, we chose to use an i.v. vasodilator since the picture was predominantly that of digital ischemia.

Conclusion

Given the delayed onset of TMA during treatment with gemcitabine, careful monitoring of laboratory parameters and more frequent monitoring of renal function and reticulocyte and haptoglobin levels should be carried out after a cumulative dose that has yet to be determined. In addition, the occurrence of digital necrosis during treatment with a combination of cisplatin and Gemzar raises the problem of an overlap in potential adverse effects. The prevalence of such adverse reactions is doubtless underestimated since the diagnosis may be misjudged, the life expectancy of patients is short and reporting is inadequate. The withdrawal of gemcitabine was recommended in both of the cases reported.

References

1 Green MR. Gemcitabine safety overview. *Semin Oncol* 1996; **23(suppl 10)**:S32–S35.
2 Flombaum CD, Mouradian JA, Casper ES, Erlandson RA, Benedetti F. Thrombotic microangiopathy as a complication of long term therapy with gemcitabine. *Am J Kidney Dis* 1999; **33**:555–562.
3 Lhotta K, Kuhr T, Rumpelt HJ, Woll E, Thaler J, Konig P. Thrombotic microangiopathy with renal failure in two patients undergoing gemcitabine chemotherapy. *Am J Nephrol* 1999; **19**:590–593.
4 Dilhuydy MS, Delclaux C, Pariente A, De Precigout V, Aparicio M. Syndrome hémolytique et urémique compliquant un traitement au long cours par gemcitabine. A propos d'un cas, revue de la littérature. *Rev Med Interne* 2002; **23**:189–192.
5 Teixeira L, Debourdeau P, Zammit C, Estival JL, Pavic M, Colle B. Thrombotic microangiopathy due à la gemcitabine. *Presse Med* 2002; **31**:740–742.
6 Banach MJ, Williams GA. Purtscher retinopathy and necrotizing vasculitis with gemcitabine therapy. *Arch Opthalmol* 2000; **118**:726–727.
7 Voorburg AMCJ, van Beek FT, Slee PHThJ, Seldenrijk CA, Schramel FMNH. Vasculitis due to gemcitabine. *Lung Cancer* 2002; **36**:203–205.

8 Moake JL. Haemolytic uraemic syndrome: basic science. *Lancet* 1994; **343**:393–397.
9 Lorhman HP, Adam W, Heymer B, Kubanek B. Microangiopathic haemolytic anemia in metastatic carcinoma: report of eight cases. *Ann Intern Med* 1973; **79**:368–375.
10 Murgo A. Thrombotic microangiopathy in the cancer patient including those induced by chemotherapeutic agents. *Semin Hematol* 1987; **24**:161–177.
11 Schiebe ME, Hoffmann W, Belka C, Bamberg M. Mitomycine C-related hemolytic syndrome in cancer patients. *Anticancer Drugs* 1998; **9**: 433–435.
12 Abratt RP, Bezwoda WR, Falkson G, Goedhals L, Hacking D, Rugg TA. Efficacy and safety profile of gemcitabine in non small cell cancer: a phase II study. *J Clin Oncol* 1994; **12**:1535–1540.
13 Ahmed I, Chen KR, Nakayama H, Gibson LE. Cytosine arabinoside-induced vasculitis. *Mayo Clinic Proc* 1998; **73**:239–242.
14 Claudy A. Pathogenesis of leucocytoclastic vasculitis. *Eur J Dermatol* 1998; **8**:75–79.
15 Marruchella A, Fiorenzano G, Merizzi A, Rossi G, Chiodera PL. Diffuse alveolar damage in a patient treated with gemcitabine. *Eur Respir J* 1998; **11**:504–506.
16 Pavlakis N, Bell DR, Millward MJ, Levi JA. Fatal pulmonary toxicity resulting from treatment with gemcitabine. *Cancer* 1997; **80**:286–291.
17 Sullivan TP, King LE, Boyd AS. Colchicine in dermatology. *J Am Acad Dermatolol* 1998; **39**:993–999.
18 Callen JP, Ekenstam FE. Cutaneous leucocytoclastic vasculitis: clinical experience in 44 patients. *South Med J* 1987; **80**:848–851.