Haemolytic uraemic syndrome culminating in terminal renal failure after gemcitabine treatment: case report and literature survey

M.P. Graas, G. Demolin, G. Houbiers, P. Gomez, C. Focan

We report the case of a woman treated for an ovarian cancer who ultimately developed terminal renal failure in the frame of a haemolytic uraemic syndrome induced by prolonged gemcitabine therapy. This case illustrates the need of a systematic screening for haemolytic uraemic syndrome in patients receiving protracted gemcitabine for over three months.
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Patient history

A 46-year old female patient was diagnosed on January 31st 2003, suffering from a staged IIIB serous poorly differentiated ovarian cancer. Therapeutic sequence included an initial hystero-ovariectomy and omentectomy, a further induction standard chemotherapy (with paclitaxel and carboplatin) followed by an optimal debulking surgery and consolidation chemotherapy. At this point, the patient was considered to be in complete response (CR). Unfortunately abdominal recurrences had to be treated (successfully) in 2005 (paclitaxel and carboplatin rechallenged), 2006 (caelyx), and 2007 (again paclitaxel and carboplatin). In March 2008, the patient was once more considered to be in CR.

Unfortunately in October of the same year, a tumour regrowth was observed. After failure of a short topotecan treatment, a choledoque compression by adenopathies imposed the placement of an endo-prothesis on December 2nd 2008. A first course associating cisplatin and gemcitabin was then administered. After this course, a transient renal insufficiency with serum creatinin up to 48 mg/l imposed to withdraw cisplatin treatment while gemcitabin was pursued as monotherapy. The disease seemingly stabilised, gemcitabin was stopped on March 31st 2009. An abdominal recurrence imposed the reset of a chemotherapy with gemcitabin alone from September 29th to December 2009 and further combined with paclitaxel from December 2009 up to May 18th 2010.

At this time, any therapy was stopped because of the occurrence of a severe renal insufficiency with serum creatinin rate up to 77 mg/l, proteinuria (0.22 g/l) and microscopic haematuria (18-65 elements/mm^3). The patient presented diffuse fluid retention and some arterial hypertension. A haemolytic anaemia was evidenced (Hb 8.5 g/dl with increased reticulocytes, presence of numerous schizocytes (*Figure 1*), haptoglobin down to 0 g/l and elevated LDH (1055 U/l). Platelets were lowered with some circulating macro-elements (*Figure 1*), fibrinogen was low and D-dimeres positive. At this time, the diagnosis of haemolytic uraemic syndrome (HUS) was acquired.

Authors: M.P. Graas MD[1], G. Demolin MD[1,2], G. Houbiers MD[1,2], P. Gomez MD[3], C. Focan MD PhD[1]. [1]Department of Oncology, Clinique Saint-Joseph, Liege, Belgium, [2]Department of Gastro-Enterology, Clinique Saint-Joseph, Liege, Belgium, [3]Department of Nuclear Medicine, Clinique Saint-Joseph, Liege, Belgium.

Please send all correspondence to: C. Focan MD PhD, Department of Oncology, Clinique Saint-Joseph, Rue de Hesbaye 75, 4000 Liege, Belgium, tel: +32 4 224 89 90, e-mail address: christian.focan@chc.be.

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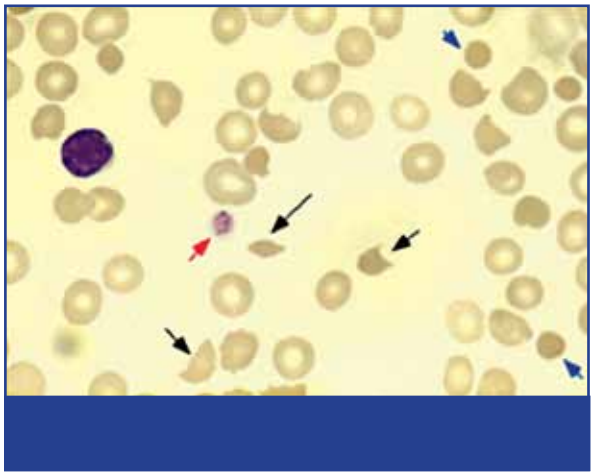

Figure 1. Peripheral blood imprint: the presence of helmet red blood cells (schizocytes) sometimes fragmented (black arrows), microspherocytes (blue arrows); a macro-platelet (red arrow) suggest thrombopaenia due to active destruction.

The patient was treated symptomatically with repeated haemodialyses, transfusions and anti-hypertensive drugs; no plasmatic exchange nor fresh frozen plasma infusion was performed. The renal failure did not disappear and the patient underwent iterative tri-weekly renal dialyses. From the tumoural point of view, if the PET-scan performed on June 1st 2010 was rather optimistic (metabolic CR and radiological partial response - *Figure 2*), the one performed on September 28th 2010 confirmed a diffuse regrowth (*Figure 2*). The $Ca125^{tumor}$ marker rose up to 4011 U/ml and the patient died on October 2nd 2010.

She had received 34 infusions of gemcitabin to a total of 49.06 g (29.02 g/m^2) over a cumulative period of fourteen months.

Discussion

The development of a HUS after protracted treatment with gemcitabin has been previously reported in the literature.[1-5] Gemcitabin, like other cytostatics such as mitomycin C, bleomycin or cisplatin seems able to engender cumulative toxicity at the level of capillaries endothelium culminating in a typical thrombotic micro-angiopathy.[1,3,6,7]

As described previously, this complication may be observed after a treatment with gemcitabin of significant duration (≥4 months). An alteration of renal function is frequently the first symptom, but this was not the case in our patient although she had had previous transient renal impaired function related to cisplatin use. The progressive increase of serum creatinin may be seldom ignored by oncologists due to the fact that initial creatinin may be low in those patients suffering frequently from muscular cachexia. Thus, in terms of screening, it would be

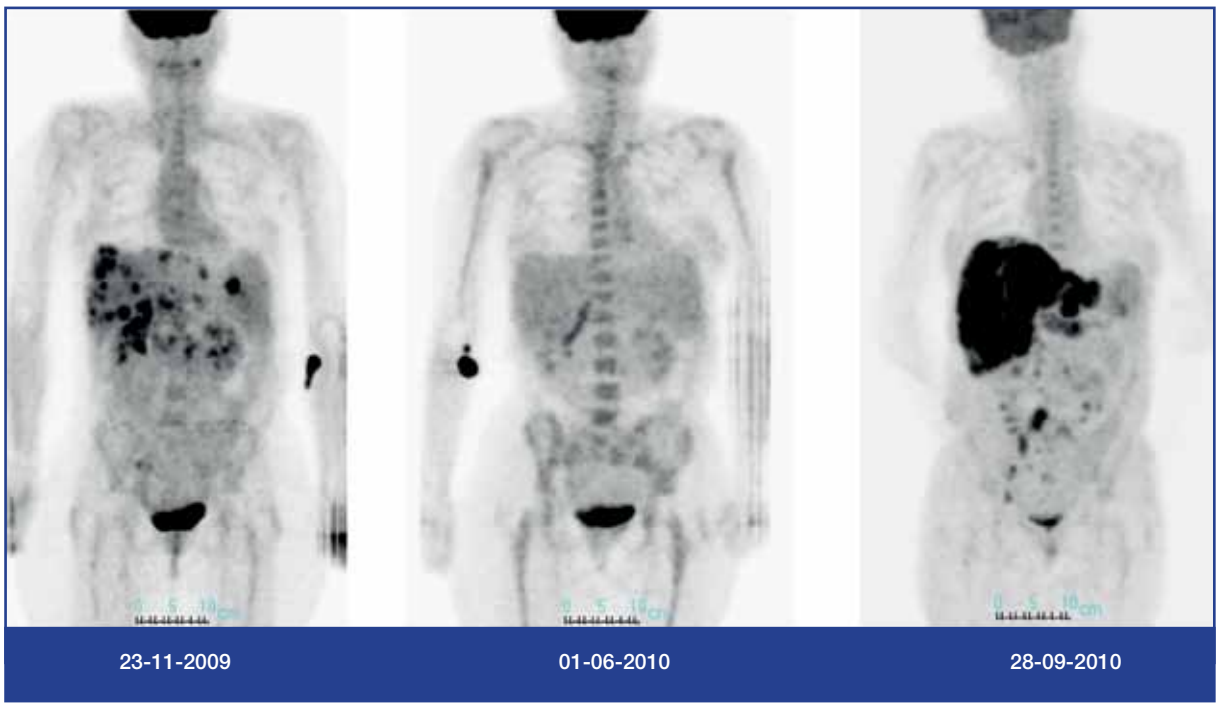

Figure 2. Evolution of PET-scans in our patient. Metabolical complete response on June 1st 2010 and further rapid tumoural regrowth.

Key messages for clinical practice

1. A screening for haemolytic uraemic syndrome (HUS) including clinical and biological elements should be performed in patients who have received gemcitabine for over three months.
2. The frequency of HUS complicating a prolonged treatment with gemcitabine may be as high as 5.5%.
3. The treatment of a HUS after gemcitabine is essentially symptomatic.

more accurate to follow creatinin clearance rather than simply its plasmatic titration.[4,6] We thus suggest to oncologists a systematic depistage for HUS in their patients receiving gemcitabin over three months. This screening would include clinical (increased blood pressure; fluid retention signs) and biological elements (anaemia with low haptoglobin levels, presence of schizocytes, decrease of creatinin clearance and appearance of proteinuria and haematuria). The frequency of HUS after gemcitabin seems to be rare, but yet significant: it may oscillate between 1.4 to 3% but up to ≥5% in those patients treated over six months.[1-5]

The spontaneous resolution of HUS after gemcitabin withdrawal is not universal and observed only between 30 to 70% cases.[1-5,8]

Due to the specific pathogenesis, cumulative endothelial toxicity, therapy with plasmatic exchanges or fresh frozen plasma infusions are not justified.[5,8,9] However, these may be useful in thrombopaenic thrombotic syndrome (Mosckowitz) which is due to the presence of autoimmune processes and inhibitor of ADAMTS-13 protein.[8]

Thus, the treatment of HUS after chemotherapy remains essentially symptomatic. Any reintroduction of the incriminated molecule must be avoided as the rapid recurrence of the syndrome is predictable.[2-4,6,8]

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