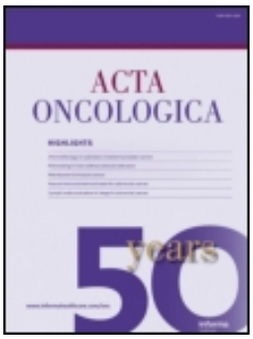

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LETTER TO THE EDITOR

Haemolytic uremic syndrome and gemcitabine: Jaundice is not always progression in cholangiocarcinoma

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Haemolytic uremic syndrome (HUS) is a rare disorder combining renal failure, microangiopathic haemolytic anaemia and thrombocytopenia. HUS has been described following the administration of multiple chemotherapy agents.

Gemcitabine is a nucleosidic analogue which is indicated in biliary, pancreatic, non-small cell lung, urothelial and ovarian cancer. In the literature, HUS has been described in patients receiving gemcitabine.

We report here two cases of patients with cholangiocarcinoma who developed HUS after gemcitabine and oxaliplatin administration.

Case reports

Patient 1

A 52-year-old man was diagnosed with metastatic cholangiocarcinoma. Treatment was offered with GEMOX (gemcitabine 1000 mg/m² on Day 1 and oxaliplatin 100 mg/m² on Day 2, given every two weeks) for six months from September 2009 to February 2010, followed by maintenance with gemcitabine monotherapy for four months, when GEMOX was restarted in June 2010 due to progressive disease.

At cycle six (after a total of 16 cycles of gemcitabine and oxaliplatin), he presented a urine coloration interpreted as haematuria immediately following oxaliplatin infusion. The renal function was normal.

At cycle seven, 30 minutes after oxaliplatin infusion, he presented shivers and fever, lumbar pain, hypertension and dark coloration of urine. Blood tests revealed acute haemolysis (anaemia 9.4 g/dl vs. 11.6 g/dl the day before, thrombocytopenia 53 G/l vs. 161 G/l the day before, LDH 1370 UI/l, total bilirubin at 62 µmol/l) and acute renal insufficiency (creatinine clearance: 31 ml/min vs. 75 ml/min the day before).

He was transferred to nephrology with the diagnosis of HUS. He received six plasma exchanges. The evolution was favourable. Positivity for antibodies directed against the complement fraction C3 was found. He then progressed in January 2011. He received best supportive care due to rapid clinical deterioration.

Patient 2

A 54-year-old man was diagnosed in 2008 with cholangiocarcinoma, and was treated with surgery. Chemotherapy with GEMOX was proposed for recurrence in September 2009. After response to treatment, "chemotherapy holidays" were offered, which lasted three months. Progressive disease was evident in October 2010, and GEMOX was then restarted.

After a total of 13 cycles of GEMOX, during the perfusion of oxaliplatin, he presented a cutaneous rash, muscular pains followed by jaundice and dark urine. Blood tests revealed haemolysis (anaemia 7.5 g/dl, thrombocytopenia 94 G/l, LDH 836 UI/l, total bilirubin 239 µmol/l) and acute renal insufficiency. HUS was diagnosed, and anti-complement fraction C3 antibodies were also found. The evolution was spontaneously favourable. He was given a therapeutic break until February 2011. Due to progression, chemotherapy with 5-FU and cisplatinum was restarted (without recurrence of HUS) but the patient finally died in July 2011.

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Discussion

The efficacy of chemotherapy in metastatic cholangiocarcinoma has only recently been proven, with the results of the ABC-2 trial [1]. This trial showed improvement in overall survival for the cisplatin-gemcitabine combination over the gemcitabine monotherapy. The combination of oxaliplatin to gemcitabine is an alternative to cisplatin-gemcitabine commonly used in France for the treatment of cholangiocarcinoma [2].

Gemcitabine is considered to have a favourable toxicity profile, and is often used in the frail population [3]. However, gemcitabine can be responsible for atypical HUS. The incidence of such an event is thought to be low (0.33–0.015%), but could be underestimated due to underdiagnosis [4]. HUS commonly occurred after multiple administrations of gemcitabine, as in the cases presented here.

Pathogenesis of atypical HUS involved dysregulation of complement proteins, particularly ADAMTS13, the von Willebrand factor cleaving protease [5]. HUS has already been linked to auto-antibodies directed against complement proteins, as in our two cases [6]. HUS could have unfavourable evolution, with death, chronic renal insufficiency and chronic cytopenia. Optimal treatment is unknown, plasma exchanges are proposed but their efficiency is unclear [7].

The cases presented here have the particularity that symptoms appeared immediately after the oxaliplatin infusion on Day 2 of the GEMOX regimen. Only one report of HUS after oxaliplatin (as part of a Folfox regimen) has been published [8]. Oxaliplatin has been more often linked to autoimmune thrombopenia [9]. We thought that gemcitabine was the drug responsible for the event in our patients. However, there is a possibility that oxaliplatin enhanced gemcitabine toxicities, as the two drugs have synergistic effects on tumoural cells [10].

These two cases illustrate the need to critically evaluate symptoms during cancer treatment. The dark coloration of urine and the clinical jaundice presented by the patients could have easily been interpreted as cholestasis in these patients with cholangiocarcinoma, and viewed as signs of progression.

In conclusion, HUS is a rare but clinically relevant event during gemcitabine plus oxaliplatine treatment. It should be known and recognised by oncologists in order to offer optimal management.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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