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Clinical report

Severe hemolytic uremic syndrome in an advanced ovarian cancer patient treated with carboplatin and gemcitabine

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Hemolytic uremic syndrome (HUS) is a rare clinical and biological entity. HUS has been reported after several anticancer chemotherapies and most often after mitomycin C-based chemotherapy regimens. Little information is available concerning the occurrence and outcome of this syndrome after administration of more recent chemotherapeutic agents. We present a case of HUS in an advanced ovarian cancer patient treated with carboplatin and gemcitabine, and described its favorable outcome after chemotherapy interruption and supportive care with a 1 year follow-up. [© 1999 Lippincott Williams & Wilkins.]

Key words: Advanced ovarian cancer, carboplatin, gemcitabine, hemolytic uremic syndrome.

Introduction

Hemolytic uremic syndrome (HUS) is an acquired syndrome, characterized by the association of microangiopathic hemolytic anemia, acute renal failure and thrombocytopenia, in the absence of disseminated intra-vascular coagulation. Two different pictures have been described: (i) an acute form, with severe hemolysis, thrombocytopenia and a rapidly progressive renal failure, and (ii) a subacute and most often insidious form, with mild or no thrombocytopenia and slowly progressive renal failure.[1] The clinical syndrome combines peripheral edema, hypertension, eventually leading to an adult respiratory distress syndrome (ARDS), and a non-cardiologic pulmonary edema. Cancer and microangiopathic hemolytic anemia were first reported to be associated by Brain *et al.*[2] This syndrome appears in 2–10% of cancer patients most often treated with mitomycin C, but is also reported with other DNA-damaging agents such as bleomycin or cisplatin.[3–5]

We report HUS in an advanced ovarian cancer patient treated with gemcitabine and carboplatin.

Case report

A 50-year-old Caucasian female with advanced bilateral ovarian carcinoma was treated with gemcitabine and carboplatin. Previous therapies included initial debulking surgery at diagnosis in April 1995, followed from May 95 to May 97 by three different chemotherapy regimens (cyclophosphamide+cisplatin+epirubicin, taxol+carboplatin and topotecan). She developed a paraneoplasic dermatomyositis while she was treated with topotecan. In July 1997, she received gemcitabine (1 g/m^2, on day 1, 8 and 15 every 28 days) combined with carboplatin (AUC=4 every 4 weeks), at the first, fourth, fifth, sixth and seventh course. After the first cycle, the serum CA125 level decreased to a normal value, but grade 4 thrombocytopenia led to interrupt carboplatin at the second and third cycle. At this time, renal function was normal with a glomerular filtration rate (GFR) measured by the [^{51}Cr]EDTA clearance method of 110 ml/min (97% of theoretical value). The urinanalysis showed neither significant proteinuria nor microscopic hematuria. In October 1997 (fourth course of gemcitabine and carboplatin), serum creatinin was still within the normal range (70 μmol/l). At this time, the patient presented a partial tumor response of her liver metastasis. After the ninth course (February 1998) she developed progressive renal failure, accompanied with anemia and thrombocytopenia. Renal function deteriorated with a progressive increase in blood urea nitrogen (65 mg/dl) and a 20% increase per month in creatininemia, for 3 months. This subacute deterioration of renal function was followed by an acute hematological

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toxicity within 2 weeks [grade IV thrombocytopenia (22 000/mm^3), grade IV anemia (hemoglobin=9.6 g/dl on 2 March, 6.1 on 16 March) and biological evidence of hemolysis (serum lactate deshydrogenases 2467 IU/l, decreased serum haptoglobin and hematocrit=16.5%)]. The urinary analysis revealed a nephrotic range proteinuria up to 6.21 g/day.

Concomitantly, the patient developed severe hypertension (160/110 mm Hg), peripheral edema, orthopnea and pulmonary edema with respiratory distress symptoms. Renal biopsy made at the onset of the HUS showed characteristic features of thrombotic microangiopathy. Four antihypertensive drugs were required to control blood pressure [furosemide, calcium channel inhibitors, β-blockers and converting enzyme inhibitors (CEI)]. Four plasma exchanges were done. Platelets, hemoglobin and serum creatinine returned to normal baseline levels within 3 days (platelets from 26 000 to 108 000/mm^3), 3 months (hemoglobin from 6.1 to 12.1 g/dl) and 7 months (creatininemia from 205 to 99 μl/l), respectively.

Twelve months after HUS, the patient had recovered normal platelet counts, although hypertension still required the association of β-blockers, diuretics, CEI and calcium channel inhibitors; serum creatinine remained within a normal range.

Discussion

We report a case of HUS developed in an advanced ovarian cancer patient treated with gemcitabine and carboplatin. She developed HUS after the ninth course of chemotherapy. The total cumulative dose of gemcitabine and carboplatin were 42.4 g, and 1075 mg, respectively. Gemcitabine is a novel nucleoside analog. It is an antimetabolite member of the family of the pyrimidine analogs. Gemcitabine is active by inhibiting DNA synthesis and ribonucleotide reductase enzyme, and through a competition with dCTP. Gemcitabine has been found active in advanced pancreatic, ovarian, breast, small cell lung, bladder, and head and neck cancers.

The dose-limiting toxicity is leukoneutropenia, and less frequently anemia and thrombocytopenia.[6] Common toxicities are liver toxicity, with mild transaminitis, nausea and vomiting, and mild changes in renal parameters, such as proteinuria. Few cases of renal failure have been reported, of uncertain etiology.[7] Bronchospasms and other allergic reactions have also been described.[6]

Our observation shows that even if the clinical and biological presentation of HUS may be severe, almost complete recovery could be achieved with a follow-up of 12 months. Platelets, hemoglobin and serum creatinine returned to normal baseline levels within 3 days, 3 months and 7 months respectively. Chemotherapy-related HUS (C-HUS) has been well described after platinum-based chemotherapy and more recently in a patient treated with gemcitabine.[8]

In our observation, several arguments suggest a causal role of chemotherapy in the development of the hemolytic and uremic syndrome. The differential diagnosis of cancer-related HUS was possible but unlikely, since the patient had no progressive disease. The patient developed HUS while on therapy, after nine courses (24 administrations). Moreover, HUS disappeared after interruption of chemotherapy. Even if the patient developed HUS while she was treated with gemcitabine alone, we cannot exclude the role of carboplatin, which was interrupted 1 month earlier.

The first case of C-HUS, reported by Krauss *et al.*,[9] was a gastric cancer patient treated with 5-fluorouracil and mitomycin C. Most often C-HUS has been observed in gastric cancer patients, probably because it is one of the main indications of mitomycin C. Some cases were reported in leukemia patients.[10]

Between 1980 and 1985, over 100 cases of mitomycin-induced HUS were reported.[11] The risk of developing C-HUS after treatment with mitomycin C was reported to rank between 4 and 15%.

The diagnosis of C-HUS is difficult and often delayed, because anticancer agents such as mitomycin C and cisplatin can be nephrotoxic, and have hematologic toxicity to account for non-specific anemia and thrombocytopenia. The overall incidence of C-HUS is unknown. A review of 85 cases of cancer-associated HUS[12] showed some characteristics of the cancer-patients developing C-HUS; adenocarcinoma was observed in 89% of the cases (26% were gastric carcinoma), and other histologic diagnoses were epidermoid carcinoma, mesothelioma, germ cell tumor and sarcoma.

C-HUS may occur independently of the disease response to therapy. In a review of 85 patients, 30 (35%) had no clinical evidence of malignant disease, 33 had stable disease under treatment, while 22 had progressive disease, when C-HUS occurred.

The total cumulative dose of mitomycin might be more important to consider than the dose per cycle or the number of cycles. Our patient developed signs of HUS, after the ninth course, the cumulative dose was 25 g/m^2 of gemcitabine and 635 mg/m^2 of carboplatin.

Many drugs have been reported to induce HUS, especially immunosuppressive drugs, such as cyclosporin.

The etiology of HUS still remains unclear. The pathologic analysis on renal biopsy usually has

revealed concentric subintimal thickening of small arteries and arterioles with loose material that look like mucoid, and fibrin thrombi in the afferent arterioles and glomerular capillaries. No histopathological differences between C-HUS and HUS-thrombotic thrombocytopenia purpura have been reported. The observation of high levels of von Willebrand factor (more than 4 times normal values) in cancer patients developing HUS suggests that this factor might play a role in the pathogenesis of the syndrome.[13-15]

C-HUS might occur through endothelial lesions, with vascular injury and fibrin deposition followed by obstruction of renal vascular lumen and the destruction of erythrocytes and platelets.[16] Another hypothesis is that HUS is immunocomplex mediated. It is suggested by the observation of an increase in circulating immunocomplexes in some patients.

The time interval between chemotherapy-induced damage and the occurrence of HUS is extremely variable. According to the literature, HUS may develop from 1 day to up to 7 months after treatment initiation and 54 days to 14 months from the last course of treatment.[4,18-22]

The proposed physiopathological therapeutic attitudes in this syndrome include an association of inhibitors of platelet aggregation (dipyridamole and salicylates), immunosuppressive drugs, anticoagulants (heparin), plasmapheresis and antihypertensive therapy, but there is no standardized established therapeutic scheme. Plasma exchanges using fresh plasma are considered as the therapy of choice. In most of the cases, therapy includes also supportive measures: diuretics for pulmonary edema, antihypertensive drugs and if necessary hemodialysis for renal failure. Erythrocytes and platelets transfusion have been associated with the progression of HUS. If the syndrome is suspected, blood transfusions should be avoided because of the risk of adverse reaction, reported in almost 50% of cases.[23] If a hematologic improvement is common after plasma exchanges, renal impairment is usually not fully reversible in most of the patients.[24]

The mortality rate is high, about 60-80%[25,26] when HUS is advanced, especially when it is associated with severe renal failure.

Conclusion

In conclusion, we reported HUS in an advanced ovarian cancer patient treated with gemcitabine and carboplatin. Detection of acute hypertension in a cancer patient should lead us to consider the diagnosis of HUS, and look for hemolysis and peripheral thrombocytopenia. New case reports of C-HUS with long follow-up may be of help to define guidelines in the management of these patients. This case report confirms that this acute and life-threatening syndrome may be reversible after adequate supportive therapy.

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