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ORIGINAL ARTICLE

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Hemolytic uremic syndrome following prolonged gemcitabine therapy: report of four cases from a single institution

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Abstract Hemolytic uremic syndrome (HUS) has been described following the administration of multiple antineoplastic agents, most notably mitomycin C. More recently, several cases of gemcitabine-induced HUS have been observed with the overall incidence of gemcitabine-induced HUS estimated at 0.015–0.25%. We here report on four patients who developed HUS following gemcitabine therapy at our institution within the last year (incidence 1.4%). All these patients had advanced-stage disease, were heavily pretreated, and received prolonged gemcitabine application, suggesting that in this subgroup of patients HUS may be more frequently encountered than documented so far.

Keywords Hemolytic uremic syndrome · Hemolysis · Gemcitabine · Thrombocytopenia · Renal failure · Microangiopathic thrombotic disease

Introduction

Hemolytic uremic syndrome (HUS) is a clinical entity characterized by renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. In some cases HUS includes de novo hypertension and pulmonary or CNS symptoms. HUS was first described by Gasser et al. in 1955 in a pediatric patient with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure following an episode of hemorrhagic diarrhea [6] and enterocolitis caused by verotoxin-producing *Escherichia coli* (VTEC), still is the most frequent cause of the syndrome. HUS, however, also may be associated with bacterial infections caused by other pathogens, viral diseases including immunodeficiency virus infection, collagen vascular diseases [in particular systemic lupus erythematosus (SLE)], pregnancy, postpartum diseases, allogeneic transplantation, radiation therapy, and various malignancies. Also, numerous drugs and toxins including ticlopidine, cyclosporine, tacrolimus, quinine, estrogen, and heroin have been implicated in inducing HUS [7, 12, 14, 18].

In addition, HUS is a well-documented complication of antineoplastic chemotherapy and the first case of chemotherapy (CTX)-induced HUS was described in 1979 in a patient treated with mitomycin C and 5-fluorouracil (5-FU) for epidermoid carcinoma [22]. Since then, multiple agents such as mitomycin C, bleomycin, adriamycin, pentostatin, interferon-alpha, cisplatin and carboplatin, or 5-FU have been reported to induce HUS [5, 13, 16]. Among these, mitomycin C still is the best-known culprit with incidence rates of up to 15% observed in some studies [10].

Over the past years several cases of HUS following gemcitabine treatment have been reported [4, 7, 19]. Gemcitabine is a nucleoside analogue structurally related to cytarabine and has shown considerable activity in a variety of malignancies such as lung, pancreatic, gallbladder, urinary, ovarian, and breast cancer, but also in lymphoma. The main side effects of gemcitabine include myelosuppression, fever, pain, and skin rashes [8, 9]. Due to its broad spectrum of activity and its relatively mild toxicity profile, gemcitabine is used frequently for the treatment of advanced and metastatic disease. So far, gemcitabine-induced HUS has been reported sporadically with an overall incidence estimated in the range from 0.015 to 0.25%. In the last year, however, we have observed HUS in association with gemcitabine therapy in a total of four patients at our institution alone.

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Case reports

Patient 1

Patient 1 was a 47-year-old man presenting in 1993 with cutaneous, bone marrow, and lymph node manifestation of a peripheral T-cell lymphoma [Lennert's lymphoma, lymphoepithelial T-cell non-Hodgkin's lymphoma (T-NHL), Kiel classification; stage IVA, Ann Arbor]. Initial treatment with five cycles of chlorambucil, procarbazine, vinblastine, and prednisone induced a complete remission lasting until 1999, when a splenic relapse was treated with splenectomy. A second relapse in 2000 was successfully treated with six cycles of mitoxantrone, chlorambucil, and prednisone. A third relapse in 2002 was treated with five cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone leading to a partial remission, and subsequent therapy with four cycles of ifosfamide, vincristine, adriamycin, and dexamethasone and one cycle of high-dose chemotherapy with 1,3-bis-2-(chloroethyl-l-nitrosourea) (BCNU), carboplatin, melphalan, dexamethasone, and autologous stem cell support resulting in a complete remission. Following a fourth relapse in April 2003, combination chemotherapy with gemcitabine (1000 mg/m^2, day 1, day 8, q4w), vinorelbine, methotrexate, and dexamethasone was instituted and resulted in a partial tumor response. At day 22 of cycle four (cumulative gemcitabine dose 14.4 g), a decrease of hemoglobin (Hb) (8.2 g/dl), thrombocytopenia (9×10^9 l^{-1}), 10–20% schizocytes in peripheral blood smears, a nondetectable haptoglobin, an elevated lactic dehydrogenase (LDH) (719 U/l), and an increase of the serum creatinine to 1.7 mg/dl (before gemcitabine treatment 1.16 mg/dl) were noted. The physical examination revealed hypertension (160/100 mmHg) and edema of both legs. At that time HUS was diagnosed. Eight days after the onset of HUS, five rounds of plasmapheresis were performed, resulting in a temporary reduction of schizocytes (down to 8%) and stabilization of creatinine. Three days after the last plasmapheresis progression of lymphoma was noted and three cycles of chemotherapy with etoposide, cytarabine, and dexamethasone were given over the next 2 months. Then the renal function deteriorated (creatinine 4.63 mg/dl, urea 119 mg/dl) and hemodialysis was started. However, the patient died 2 days later.

Patient 2

Patient 2 was a 61-year-old woman diagnosed with a locally advanced adenocarcinoma of the bile duct in July 2002. Beginning in August 2002, she was treated with vinorelbine, cisplatin, and 5-FU. After two cycles the therapy was stopped due to side effects (fatigue) and treatment with mitomycin C (15 mg, q4w) in combination with 5-FU was initiated. After two cycles, however, progressive disease was observed. Therapy with gemcitabine (1000 mg/m^2, day 1, day 8, day 15, q4w) was initiated, resulting in a regression of the bile duct tumor over the following 6 months. On admission for cycle seven (cumulative gemcitabine dose 28.8 g) the patient presented with anemia (Hb 8.8 g/dl), a moderately reduced platelet count (112×10^9 l^{-1}), 5–10% schizocytes on peripheral blood smears, nondetectable haptoglobin levels, an elevated reticulocyte count (4.0%), an elevated LDH (315 U/l), and an increase of serum creatinine to 1.2 mg/dl. HUS was diagnosed and treatment with gemcitabine was stopped. Hemolysis as well as renal function improved gradually over the following weeks. Four weeks after cessation of therapy, tumor progression was noted and chemotherapy with mitoxantrone (20 mg, 1qw) was given. After two applications progression of the HUS was observed with 5% schizocytes on peripheral blood smear and an increase of serum creatinine from 1.1 to 1.9 mg/dl. At this point chemotherapy was changed to vinorelbine and 5-FU/folinic acid and renal function improved again (creatinine 1.5 mg/dl). Two months later, however, the patient died, most likely due to progression of the bile duct tumor.

Patient 3

Patient 3 was a 38-year-old male first diagnosed in June 2003 with a high-grade non-Hodgkin's lymphoma (large cell, B-type, anaplastic) secondary to Hodgkin's disease. The Hodgkin's disease originally presented in 1999 with cervical, infraclavicular, mediastinal, and intra-abdominal lymph node manifestation (stage IIIB, Ann Arbor) and was treated with eight cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) followed by radiotherapy to the mediastinum and the cervical area (30.6 Gy), resulting in a complete remission. Two years later, in August 2002, a first relapse (intra-abdominal, no histology) of Hodgkin's disease was diagnosed. The patient was treated with two cycles of ifosfamide, vincristine, adriamycin, and dexamethasone, followed by two cycles of high-dose chemotherapy with carboplatin, BCNU, melphalan, and autologous stem cell support. For consolidation the patient was treated with radiotherapy (inverse Y-field, 30 Gy). In April 2003 a second relapse (intra-abdominal and bone, no histology) was diagnosed and therapy with gemcitabine (1000 mg/m^2 day 1, day 8, day 15, q4w) was started. In June 2003 the histologic diagnosis of the tumor was changed to a secondary high-grade lymphoma on the grounds of a biopsy obtained from a ventricular ulcer. Therapy with gemcitabine (cumulative dose 19.2 g) was continued but complemented with the monoclonal antibody rituximab (375 mg/m^2, q4w). In October 2003 the patient developed edema of his legs and a mild hypertension (145/90 mmHg). A serum creatinine of 1.74 mg/dl (normal before gemcitabine treatment), anemia (Hb 8.2 g/dl), thrombocytopenia (26×10^9 l^{-1}), a nondetectable haptoglobin, 10% schizocytes in the peripheral blood smear, an elevated LDH (742 U/l), and a reticulocyte count of 2.5% were observed and HUS was diagnosed. Two days later eight rounds of plasmapheresis (over a 10-

day period) were performed, during which the patient additionally developed increasing somnolence and an epileptic fit. Hemolysis improved moderately (LDH 279 U/l), but plasmapheresis failed to improve renal function. Thus, dialysis three times a week was started. Due to tumor progression, chemotherapy, this time with vinorelbine, ifosfamide, and cyclophosphamide, was reinitiated. However, the patient died 1 month later due to progressive disease.

Patient 4

Patient 4 was a 72-year-old female diagnosed with adenocarcinoma of the gallbladder in July 2001. At that time R_0 resection of the gallbladder tumor and partial liver resection eliminating three hepatic metastases was performed. One year later a hepatic relapse was diagnosed and two cycles of mitomycin C (15 mg, q4w) were administered. However, progressive disease was observed and treatment with gemcitabine (1000 mg/m^2 day 1, day 8, day 15, q4w) was initiated and continued for nine cycles (cumulative dose 30.4 g), resulting in regression of the hepatic metastases. At the end of the ninth cycle a hemolytic anemia (Hb 10.5 g/dl) with 10% schizocytes on peripheral blood smear, nondetectable levels of haptoglobin, an elevated LDH (297 U/l), a moderately reduced platelet count (112×10^9 l^{-1}), and an increase of serum creatinine to 1.9 mg/dl were noted and HUS was diagnosed. Gemcitabine treatment was stopped and changed to capecitabine (3 g/d, days 1–14). Over the next few weeks hemolysis receded, but renal function did not improve. Thus, 6 weeks after the diagnosis of HUS, hemodialysis had to be started. Therapy with capecitabine was stopped after two cycles due to severe mucositis and the patient went on to palliative care only. Ten months after the diagnosis of HUS the patient died of tumor progression.

Summary of cases and discussion

We here report on four cases of HUS observed at our institution in patients treated with gemcitabine during the year 2003. Two patients suffered from non-Hodgkin's lymphoma and two from adenocarcinoma of the bile ducts or gallbladder, respectively. All patients had advanced-stage disease and all patients were on prolonged gemcitabine therapy (4–9 months) when HUS was diagnosed. Cumulative gemcitabine doses at that point ranged from 14.4 to 30.4 g (mean: 23.2 g). Before gemcitabine all patients had received other chemotherapeutic regimens for at least 4 and up to 26 months. While gemcitabine was second-line and third-line therapy in the patients with gallbladder and bile duct cancer, pretreatment in the two lymphoma patients was more extensive with four and five different regimens administered.

Given the total of 291 patients exposed at our institution to gemcitabine in the year 2003, these four cases correlate to an incidence of gemcitabine-associated HUS of 1.4%. Occurrence of HUS was confined to patients on prolonged gemcitabine treatment receiving high cumulative gemcitabine doses (mean dose given at our institution in 2003: 9 g). These data correlate well with other studies also reporting HUS in association with high cumulative doses of gemcitabine (median: 18.3, range: 2.5–40.3 g/m^2) and describing a median duration of gemcitabine therapy prior to the occurrence of HUS from 3.8 to 13.1 months [17, 20]. However, the incidence rate of gemcitabine-associated HUS of 1.4% at our institution was considerably higher than published previously. For instance, for 1997 in a total of 78,800 patients exposed to gemcitabine worldwide an overall incidence rate of 0.015% was determined, with an incidence rate of 0.078% (6 of 7654) for clinical trials and 0.008% (6 of 71,200) for out-of-study use [17, 20], and in 2003 the gemcitabine product information from Eli Lilly reported an incidence rate of 0.25% (6 of 2429 patients) for clinical trials. These figures are clearly lower than the 1.4% incidence rate reported in our paper, and we attribute these differences to the high percentage of patients with extensive pretreatment and advanced-stage disease treated at our institution.

Given the advanced disease and the extensive pretreatment in our patients, certainly also factors other than gemcitabine—alone or in combination—have to be considered in the development of HUS, as HUS in cancer patients not only can be induced by chemotherapeutic agents, but also may be caused by the malignancy itself (paraneoplastic) [17, 20]. In addition, it has been described that in CTX-induced HUS drug application may precede onset of symptoms by 6–10 months, in particular following the administration of mitomycin C. Therefore, for a given patient it may be difficult or even impossible to exactly identify the causative drug or condition—especially in the context of progressive malignant disease and extensive pretreatment. Nonetheless, gemcitabine appears as the most likely cause of HUS in all our patients. At the onset of symptoms all patients had received gemcitabine for an extended period of time and at high cumulative doses and only two patients concomitantly received other antineoplastic therapy (vinorelbine, methotrexate, and dexamethasone in patient 1, rituximab in patient 4). In general, these agents have not been associated with HUS. Two of our patients were treated with mitomycin C 6 and 8 months prior to onset of HUS, thus fitting into the time frame described for mitomycin C to induce HUS. However, mitomycin C-induced HUS in general is correlated with high cumulative doses (over 60 mg) of the drug [10], while our patients only received total doses of 30 mg. In addition, in both mitomycin C-pretreated patients renal function and/or hematologic abnormalities improved following the discontinuation of gemcitabine, strongly supporting the idea of gemcitabine being the promoting agent for HUS in our patients.

The prognosis for HUS associated with malignancy is rather poor. While in general HUS is associated with mortality rates of 10–20%, prognosis for CTX-induced HUS is clearly worse with mortality rates of 40–90%

reported in most studies [11, 13, 17, 20]. To a large extent this poor prognosis is determined by the underlying malignancy, as paraneoplastic as well as CTX-induced HUS frequently occurs in advanced disease. This is also reflected in the fate of our four HUS patients, as three of them died—due to HUS itself, progressive malignant disease, or a combination thereof—within 8 weeks after the diagnosis of HUS, and the remaining patient survived for 10 months.

General guidelines for the treatment of HUS include control of fluid and electrolyte balance, treatment of high blood pressure as well as discontinuation of any causative agents (if identified). Renal dialysis should be administered as required. Aspirin, dipyridamole, and corticosteroids have been described as beneficial by some groups [2, 15], but there still is lack of convincing evidence on this point. Thus, these drugs were not given in our patients. Two of our patients were treated with conservative measures only, resulting in one patient in an improvement of hemolysis as well as renal function. In the other patient hemolysis could be reduced, but renal function did not improve and the patient went on to dialysis.

Successful treatment of HUS with plasma exchange therapy—similar to the closely related condition thrombotic thrombocytopenic purpura (TTP)—has been described by several groups. This treatment is based on the assumption that circulating immune complexes play a critical role in maintaining the disease process. While this is reasonably well established for acute TTP, correlating with a drop of mortality rates from over 90 to 10–30% with the institution of early plasma exchange therapy in this disease, the evidence for a causative role of immune complexes in HUS associated with bone marrow transplantation, malignancy itself, or CTX is less conclusive and a therapeutic role of plasma exchange in these patients has remained controversial [1, 23]. More encouraging results for the treatment of CTX-induced HUS have been reported for protein A immunoadsorption with response rates of 45–75% observed in some studies [3, 21]. In general, improvement of hematological parameters has been reported relatively frequently with plasma exchange therapy, whereas renal function only rarely responds. Temporarily improved hematological parameters, but few effects on renal function also were seen in the two of our patients undergoing probatory plasma exchange therapy. In both patients effects were only transient and dialysis had to be initiated within 4 or 11 days after the diagnosis of HUS, respectively.

Summing up our experience HUS represents a rare, though severe, side effect of antineoplastic chemotherapy, which should be kept in mind also for newer type antineoplastic agents. CTX-induced HUS carries a particularly poor prognosis, definite therapeutic guidelines have been difficult to establish, and therapy often remains probatory. In the case of gemcitabine, our data suggest that in heavily pretreated patients suffering from advanced-stage disease and following prolonged treatment with this drug the incidence of HUS may be higher than previously described.

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