GEMCITABINE-ASSOCIATED HEMOLYTIC-UREMIC SYNDROME: A CASE REPORT

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Gemcitabine is a novel pyrimidine antimetabolite with a broad spectrum of anticancer activity. The drug has generated enthusiasm in the treatment of advanced adenocarcinoma of the pancreas because of good patient tolerance and relatively few side effects. However, hemolytic-uremic syndrome has recently been reported in association with the use of gemcitabine. Hemolytic-uremic syndrome is a rare, devastating, and potentially fatal condition characterized clinically by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. We report on a 62-year-old male patient with pancreatic cancer who, after having received chemotherapy with gemcitabine for one year, developed clinical and laboratory findings compatible with hemolytic-uremic syndrome. Renal biopsy specimens showed the characteristic features of thrombotic microangiopathy. Despite aggressive therapy, including corticosteroid, plasma infusion, and plasma exchange, renal function was never recovered, and the patient was maintained on regular hemodialysis from that time until his death from metastatic carcinoma 5 months later. Since gemcitabine is now widely used for treatment of solid organ cancers, clinicians should be aware of gemcitabine-associated hemolytic-uremic syndrome as a rare but potentially fatal complication. Fewer than thirty cases have been reported in the literature, as determined by a MEDLINE search, and this is the first case reported in Taiwan. (Acta Nephrologica 2004; 18: 36-40)

Key words: Gemcitabine, chemotherapy, hemolytic-uremic syndrome, thrombotic microangiopathy

INTRODUCTION

Gemcitabine (2',2'-difluorodeoxycytidine) is a novel cytotoxic drug with promising activity against cancer of the pancreas. It is now indicated as a first-line treatment for patients with locally advanced or metastatic adenocarcinoma of the pancreas. It is also being used in patients with advanced non-small cell lung cancer, and a variety of other solid tumors. The drug is generally well tolerated, and the undesirable effects reported have been minor, including mild and short-lived myelosuppression, transient increase in liver function test, flu-like symptoms, peripheral edema, and skin rashes. Renal toxicity is minimal. A significant increase in serum creatinine has been reported in less than 1% of patients on gemcitabine monotherapy, but mild changes of urinalysis have frequently been reported, including mild proteinuria in 58% of patients and microscopic hematuria in 41%.

In a phase II trial of patients with pancreatic cancer in 1994, Casper et al. were the first to report the association of gemcitabine and hemolytic-uremic syndrome (HUS). Since this report, sporadic cases of HUS associated with gemcitabine have been reported, and a crude overall incidence rate of 0.015% (range, 0.008-0.078%) has been determined, showing that HUS associated with gemcitabine treatment still appears to be rare. Nonetheless, HUS is a severe and potentially fatal adverse side effect. In addition, adult HUS is secondary to probable causative factors in nearly half of all cases, and chemotherapeutic agents are one of these causative factors. Therefore, clinical awareness, timely detection, and immediate discontinuation of the drug are essential to avoid this rare but disastrous complication. We report here on a case of HUS after prolonged chemotherapy with gemcitabine for pancreatic cancer.
CASE REPORT

A 62-year-old man was admitted in August 2001 because of 3-month history of abdominal pain, post-prandial vomiting, and a weight loss of 10 kg during this period. He was diagnosed as having adenocarcinoma of the pancreas, which had infiltrated the adjacent soft tissue and invaded the duodenum. Commencing in September 2001, single-drug chemotherapy with gemcitabine was given in a monthly cycle of 1,500 mg (1,000 mg/m²) intravenously once a week for 3 consecutive weeks, followed by 1 week of rest to have the greatest degree of efficacy with minimal toxicity. Over the next 12 months the patient received 38 doses, with a cumulative dose of 57,000 mg (38,000 mg/m²). Response to chemotherapy was considered excellent, with a slight reduction of tumor size from 3 cm to 2.5 cm demonstrated by means of computed tomography follow-up 6 months after chemotherapy. Gemcitabine was well tolerated until 6 weeks before admission, during the eleventh month of chemotherapy, when anemia (hemoglobin 6.4 g/dL) and leukopenia (white blood cell (WBC) count 2,300/mm³), attributed to myelosuppression of the anticancer agent, were observed. The platelet count was 190,000/mm³, renal function test remained within normal range (serum creatinine 1.3 mg/dL), and no hypertension was recorded. Two units of packed red cells were transfused and the chemotherapy was continued. Three weeks before admission, the patient presented with general weakness and loss of appetite. The laboratory values revealed hemoglobin of 5.4 g/dL, a WBC count of 1,700/mm³, and a platelet count of 5,000/mm³. Renal dysfunction with an increase in serum creatinine from 1.3 mg/dL to 1.8 mg/dL was also first recorded. At this time, the weekly chemotherapy was discontinued because of the severe thrombocytopenia and anemia, which were still assumed to be the myelotoxic side effect of gemcitabine, and 4 units of packed red cells and 12 units of multiple donor concentrated platelets were transfused. One week later, the chemotheraphy was resumed when complete blood cell counts had become acceptable (hemoglobin 7.1 g/dL, WBC count 3,700/mm³, platelet count 128,000/mm³).

At the beginning of September 2002, one week after the last dose of gemcitabine, the patient was readmitted because of dyspnea and severe hypertension. At the time of physical examination, the patient’s temperature was 36.6°C, pulse rate was 65 beats/min, and respiratory rate was 22 breaths/min. Blood pressure was 203/116 mmHg, and a mild narrowing of the arterioles was noted upon funduscopic examination, which was suggestive of grade I hypertensive retinopathy. The patient had pale conjunctiva and no icteric sclera. His neck was supple and showed normal jugular venous distention. There was no cervical lymphadenopathy. The patient was orthopneic, with auscultation disclosing crackles over both lungs, and the chest X-ray showed bilateral diffuse infiltrates. Heart sounds were normal, the abdomen was soft and nontender, and there was bilateral pedal edema. The initial laboratory investigations revealed the following: hemoglobin, 4.0 g/dL; reticulocyte count, 5.6%; WBC count, 4,250/mm³; platelet count, 16,600/mm³; blood urea nitrogen, 61.5 mg/dL; creatinine, 2.2 mg/dL; alanine aminotransferase, 23 U/L; total bilirubin, 1.5 mg/dL; and lactic dehydrogenase (LDH), 1,849 U/L. Coagulation parameters were within normal range, but serum haptoglobin levels fell to an undetectable range. Review of the peripheral smear showed the appearance of schistocytes. Based on these clinical features, a diagnosis of microangiopathic hemolytic anemia was made immediately following admission, and was first diagnosed as a complication of metastatic carcinoma. However, the renal dysfunction was overlooked and hence HUS was not taken into account. In the following days, supportive treatment only was given, including anti-hypertensive agents for blood pressure control, diuretics for fluid retention, and blood components transfusions. Two weeks after admission, the nephrologist was consulted because of progressive renal failure and severe hypertension refractory to standard therapy. At this time the serum creatinine level had reached 5.4 mg/dL, the hemoglobin was 6.1 g/dL, platelet count was 27,000/mm³, and LDH was 1,897 U/L. Further investigations revealed 4+ protein, 3+ occult blood in the urinalysis, 24-hour urinary protein of 4.2 g, and normal-sized kidneys on ultrasonography. Serologic evaluation showed antinuclear antibody, antineutrophil cytoplasmatic antibody, hepatitis B antigen, and hepatitis C antibody all to be negative. Complement levels were also normal, but the serum creatinine continued to rise, and at this point a kidney biopsy was performed, showing the characteristic findings of thrombotic microangiopathy (Fig. 1, 2). The patient was then treated with a short course of corticosteroid, plasma infusion, and six sessions of plasma exchange with substitution of fresh frozen plasma. As the serum creatinine value increased to 9.1 mg/dL and the dyspnea worsened due to pulmonary edema, hemodialysis was performed beginning on the 21st day. Aggressive treatment achieved prompt resolution of hemolysis and thrombocytopenia, and the hypertension was well controlled by three-drug regimen comprised of amlodipine, lisinopril, and minoxidil. However, renal function never recovered and the patient was maintained on chronic hemodialysis thrice weekly afterward. Since the therapy for HUS failed, further chemotherapy was abandoned and merely palliative treatment was given. The patient died of met-
Fig. 1. The glomerulus displays thickening of the capillary walls. The afferent arteriole is occluded by fibrin thrombus (arrow) (hematoxylin and eosin stain, original magnification ×400).

Fig. 2. Double tracts (arrow) are seen in some areas of glomerular capillary walls (periodic acid-Schiff stain, original magnification ×400).

astatic carcinoma 5 months after the diagnosis of HUS.

DISCUSSION

HUS is a rare condition that is severe and potentially fatal. It was first described in 1955 by Gasser et al. who observed a pediatric patient with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure after an episode of bloody diarrhea. Initially, it was believed to be a disease occurring mainly in
children after an acute gastrointestinal infection caused by E. coli O157:H7, or other organisms such as Shigella dysenteriae. Indeed, the majority of adult cases occur without preceding episodes of diarrhea and the etiology of HUS in adults demonstrates a greater variation than in children. It is now widely known that HUS may be associated with a variety of conditions, such as nonenteric infections, pregnancy, drugs, toxins, malignant hypertension, cancer, transplantation, primary glomerulonephritis, and collagen vascular disorders (e. g., systemic lupus erythematosus and scleroderma). In contrast to children, adults with HUS have high overall mortality rates of 14-37% despite medical intervention. Furthermore, nearly half of all adult cases are of the secondary form. Therefore, early diagnosis and detection of causative factors are necessary to improve the poor outcome in cases of adult HUS.

HUS also occurs in cancer patients, as early as 1962 it was reported that HUS was associated with widespread metastatic cancer in patients not receiving chemotherapy. In 1980, the first report of HUS in patients treated with mitomycin C was published. Since this report, a growing number of chemotherapeutic agents, mainly mitomycin C, cisplatin, and bleomycin, have been linked to incidents of HUS. Gemcitabine has a structure similar to that of cytosine-arabinoside, a drug not previously associated with HUS, but cases of HUS associated with gemcitabine have been reported since 1994. Although HUS still appears to be rare, with a incidence rate of 0.015%, it is possible that reported incidents will increase as clinicians become more aware of this complication. A recent review by Walter et al. showed that gemcitabine-induced HUS seems to be related to the cumulative dose. The mean duration of treatment is 7.4±3.5 months, or 21.9±10.9 doses, and the median cumulative dose is 20,000 mg/m². The exact mechanism is incompletely understood, but it is believed that the drug’s toxic effect on the endothelium is the primary event in the pathogenesis.

Gemcitabine is commonly used for various tumors at advanced stages. It is essential to discriminate between HUS caused by underlying cancer and that caused by chemotherapy, because they are two distinct conditions. Further chemotherapy is beneficial in the first case, while it is harmful in the other. There are reports suggesting that cancer-associated HUS usually occurs in widespread metastatic or poorly controlled diseases, whereas chemotherapy-associated HUS is more common when the patient is in remission or has minimal tumor burden. In addition, advanced malignancy is not a common cause of HUS except in the context of concomitant chemotherapy. Lesesne et al. reviewed 85 cases of cancer-associated HUS, and found that mitomycin was part of the chemotherapy regimen in 84 cases. Thus, HUS manifesting during the course of a stable neoplastic disease being treated with chemotherapy appears to be mainly attributable to the toxic effect of chemotherapy. In our patient’s case, his cancer was stable and there was no clinical evidence of widespread disease at the time HUS occurred. In fact, clinical worsening of the cancer was noted only after discontinuation of gemcitabine. Furthermore, no other known causative factors were present. Therefore, gemcitabine was the most probable factor responsible for the development of HUS. However, diagnosis of HUS might have been delayed by at least 1 month, because as early as 3 weeks before admission, the patient’s anemia and thrombocytopenia were attributed exclusively to the myelosuppressive action of gemcitabine, and the mild renal dysfunction was ignored. Not being alert to the possibility of HUS, no further investigations were performed. Subsequent chemotherapy might have led to further damage to the kidney, although the microangiopathic hemolytic anemia was detected immediately upon admission, it was erroneously considered as a complication of the cancer. Because coexisting renal failure has not been a prominent abnormality described in patients who develop microangiopathic hemolytic anemia as a consequence of cancer, HUS should be considered, and could even be clinically diagnosed at this time. Gemcitabine should be discontinued and aggressive treatment was given thereafter, but it might be too late when irreversible renal damage has occurred.

Treatment of gemcitabine-associated HUS is based primarily on anecdotal reports. Early detection and timing of drug discontinuation are the first line of treatment. Various adjunctive therapies have been used with varying degrees of success. These include corticosteroid, plasma infusion, plasma exchange with fresh frozen plasma replacement, or various therapies in combination. Nonetheless, the outcome remains poor. Walter et al. recently reviewed 26 cases and showed that 11 of 23 patients with reported outcome died of HUS-related complications or cancer progression within weeks to months. As for renal prognosis, only 3 surviving patients developed dialysis-dependent renal failure. Reintroduction of the drug was reported in 3 patients but was uncomplicated in only one. Long-term outcome has not yet been reported, but it is assumed that those who have survived HUS will not survive cancer, because further chemotherapy is abandoned in the majority of those cases.

In conclusion, the new anticancer drug gemcitabine is now increasingly used in the treatment of a variety of solid tumors, and despite the low incidence of HUS associated with the drug, a high degree of vigi-
lance regarding this potentially fatal complication is essential in treating cancer patients undergoing long-term chemotherapy with gemcitabine. The diagnosis of HUS is often delayed because anemia and thrombocytopenia may mistakenly be attributed to myelotoxicity of gemcitabine. Therefore, any worsening of anemia or thrombocytopenia should be further evaluated. It has been suggested that reticulocyte count is a simple test to differentiate between hyporegenerative anemia due to myelosuppression of gemcitabine and hyperregenerative anemia due to HUS associated with gemcitabine. Finally, physicians should bear in mind that unexplained renal dysfunctions, however mild, or new instances of hypertension may be the first signs of HUS and should not be overlooked.

REFERENCES