A Review of Hemolytic Uremic Syndrome in Patients Treated with Gemcitabine Therapy

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BACKGROUND. Hemolytic uremic syndrome (HUS) is a rare condition that occasionally is reported in cancer patients. Recently it has been observed that gemcitabine rarely may be associated with this condition.

METHODS. The manufacturer's safety database and literature were reviewed for any report regarding gemcitabine associated with renal and hematologic abnormalities. Descriptive analysis was used to examine each case for an association between gemcitabine therapy and HUS and to identify its incidence and risk factors.

RESULTS. Through December 31, 1997, 12 cases were identified that fit either the clinical (uremia, microangiopathic hemolytic anemia, and thrombocytopenia) or pathologic (renal biopsy) criteria for HUS. There were 7 males (58%) and 5 females (42%) with a median age of 55.5 years (range, 37–73 years). The median duration of gemcitabine therapy was 5.8 months (range, 3.8–13.1 months). Six patients died, five improved, and one patient's outcome was unknown. Among the six deaths, three patients died of cancer progression, one patient died of an unrelated myocardial infarction, and two patients died of HUS or HUS-related complications. For the five patients who improved, treatment was comprised of dialysis, plasmapheresis, splenectomy, or a combination. Attempts to correlate patient demographics, primary malignancy, and cumulative gemcitabine dose failed to identify consistent risk factors in predisposing patients to HUS. Confounding factors were common, including mitomycin-C and/or 5-fluorouracil exposure, advanced stage tumors, or preexisting renal dysfunction.

CONCLUSIONS. Based on a patient exposure of 78,800, a crude overall incidence rate of 0.015% (range, 0.008–0.078%) was determined, showing that HUS associated with gemcitabine treatment appears to be rare. Nonetheless, as with other cancer treatments, clinicians should weigh the appropriate risk/benefit ratio in using gemcitabine to treat their patients. ***Cancer* 1999;85:2023–32.**

KEYWORDS: acute uremia, gemcitabine, hemolytic uremic syndrome, microangiopathic hemolytic anemia, thrombotic microangiopathy.

Hemolytic uremic syndrome (HUS) is a rare condition that is severe and may be fatal.[1-15] It first was described in 1955 in Switzerland by Gasser et al., who observed a pediatric patient with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure after an episode of bloody diarrhea.[16] Initially believed to be a disease mainly occurring in children after an acute bacterial or viral gastrointestinal infection, it now is known that HUS may be associated with a wide variety of conditions.[5,8,9,14,17,18] Indeed, the majority of adult HUS cases occur without preceding episodes of diarrhea.[5,8,17–19]

It was noted that HUS can be associated with malignancies, especially metastatic adenocarcinomas such as those of the stomach, colorectum, breast, lung, and, less commonly, metastatic prostate

carcinoma.[20–27] In 1979, the first case of chemotherapy-induced HUS was recognized in a patient with epidermoid carcinoma treated with mitomycin C (MMC) and 5-fluorouracil (5-FU).[28–43] Since then, several other chemotherapeutic agents, including cisplatin and bleomycin, have been reported to be associated with HUS.[44–51] This condition also has occurred in association with radiation therapy and after bone marrow transplantation.[52–58]

Gemcitabine is a novel nucleoside analogue with activity against pancreatic adenocarcinoma and non-small cell lung carcinoma (NSCLC) as well as other solid tumors.[59–61] It recently has been observed that gemcitabine rarely may be associated with HUS.[62,63] This review examines the incidence of HUS associated with gemcitabine in the Eli Lilly and Company Worldwide Pharmacovigilance and Epidemiology safety database and attempts to identify the incidence of risk factors with such occurrences.

METHODS

A search was performed using the Eli Lilly and Company Worldwide Pharmacovigilance and Epidemiology safety database, which also is known as the Drug Experience Network (DEN) database. DEN is a computerized system established in 1983 for the worldwide collection, storage, and reporting of adverse events involving the manufacturer's products. DEN includes clinical trial events described as "serious" according to U. S. Food and Drug Administration regulations as well as serious and nonserious adverse events reported spontaneously from postmarketing experience (including reports from the scientific literature). The adverse event cases were collected and entered into the database using the Coding Symbol and Thesaurus for Adverse Reaction Terminology (COSTART) mapping classification.

Today, HUS commonly is defined by the clinical triad of acute uremia, microangiopathic hemolytic anemia, and thrombocytopenia.[1–3,7,8,12,15,16] To capture all spontaneous and clinical trial cases that potentially could be related to HUS, the DEN database was searched from August 1, 1987 to December 31, 1997, the 10-year period since gemcitabine first was studied in humans. In addition to the terms "HUS" and "thrombotic thrombocytopenic purpura (TTP)," a comprehensive search of possible terms related to renal and hematologic abnormality was conducted. (Although TTP is included in the COSTART mapping dictionary, HUS is not. HUS customarily is mapped to "uremia" in safety adverse event reporting.) The 18 COSTART terms used in the search are as follows: uremia, kidney failure, acute kidney failure, kidney function abnormal, blood urea nitrogen (BUN) increased, creatinine increased, creatinine clearance decreased, renal hypertension, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, thrombocytopenia, lactate dehydrogenase (LDH) increased, hemolysis, hemolytic anemia, hemolytic anemia—direct Coombs test negative, hemolytic anemia—direct Coombs test positive, hemolytic anemia—indirect Coombs test negative, and hemolytic anemia—indirect Coombs test positive.

Cases generated were reviewed individually to evaluate patient demographics, gemcitabine dosing details, clinical presentation, and outcomes. Duplicate cases were eliminated. In addition, although there were some cases generated in the initial search with isolated hemolysis or thrombocytopenia (e.g., due to bone marrow suppression), close review of the details found that they did not meet the classic clinical (uremia, microangiopathic hemolytic anemia, and thrombocytopenia) or pathologic (renal biopsy) criteria of HUS. Thus, only 12 cases were considered amenable for analysis, 6 of which were from clinical trials (Cases 1–6) and 6 of which were postmarketing reports (Cases 7–12).

Attempts were made to validate individual cases and to examine risk factors that may have predisposed patients to HUS. A crude incidence rate was calculated using worldwide gemcitabine patient exposure data from clinical trial and commercial use. Based on the worldwide sales data and internal census on clinical trials, it is estimated that through December 31, 1997 there were 71,200 postmarketing patients and 7654 clinical trial patients, for a total of 78,800 patients exposed to gemcitabine worldwide. A descriptive statistical approach was used for the current analysis. An additional literature search did not reveal any other cases not already in the manufacturer's safety database.

RESULTS

Demographic and Malignancy Type

The basic demographic information of the 12 HUS cases is displayed in Table 1. Based on an estimated worldwide gemcitabine patient exposure of 78,800, a crude incidence rate of 0.015% was determined overall, with an incidence rate of 0.078% (6 of 7654) for clinical trials and 0.008% (6 of 71200) for spontaneous sources (reported by practicing oncologists). The cases included 7 males (58%) and 5 females (42%) with a median age of 55.5 years (range, 37–73 years). Overall, there did not appear to be any specific correlation between gender and age with the reported incidence of HUS. Although there appeared to be more patients between the ages of 50–69 years and a slightly higher representation of males in the current review, this observation may be more representative of the natural

TABLE 1
Demographic, Tumor Type, and Prior Chemotherapy Treatment

Patient no.	Age (yrs)	Gender	Primary tumor	Stage	Prior chemotherapy
1	64	F	NSCLC	IIIA	None
2	37	M	NSCLC	IIIA	None
3	65	M	Pancreatic	IV	None
4	43	M	Gastric	IV	None
5	59	M	Pancreatic	IIIA	MMC
6	73	F	Pancreatic	IV	MMC and 5-FU
7	62	M	Pancreatic	IV	5-FU
8	52	F	Pancreatic	IV	None
9	50	M	NSCLC	Unknown	None
10	59	F	Biliary	IV	None
11	45	M	NSCLC	IV	None
12	52	F	Pancreatic	IV	5-FU

F: female; NSCLC: nonsmall cell lung carcinoma; M: male; MMC: mitomycin C; 5-FU: 5-fluorouracil.

disease prevalence among these patients (e.g., lung carcinoma is more common among middle-aged male smokers) rather than any gender or age sensitivity to this event.

An analysis was performed to evaluate whether the primary tumor itself had any correlation with the HUS event. Again, there did not appear to be any particular tumor in this small group of patients that would make patients more susceptible to HUS. The primary malignancies were those of the pancreas (50%), lung (33%), stomach (8.5%), and biliary tract (8.5%). The slightly higher representation of lung and pancreatic carcinomas merely reflect the current indications for the use of gemcitabine among these patients.

Symptoms and Diagnosis

Among the 12 patients, 6 patients had a renal biopsy with classic microangiopathic changes in the renal arterioles and another patient died and underwent an autopsy that confirmed the diagnosis. All patients experienced acute uremia and eight were known to have been treated by dialysis. With the exception of two patients for whom some hematologic data were not available (diagnoses were made by renal biopsy), all patients exhibited the classic triad of acute uremia, microangiopathic hemolytic anemia, and thrombocytopenia.

In addition to renal and hematologic manifestations, hypertension was the most common other finding with 7 of the 12 patients having either new onset hypertension or exacerbation of underlying hypertension. Pulmonary symptoms and central nervous system (CNS) symptoms also were common with six patients having pulmonary complications and four patients reporting nonspecific CNS symptoms such as headache, blurred vision, or confusion. The clinical characteristics of these patients are presented in Table 2.

Dose Response Relation/Time of Event in Relation to Last Treatment

An attempt was made to evaluate whether a dose response effect could be demonstrated with gemcitabine and the reported incidence of HUS. Table 3 shows the dose and duration of treatment among these 12 patients. The median duration of therapy was 5.8 months (range, 3.8–13.1 months).

The duration between the last gemcitabine infusion and the onset of the event was reviewed. The data showed that 8 patients developed HUS within 1 month from the time of the last infusion and 4 patients developed the condition between 1–2 months from the time of the last infusion. Of note is that the majority of patients had advanced disease (8 of the 12 patients had metastases). This contrasts with what is suggested in the literature, namely that the majority of chemotherapy-induced HUS occurs when patients have a low tumor burden.

An analysis was performed for all 12 cases to evaluate whether a dose response relation existed between the total number of doses given and the HUS event. The analyses were based on the number of gemcitabine doses given to the patients. There was a median of 17.5 doses (or approximately 6 cycles of treatment with 3 infusions per cycle) with a range of 8–39 doses. In these patients, there did not appear to be a dose response relation between the number of gemcitabine doses given and the HUS event.

An alternate analysis was performed to evaluate whether the HUS event demonstrated any dose response relation with the cumulative quantity of gem-

TABLE 2
Clinical Presentation, Pathologic Diagnosis, and Outcome of the 12 Patients

Patient no.	Clinical triad[a] U	T	M	Pathologic studies	Other symptoms	Remarks
1	X	X	X	Renal biopsy at autopsy showed microangiopathic lesions consistent with HUS.	New onset hypertension, dyspnea and abnormal ABG.	Treated with dialysis. Died of pneumonia and acute renal failure.
2	X	X	X	Renal biopsy showed microangiopathic changes.	Nocturnal dyspnea, headache, and blurred vision.	Treated with dialysis. Died of disease progression.
3	X	N/A	N/A	Renal biopsy showed thrombotic angiopathic changes and nephritis.	New onset hypertension.	Died of unrelated MI.
4	X	X	X	No biopsy performed.	Dyspnea, orthopnea, and exacerabtion of existing hypertension.	Treated with dialysis and improved.
5	X	X	X	Schistocytes on blood smear.	No other symptoms noted.	Unknown.
6	X	X	X	Schistocytes and burr cells on blood smear.	No other symptoms noted.	Treated with plasmaphoresis; died of disease progression.
7	X	X	X	Kidney biopsy showed microangiopathic lesions. Schistocytes and fragmented RBCs on blood smear.	Dyspnea, pulmonary edema, and exacerbation of existing hypertension.	Treated with dialysis and plasmaphoresis. Died of renal failure and other complications.
8	X	X	X	No biopsy performed.	New onset hypertension.	Treated with plasmaphoresis, immunoglobulins, and splenectomy and improved.
9	X	N A	X	Renal biopsy showed microangiopathic lesions.	No other symptoms noted.	Treated with dialysis and plasmaphoresis and improved.
10	X	X	X	Renal biopsy showed thrombotic microangiopathy of the arterioles.	Dyspnea, headache, and new onset hypertension.	Improved on dialysis.
11	X	X	X	Renal biopsy showed occlusion of small renal arteries due to mucoid widening of the intima and presence of fibrin thrombi, thickening of the glomerular capillary walls, diffuse interstitial fibrosis, and chronic tubular damage. Schistocytes found on blood smear.	Headache, new onset hypertension, jaundice, and febrile.	Treated with plasmapheresis, steroids and hemodialysis. Hemolysis resolved but patient progressed to develop chronic renal failure.
12	X	X	X	Peripheral blood smear showed fragmented RBCs and schistocytes.	Pulmonary edema and confusion.	Treated with dialysis. Died of disease progression.

U: uremia (anuria, oliguria, or elevated blood urea nitrogen/creatinine with or without the need for hemodialysis); T: thrombocytopenia; M: microangiopathic hemolytic anemia (fragmented red blood cells, schistocytes, burr cells, increased reticulocyte count, indirect bilirubin, lactate dehydrogenase, or fibrin split products); HUS: hemolytic uremic syndrome; ABG: arterial blood gas; MI: myocardial infarction; RBCs: red blood cells; NA: not available.

citabine infused (mg/m^2). The median quantity of gemcitabine infused was 18,252 mg/m^2 (range, 2450–40,269 mg/m^2). Again, no dose response relation was demonstrated.

Patient Outcomes

The outcomes of the 12 patients were analyzed to determine whether these patients recovered or died. As of December 31, 1997 (the data lock point of the current review), outcomes showed that six patients died, five patients improved, and the outcome was unknown for one patient. Of the six patients who died, three patients died of disease progression and one died of an unrelated myocardial infarction. Two patients died of HUS or HUS-related complications. Of these deaths, the duration between the time of HUS diagnosis to the time of death ranged from 1–21 weeks (median, 11.5 weeks). For the five patients who improved, treatment was either dialysis (two patients), a combination of dialysis and plasmapheresis (two patients), or plasmapheresis and splenectomy (one patient).

Confounding Factors

Confounding factors were fairly common. All patients except one had advanced stage disease. Two patients also had preexisting renal dysfunction. A total of four patients had received other prior chemotherapy treatment (Table 1), but none received combination chemotherapy with gemcitabine. One patient had prior treatment with MMC, two patients received prior 5-FU, and one patient received both MMC and 5-FU. Except for the patient receiving single agent MMC whose elapsed time since receiving a prior chemother-

TABLE 3
Dose and Duration of Treatment

Patient no.	Duration of treatment (mos)	No. of doses received	Cumulative dose received (mg/m^2)
1	3.8	12	9204
2	5.0	18	18,720
3	13.1	39	40,269
4	5.4	16	25,200
5	6.0	20	15,750
6	6.5	20	20,000
7	10.8	29	29,000
8	5.5	17	17,000
9	5.8	8	2450
10	5.8	18	17,784
11	7.0	17	21,250
12	4.5	15	12,000
Median	5.8 months	17.5	18,252 mg/m^2

The usual dose of gemcitabine is 1000 mg/m^2 for 3 weeks (with 1-week rest) per cycle for nonsmall cell lung carcinoma and 1000 mg/m^2 for 7 consecutive once weekly doses initially for pancreatic carcinoma followed by cycles of treatment 3 of every 4 weeks thereafter.

apy regimen was unknown, the elapsed time between the prior chemotherapy and the initiation of gemcitabine for the other 3 patients ranged from 1–12 months (median, 6 months). Overall, although these four patients had received other chemotherapy that was reported to be associated with HUS, the exact contributory roles of these agents to the HUS events observed at the time of our study were difficult to delineate.

Statistical Analysis

In the majority of drug safety or spontaneous adverse event reporting system analyses, it is common to use a descriptive statistical approach to review the data due to the nature of the data collection. Therefore the descriptive statistical approach was used in this report rather than the more conventional *P* value comparison. A potential reporting bias (either underreporting or overreporting) always is possible in spontaneous adverse event reporting and cannot be eliminated completely nor determined accurately. Because of the small number of cases, a full statistical comparison was not believed to be meaningful. Overall, the major objective of the cases reported in this review was to reflect our current experiences and to serve to illustrate some characteristics of these patients.

DISCUSSION

HUS is a rare clinical condition that occasionally is reported in cancer patients.[1–15] It can be caused by the underlying malignancy itself[20–27] and also has been associated with some chemotherapeutic agents.[28–51] For example, metastatic adenocarcinomas such as those of the stomach, colorectum, breast, lung, and, less commonly, metastatic prostate carcinoma have been reported to cause HUS.[20–27] In addition, therapy with MMC, 5-FU, cisplatin, and bleomycin also have been reported to be associated with this condition.[28–51]

In addition to malignancy and chemotherapies, there are several other conditions reported to be associated with HUS.[5,8,9,14,17,18] In addition to the originally described condition preceded by acute gastrointestinal infection (viral or *Escherichia coli* E157:O1), other conditions such as human immunodeficiency virus infection, collagen vascular disease (e.g., systemic lupus erythematosus or scleroderma), pregnancy, and postpartum condition have been reported to be associated with HUS.[5,8,9,14,17,18] Many nonchemotherapeutic drugs such as cyclosporine A, FK-506, and estrogens also have been implicated in HUS.[8,9,53,64] Because of the variety of conditions and drugs associated with HUS, it is difficult to ascertain the contribution of each to HUS, especially if such factors coexist in the same patient.

It can be difficult to discriminate between HUS that is caused by an underlying malignancy and that caused by chemotherapy.[24,39,64] There are literature reports suggesting that malignancy-associated HUS usually occurs during widespread metastatic disease or poorly controlled carcinomas, whereas chemotherapy-associated HUS is more common when the patient is in disease remission or has minimal tumor burden.[64–66] However, the distinction is not always clear. For example, as reported by Lesesne et al. in a series of 85 patients with HUS in which MMC was used in the majority of cases, only 30 patients (35%) were in disease remission or had no evidence of tumor at the time the HUS syndrome manifested.[39] In another series of 39 HUS patients studied by Sheldon and Slaughter, 82% had received MMC but only 60% of the patients were in disease remission.[15] In the current study 67% of the patients developed HUS within 1 month of the last infusion and all patients were diagnosed with HUS within 2 months of the last infusion. However, nearly all patients in this series had persistent advanced disease at the time they presented with HUS.

Murgo attempted to distinguish the characteristics of malignancy-induced and chemotherapy-induced HUS and identified several features to separate the two.[65] However, as shown by Gordon and Kwaan,[64] there actually are more similarities than differences. For example, both types are associated with adenocarcinoma, and the higher female prevalence in chemotherapy-related HUS can be accounted for eas-

ily by the large number of breast carcinoma patients who received MMC. Some researchers suggest the level of serum factors such as tumor necrosis factor-α, interleukin-1β, and interleukin-6 as well as von Willebrand factor (vWF) antigen and low molecular weight vWF multimers may be used to distinguish between malignancy-associated HUS and chemotherapy-associated HUS.[67–73] However, such studies remain experimental and are not readily available in the majority of community settings.

A literature review of all publications regarding HUS with the use of gemcitabine identified only two publications that had been entered into our safety database and are included in the current review. The first case (Patient 3) was described by Casper et al. from the results of a Phase II clinical trial of gemcitabine in adenocarcinoma patients.[62] A 65-year-old man had been receiving gemcitabine treatment for pancreatic carcinoma for $>$ 1 year and developed mild to moderate elevation of BUN and creatinine levels (BUN/creatinine = 54/2.2). A renal biopsy showed thrombotic microangiopathic changes and nephritis. The patient subsequently died of an unrelated myocardial infarction.

The second literature case (Patient 11) was reported by Brodowicz et al.[63] A 45-year-old man was treated with gemcitabine for NSCLC for approximately 7 months. Baseline renal function and hematologic parameters were reported to be normal. After therapy, the patient was found to have renal failure (BUN/creatinine = 58/7.4), thrombocytopenia (decreased from 450,000 to 60,000), and hemolytic anemia (fragmented red blood cells; an elevated LDH, bilirubin, and reticulocyte count; and decreased haptoglobin). Urinalysis showed mild proteinuria, microscopic hematuria, and cylindruria. The patient also had hypertension and headache and was jaundiced and febrile. A renal biopsy showed occlusion of small renal arteries due to mucoid widening of the intima and the presence of fibrin thrombi. There was prominent thickening of the glomerular capillary walls with double contour appearances, moderate diffuse interstitial fibrosis, and chronic tubular damage. The patient was treated with plasmapheresis, corticosteroids, and hemodialysis. The hemolysis resolved after approximately 5 weeks of treatment but the patient progressed to chronic renal failure. Both patients appeared to experience classic findings of HUS after a treatment period of 7–12 months.

Although a dose response relation is well documented for MMC-induced HUS,[15,43,74,75] our data do not support such a correlation for gemcitabine in our review of the 12 patients in this study. Plots of either the number of doses each patient received, the cumulative dose exposure (as mg/m^2), or the duration of treatment did not show a dose effect or time effect correlation. Thus, although the gemcitabine therapy may be associated temporally with HUS, the exact contributory role remains unclear.

Over the years, there have been many different types of treatment for patients with HUS.[34,39,76–83] These treatments have been comprised of four main categories: immunocomplex removal (plasmapheresis, immunoadsorption, hemodialysis, or exchange transfusion), antiplatelet/anticoagulant therapies (antiplatelet drugs, heparin, prostacyclin, or splenectomy), immunosuppressive therapies (corticosteroids, vincristine, or azathioprine), and miscellaneous (fresh frozen plasma transfusion). Many of these therapies are safe and quite effective, especially if performed in specialized institutions. Despite the availability of these treatments, HUS remains a highly fatal disease. Estimates of mortality have ranged from approximately 10–40% in the majority of series[1,2,6,7,10] but have been reported to be as high as 60–70% in others.[15,36,39] Our current review showed a mortality rate similar to that of the literature. Although 6 of the 12 patients died, only 2 died of HUS or HUS-related complications. This mortality rate (50%) is not surprising because the majority of these patients had advanced disease. For the five patients who improved, treatment was either dialysis, plasmapheresis, splenectomy, or a combination therein.

HUS perhaps is immunologic in etiology as demonstrated by improvement with therapies aimed at removing circulating immunocomplexes.[51,78,80–82] Other authors postulate that microvascular injury is the cause of the condition.[67-73] However, to our knowledge there is no known mechanism to account for gemcitabine being a causative agent of HUS. MMC, a chemotherapy agent known to be associated with HUS, is an antibiotic that contains quinone, urethane, and aziridine groups.[84–85] It is activated chemically and metabolically to a variety of alkylating moieties. However, gemcitabine is a pyrimidine antimetabolite[59–61] and to our knowledge there is no structural or pharmacologic similarity between MMC and gemcitabine. Other chemotherapeutic agents such as cisplatin, bleomycin, and 5-FU, with which HUS occasionally has been reported to be associated, also have no structural similarity with gemcitabine. Conversely, cytarabine is another oncolytic that contains a cytidine base like gemcitabine. However, although cytarabine has been reported to cause mild renal dysfunction, it has not been noted to result in acute renal failure or HUS.[86,87] Thus, it is unlikely that the observed event is due to a drug class effect.

Nearly all 12 patients had advanced stage tumors

whereas others also had preexisting renal dysfunction. In addition, in view of the fact that the majority of patients had metastatic diseases from a gastrointestinal or lung primary tumor (the presumed prototypic patients for malignancy-induced HUS) and nearly none of the patients were in disease remission, it will be difficult to delineate the exact role of gemcitabine in contributing to the observed HUS. In addition, four patients had received prior chemotherapy with MMC or 5-FU. The contribution of these agents also is unclear.

Among the 12 cases presented in this review, 6 were from clinical trials and the other 6 were from "spontaneous" sources reported by practicing oncologists. As of December 31, 1997, a total of 7654 patients had received gemcitabine in the clinical trials. In addition, based on sales and other marketing data, it was estimated that approximately 71,200 patients had been exposed to commercially available gemcitabine. Thus, the crude incidence of HUS was estimated to range from 0.078% (6 of 7654) in the clinical trials to 0.008% (6 of 71,200) reported from spontaneous sources, with an overall incidence of 0.015% (12 of 78,854). Although potential underreporting is possible (especially from spontaneous sources), when compared with the incidence rates ranging from 2.6–13.0% cited in the literature for either malignancy-induced or chemotherapy-induced HUS,[15,34,46,53,64] the incidence of HUS associated with gemcitabine therapy is relatively rare.

Although HUS can be underdiagnosed if clinicians do not maintain a high vigilance, it equally can be overdiagnosed easily, especially by clinicians who are not familiar with its diagnostic criteria. One of the difficulties in diagnosing HUS in cancer patients is that chemotherapy is known to be associated with myelotoxicities such as thrombocytopenia and anemia. In addition, because these patients usually are seriously ill and may have decreased fluid intake, decreased cardiac output due to third spacing (e.g., ascites), or baseline cardiac problems, they are susceptible to a prerenal state. Furthermore, many patients with pancreatic or lung tumors (the two major indications for gemcitabine use) are of older age and are likely to have other common medical conditions such as hypertension, diabetes, or other vascular diseases that by themselves may result in baseline renal compromise. Thus, a misdiagnosis of HUS easily can occur if such a diagnosis is based on individual observations of renal insufficiency along with common hematologic derangements of thrombocytopenia and anemia from chemotherapy without verifying the diagnosis or without exploring the possibility of alternate etiologies.

One way to distinguish isolated renal insufficiency in the presence of myelotoxicity from a true case of HUS is that in the former instance patients usually do not have a laboratory suggestion of hemolysis with microangiopathy (fragmented red blood cells; schistocytes; burr cells; increased reticulocyte count, indirect bilirubin, and LDH; or fibrin split products). In addition, the Coombs test should be negative in patients with renal insufficiency unrelated to HUS and the anemia and thrombocytopenia from myelosuppression should be more severe. A renal biopsy, if performed, will not show the classic microvascular damages with arterioles and small arteries occluded by eosinophilic hyaline thrombi containing fibrin and platelet aggregates. In addition, the mild renal insufficiency should resolve quickly or return to baseline on rehydration or treatment of the underlying prerenal state.

Conclusions

In a comprehensive review of our database, very few cases of confirmed HUS related to gemcitabine therapy were found. The crude rate suggests that the incidence is quite rare and no consistent risk factors were identified. Confounding factors such as the primary malignancies or other underlying conditions may have contributed to some of these cases. To our knowledge there is no structural similarity between gemcitabine and MMC or other chemotherapeutic agents known to cause HUS, nor any known mechanism for a relation between gemcitabine administration and HUS. In view of the large patient exposure, HUS remains a rare event. Nonetheless, as with other treatments for malignancy, clinicians should exercise prudent judgment in weighing the appropriate risk versus benefit ratio when using gemcitabine in the treatment of their patients.

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