Gemcitabine-induced thrombotic microangiopathy: a systematic review

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Thrombotic microangiopathy (TMA) is a microvascular occlusive disorder characterized by predominantly platelet thrombi in the renal and/or systemic circulations. Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are the clinical entities comprising TMA, with predominantly renal manifestations in the former, while the latter more often presents with systemic and neurological findings. In some cases, TMA includes de novo hypertension and pulmonary or central nervous system symptoms. TMA is a rare condition, which is severe and may be fatal.

Globally, two biological abnormalities explain TMA, namely: ADAMTS13 (A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 repeats) deficiency and various complement component deficiencies. Studies aimed at determining these deficiencies in cases of chemotherapy-induced TMA were not systematically available in the articles reviewed.

Gemcitabine was approved by the US Food and Drug Administration (FDA) in 1996 for the treatment of patients with metastatic pancreatic cancer and is currently used for the treatment of a wide range of malignancies, including lymphoma, lung, bladder and breast cancer. Casper et al. [1] first linked TMA to gemcitabine therapy in 1994, during a phase II trial of pancreatic cancer patients receiving this agent. The reported incidence of gemcitabine-associated TMA in the literature is very low, with a manufacturer’s estimate of 0.015% (range 0.008–0.078%) according to adverse event reports in 1997 [2], contrasting with the apparent frequency of patients with gemcitabine-associated TMA at local institutions [3,4].

Since most gemcitabine-treated patients presenting with TMA have far advanced disease and some have received other agents known to be associated with TMA, the exact role of the underlying disease and chemotherapeutic agents is not easily delineated. Although microangiopathy caused by disseminated cancer and chemotherapy-associated TMA may represent two distinct syndromes, and distinguishing clinical and histological features have been identified for these two conditions, there may be more similarities than differences. Nevertheless, clinical improvement after gemcitabine withdrawal in some cases and the result from re-exposure to the drug strongly suggest gemcitabine to be causative for TMA.

We report three patients who developed gemcitabine-associated TMA from January 2001 to December 2005, and we undertook a retrospective review to investigate the clinical manifestations and outcomes associated with this condition in case reports and Phase II/III trials.

Methods and patients

Criteria for diagnosis of thrombotic microangiopathy

There are no standard laboratory values that define TMA, but the clinical triad of renal failure, thrombocytopenia and microangiopathic haemolytic anaemia is considered the hallmark of TMA syndromes. Patients who were included in the study had kidney biopsy-proven TMA and met the following criteria within the 2 weeks leading up to diagnosis: platelet counts <120 x 10^9/l; creatinine levels >1.5 mg/dl; and evidence of microangiopathic haemolytic anaemia, including normal fibrinogen along with ≥1 schistocytes on peripheral smear, lactate dehydrogenase levels >1.5 x the upper limit of normal in the absence of another obvious cause, and/or low serum haptoglobin levels. Data such as age, gender, race, body surface area, malignancy type and stage, medical history, creatinine levels and platelet counts

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at the start of gemcitabine therapy, total dose of gemcitabine, time to development of TMA, blood pressure, laboratory parameters at the time of diagnosis of TMA, treatments received and outcome were systematically extracted from the clinical record. Patients were considered to have existing hypertension if they were receiving antihypertensive medications or had three documented blood pressure readings >140 mmHg systolic (SBP) or 90 mmHg diastolic (DBP). New or exacerbated hypertension after the initiation of gemcitabine therapy included a documented SBP reading ≥170 mmHg and a sustained increase (over two or more readings separated by at least 1 week) of >20 mmHg relative to baseline in either SBP or DBP. Due to our small sample size, no statistical analysis was performed.

Patient selection and protection of study participants

The three patients with gemcitabine-associated TMA were identified by inquiring with faculty members in the divisions of nephrology and oncology at Pitie-Salpetriere Hospital. Research data were coded to protect patient confidentiality, as required by the Department of Health and Human Services Regulations for the Protection of Human Subjects. The total number of patients treated during the study period was determined by reviewing pharmacy database records for on-label administration of gemcitabine at Clinical Oncology Department.

Furthermore, a MEDLINE search up to 31 December 2005 was conducted to identify previous reports of gemcitabine-associated HUS. The search was performed by intersecting gemcitabine with acute uraemia, haemolysis, HUS, microangiopathic haemolytic anaemia, (acute) renal failure, thrombocytopenia and TMA. Identified articles were read carefully for references to other articles eventually not found by MEDLINE. Only cases meeting classic clinical or histological criteria for HUS were included in the review.

Cases

Case 1. A 78-year-old Caucasian woman underwent modified right radical mastectomy after a Stage I infiltrating ductal carcinoma of the breast was detected. Radiotherapy and adjuvant hormone therapy with vinorelbine were performed. She was otherwise asymptomatic. Past medical history included longstanding hypertension. Five years later, multiple vertebral metastases were detected. At this time, serum creatinine level was 0.9 mg/dl. Chemotherapy with intravenous gemcitabine (1000 mg/m² on days 1, 8 and 15) and zoledronic acid (4 mg monthly), both every 4 weeks, was initiated. After her sixth cycle (with a cumulative dose of 19200 mg for gemcitabine), the patient was hospitalized with progressive shortness of breath and peripheral oedema. Admission laboratory data revealed haemoglobin of 9.6 g/dl, platelet count of 115 000 and creatinine of 2.33 mg/dl, haptoglobin decrease and new onset proteinuria. The reticulocyte count was 1.8% and lactate dehydrogenase (LDH) elevated at 700 IU/l (reference range 120–240 IU/l). Renal function continued to decline with serum creatinine rising to 2.6 mg/dl. Urinary protein excretion amounted to 4.8 g/24 h. Renal ultrasound was normal. Renal biopsy revealed global glomerular capillary thrombosis. Small arterioles had arteriolar thickening (onion skinning) associated with fibrinoid necrosis and luminal thrombosis (arrowheads). These features are pathognomonic of arterial TMA. Treatment with gemcitabine was discontinued, and her condition improved with symptomatic and corticosteroid treatments, and she was discharged. Neither plasmapheresis nor haemodialysis was performed. Three months later serum creatinine and creatinine clearance remained stable at 1.6 mg/dl and 28 ml/min, respectively. Laboratory data revealed haemoglobin of 12 g/dl, platelet count of 255 000 and proteinuria of 0.50 g per day. She is currently receiving 5-FU and oxaliplatin combination every 3 weeks, based on creatinine clearance with persistent but stable cancer disease. Zoledronic acid was discontinued.

Case 2. A 30-year-old Caucasian woman was given first-line adjuvant treatment, with a combination of gemcitabine and a platinum salt, for pulmonary adenocarcinoma <2 months after surgical management. The patient received two cures of chemotherapy, i.e. a cumulative dose of gemcitabine 3000 mg. Three days after the end of the second cure, acute renal failure occurred with new-onset hypertension and pulmonary oedema. Laboratory results confirmed mechanic (rare schistocytes) haemolytic anaemia and thrombocytopenia. Urinalysis showed microscopic haematuria with a mild proteinuria (2.2 g/day). Immunological tests [antinuclear factors, anti-double-stranded DNA, serum complement level, anticardiolipin, anti-β2-glycoprotein (GP) and anti-ENA antibodies, cryoglobulin, cryofibrinogen] were negative. The reticulocyte count was 1.8% and LDH elevated at 700 IU/l (reference range 120–240 IU/l). Renal function continued to decline with serum creatinine rising to 2.6 mg/dl. Urinary protein excretion amounted to 4.8 g/24 h. Renal ultrasound was normal. Renal biopsy findings were consistent with TMA [fibrin thrombi in glomerular capillary (Figure 1A) and pre-glomerular arteiole (Figure 1B)]. ADAMTS13 activity level was 60% with normal complement levels. Treatment with gemcitabine was discontinued and daily oral corticosteroid and plasmapheresis were initiated, with improvement of renal function excluding the need for haemodialysis. However, despite 30 total plasmapheresis treatments, intravenous immunoglobulin and corticosteroid therapies, haemoglobin level (requiring repeat red blood cell transfusions), platelet count and serum haptoglobin levels remained low. She was then treated with doxycycline 200 mg daily for 2 months. Her RBCs and platelet count rose without transfusions to 10 g/dl and 140 000/mm³ after 2 and 3 weeks, respectively, and she remained definitively free of TMA stigmata. Serum creatinine remains stable at 1.0 mg/dl.

Case 3. A 68-year-old Caucasian woman with a history of mild hypertension underwent chemotherapy for Stage IIIC papillary serous adenocarcinoma of the ovary in January 2002. She received five cycles of gemcitabine (cumulative dose, 27 g). Her baseline creatinine was 0.8 mg/dl. Surveillance laboratory data after the fifth infusion were significant for an increased creatinine to 2.5 mg/dl with
elevated LDH 1074. Her creatinine peaked at 3.6 mg/dl. Admission laboratory data revealed haemoglobin of 6.6 g/dl, platelet count of 64 000, low haptoglobin level and new onset proteinuria. The reticulocyte count was 2%. The peripheral smear revealed rare schistocytes, less than one per 1–2 oil fields. Urinalysis showed microscopic haematuria with a severe proteinuria (8 g/day). Concomitantly, the patient’s blood pressure increased from a baseline of 140/70 to 190/100 mmHg with non-cardiogenic pulmonary oedema. Blood pressure control was achieved with triple therapy and she was diuresed with furosemide. Renal biopsy revealed glomerular and arterial TMA thrombosis. Her condition improved with symptomatic, corticosteroid treatments and fresh plasma perfusion. Neither plasmapheresis nor haemodialysis was performed. Gemcitabine treatment was discontinued. She chose hormonal therapy and she remained definitively free of TMA stigmata. Her serum creatinine remained stable at 1.3 mg/dl for 23 months. However, she died of tumour progression in November 2003.

Results

Given the total of 706 patients exposed at our institution to gemcitabine during the last 5 years, these three cases indicate an incidence of gemcitabine-associated TMA of 0.4%.

Including our three cases and considering double and triple identical publications in the literature, 85 TMA cases associated with gemcitabine were identified up to 31 December 2005 [1–24]. Because of the varying completeness of reporting, findings are not presented in tabular form.

Information was available for 56 patients of which 27 were women and 29 men. Median age was 56.4 years (range 26–78 years). Primary diagnosis included primary pancreatic (n = 24), small cell lung (n = 8), ovarian (n = 6), biliary (n = 3), hepatic adenocarcinoma (n = 2), non-Hodgkin lymphoma (n = 2) and other malignancies (n = 11). All tumours were at an advanced stage except for our case 2. Prior chemotherapy had been available for 24 patients, and only four patients had previously received MMC. In 11 patients, platinium derivates were administered prior to or concomitantly with gemcitabine. The mean duration between initiation of gemcitabine therapy and onset of TMA was 7.56 ± 3.44 months (range 0.5–19 months). Information on the cumulative dose was missing in two patients; for 25 patients, only total-milligram doses were noted (28.9 ± 15.06), whereas for 29, the dose was indicated in mg/m² (19 ± 12.27). For estimation, we assumed the resulting calculated median cumulative dose was 22 480 ± 14 010 mg (range 2000–70 000 mg).

Diagnosis of TMA was confirmed by renal biopsy in 21 patients. In the other 35 patients, diagnosis was ascertained by features of microangiopathic haemolytic anaemia with fragmented red blood cells, transient thrombocytopenia, rising LDH and low haptoglobin levels.

No World Health Organization (WHO) grade 4 toxicity was seen for blood urea nitrogen or creatinine during treatment with gemcitabine. There was no suggestion of cumulative toxicity. Proteinuria was frequently reported (23 out of 35 patients, 66%), but was mild in the majority of cases. WHO grade 3 proteinuria toxicity (‘4+’ on urine dipstick or greater than 10 g/l) was seen in only one patient (3%). WHO grade 2 toxicity (‘2+’ or ‘3+’ or 3–10 g/l) occurred in six patients (17%). WHO grade 1 toxicity (‘1+’ or below 3 g/l) occurred in 16 patients (46%). The incidence of low-grade proteinuria might reflect the sensitivity and specificity of the urine sample dipstick as well as the possible toxicity of the drug. Haematuria was assessed by different methods, including both conventional ‘urine dipstick’ as well as formal laboratory microscopy. There were only reports of grade 1 haematuria in 21 out of 35 patients (60%).

New-onset hypertension or exacerbation of underlying hypertension was present in 42 of 56 subjects (75%) with dyspnoea, oedema of the ankles or lower leg, with or without pulmonary oedema. At 9 months, 75% of patients were haemodialysis-free (Figure 1). Gemcitabine was discontinued in 43 patients, without the need for further treatment in five patients and without information in 13 patients. A variety of different treatments were tried in the remaining
patients, including plasmapheresis (20 patients), steroids (eight patients) and fresh frozen plasma (four patients). In one patient, gemcitabine was continued at 14000 mg/m² with at least stabilization of renal function. Re-exposure to gemcitabine was reported in two additional patients. In one patient, the drug was re-introduced several months later because of tumour progression. After the administration of 3000 mg, the patient was noted to be ‘doing well without any recurrence of TMA’. In a second patient, in whom re-introduction was attempted, an acute myocardial infarction occurred after the second dose, resulting in death without recurrence of HUS at the time of the cardiac event. A total of 33 patients (59%) died as a result of tumour progression. Median survival was 16.5 months (95% CI, 11–24, Figure 2). Treatments and outcome were not reported in two patients. A total of 26 patients (46.42%) remained alive for variable periods (4–13 months).

Patients treated with plasmapheresis and/or haemodialysis and/or steroids and/or fresh frozen plasma improved following weeks (2–24) on haematological findings (29 out of 35 patients, 82.85%), although with persistent chronic renal failure (39 out of 56 patients, 69.64%). Twenty patients underwent haemodialysis. In only five of these patients was an improvement of renal function was noted. In one patient, death was attributed to acute renal failure, and in one patient, death was suspected to be due to the consequences of TMA. One patient underwent plasmapheresis and splenectomy, and received immunoglobulins resulting in improved renal function.

During the period January 1998 to April 2003 where 13854 patients were included in 233 phase 2 and 3 trials using gemcitabine (using a day 1, 8, 15 q 28 day, 800–1250 g/m² dose schedule), 10 cases of TMA were reported with an incidence of 0.72 [25,26].

Discussion

Incidence

Although potential under-reporting is possible (especially from spontaneous sources), when compared with the incidence rates ranging from 2.6 to 13.0% cited in the literature for either malignancy-induced or chemotherapy-induced HUS [6,27], the incidence of HUS associated with gemcitabine therapy is relatively rare. The incidence rate of gemcitabine-associated HUS of 0.4% at our institution was considerably higher than published previously, compared with the manufacturer’s initial crude estimate of 0.015% (range 0.008–0.078%) [2]. For instance, for 1997, in a total of 78800 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 71200) for out-of-study use [28], 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 0.4% incidence rate reported in our institution. Furthermore, more recently, Flombaum [8] reported 29 cases of gemcitabine-induced HUS from a single institution [8]. This might be explained by an increased awareness and a bias toward a systematic clinical and laboratory screening for it. One possible explanation for this discrepancy is that only patients with more severe manifestations were diagnosed as suffering from gemcitabine-associated TMA. However, the relatively high percentages of renal toxicity observed while using this molecule suggest that the frequency of HUS is underestimated because of the lack of medical awareness.
Time course between gemcitabine therapy and the development of HUS

It has been described that in chemotherapy-induced HUS, drug application may precede the onset of symptoms by 6–10 months, in particular following the administration of MMC. The time course between gemcitabine therapy and the development of HUS is variable, as is the cumulative dose received before symptom manifestation. The interval between the last dose of gemcitabine and the development of HUS ranged from 1 day to several months [6] as in our patients (3 days, 9 months and 24 months, in cases 2, 1 and 3, respectively). Gemcitabine-associated HUS developed after an estimated median cumulative dose of 20,000 g/m² with a range from 2450 to 48,000 mg/m² [28] as for our patients (2000, 7000 and 15,000 mg/m², in cases 2, 1 and 3, respectively). Fung et al. [2] analysed 12 patients who developed HUS while receiving gemcitabine therapy. The median duration of cytotoxic therapy was 5.8 months, with a median of 17.5 doses and cumulative therapy of 18,252 mg/m² [2]. No dose–response relationship was seen. Walter et al. [4] reviewed 26 cases of HUS associated with gemcitabine therapy via a MEDLINE literature search (including the 12 patients analysed by Fung et al. [2]). These authors found a mean time of 7.4 months between therapy start and onset of HUS, with a median cumulative dose of 20,000 mg/m² or 21.9 doses [4]. In the Flombaum report, median cumulative dose was 22,000 mg/m² (4–81) given over 7½ months (1.75–34) [8].

Symptoms

Clinically, an individual patient with gemcitabine-associated HUS may present with worsening of anaemia, thrombocytopenia, and increments of LDH or serum creatinine, elevated blood pressure, dyspnoea, peripheral oedema, proteinuria and/or haematuria, and neurological signs. However, lab signs may be isolated at the beginning of the affection [2,4,7,17,19,22,23]. This may mean that there are forms of HUS with gradual progression, and indicates the importance of a screening for suggestive anomalies (complete blood count, serum creatinine and urine dipstick) before each cycle of gemcitabine treatment. In case, renal functional alterations are noted along with anaemia and/or thrombocytopenia, complementary investigations (reticulocyte count, schizontocytes, serum haptoglobin, LDH level…) are recommended, even if a number of cases of renal failure of uncertain aetiology have been reported during treatment with gemcitabine.

Haematological findings. Accurate diagnosis of the disorder may be delayed because anaemia and thrombocytopenia may be attributed to myelotoxicity of the anticancer agents. Although an elevated reticulocyte count may be an important clue to the hyperregenerative haemolytic anaemia characterizing HUS [7], it may be low because of prior blood transfusions or myelosuppression [17]. When the diagnosis is suspected, peripheral blood smears should be screened for the presence of fragmented red blood cells. These were missing in only a few of the biopsy-proven cases of gemcitabine-associated HUS. Likewise, increased levels of LDH are observed frequently in tumour patients, but a marked increase in LDH suggest the potential development of HUS [21,24]. In the Flombaum report, anaemia and thrombocytopenia of varying degrees and elevated LDH level were present in all patients. Haptoglobin was measured in 26 patients, and it was low or undetectable in 23. Schistocytes were present in 21 of the 24 patients who had their blood smears reviewed [8]. Absence of anomalies in coagulation profile virtually excludes the diagnosis of disseminated intra-vascular coagulation otherwise frequently associated with neoplastic diseases [6].

Renal findings. Renal signs are widely variable and may appear in the form of a moderate increase in serum creatinine preceded by mild proteinuria and microscopic haematuria, or present dramatically by acute oliguric or anuric renal failure with salt and water retention as in our cases [2,5,21–24].

Proteinuria and microscopic haematuria were found at 65 and 60%, respectively, in this retrospective analysis, and at 93% in the Flombaum report [8]. Phase II trials of gemcitabine showed that WHO Grade 1/2 proteinuria, microscopic haematuria, elevated levels of blood urea nitrogen and creatinine occurred in 58, 41, 17 and 8% of patients, respectively [29]. These subclinical toxicities may reflect transient glomerular endothelial damage caused by gemcitabine. It is possible that in a small subset of patients, particularly those with stable or expanding disease who continue to receive the drug for an extended period of time, the cumulative effect of this glomerular endothelial damage may results in the development of clinically evident TMA.

A definitive diagnosis theoretically depends on a renal biopsy where glomerular and/or arteriolar fibrin deposits are demonstrated using immunofluorescence techniques [2,11,21,24]. One should not forget, however, that renal biopsy is an invasive procedure with haemorrhagic risks even with the transjugular approach if low platelet count contraindicates the percutaneous one. It is not indispensable if suggestive clinical and biological signs are present. However, some authors still recommend that renal histology be performed, since it allows quantification of irreversible sclerotic lesions that may influence renal prognosis. Furthermore, in some cases, clinical and biological signs remain discreet and renal histology is mandatory to establish the diagnosis of MAT. Indeed, localized renal TMA can develop in the absence of the typical haematological disturbances, and cases have been described in which localized TMA was diagnosed by renal biopsy and subsequently progressed to other organs [30]. Furthermore, localized renal TMA can
develop in the absence of the typical haematological disturbances, and cases have been described in which localized TMA was diagnosed by renal biopsy but subsequently progressed to other organs [30].

Renal outcome was variable. Full or partial recovery of renal function occurred in 66% of patients (after requiring dialysis for several months). A total of 34% of the patients developed chronic renal failure in which 24% progressed to end-stage renal failure needing dialysis [8], as in our review of the literature (23%).

Hypertension. Hypertension very often accompanies TMA syndromes (75% in this retrospective analysis), and the severity of hypertension and associated arteriolar changes is correlated with poor outcome in some series [31]. Fung et al. [2] reported new hypertension in 7 out of 12 patients, but did not investigate the timing of this finding relative to diagnosis. Flombaum [8] described worsening of pre-existing hypertension or new onset of severe hypertension in 90% of the patients. Oedema and chronic heart failure was present in 72 and 24%, respectively. In the Humphreys series, three patients had a significant lag (6–10 weeks) between the documentation of SBP elevation and the diagnosis of TMA [3]. This suggests that new or exacerbated hypertension could be used as a clue in diagnosing a developing TMA syndrome earlier than it would otherwise be detected. Weekly visits to the infusion unit, where vital signs are measured, present a unique chance to detect new hypertension as it develops. Because hypertension plays a prominent role in TMA syndromes in general and in drug-associated TMA syndromes in particular, more widespread recognition of this important association could lead to earlier diagnosis in some patients.

Outcome. The prognosis for HUS associated with malignancy is rather poor. While in general HUS is associated with mortality rates of 10–20%, prognosis for chemotherapy-induced HUS is clearly worse with mortality rates of 40–90% reported in most studies [28,32]. To a large extent this poor prognosis is determined by the underlying malignancy, as paraneoplastic as well as chemotherapy-induced HUS frequently occurs in advanced disease. In one prospective study, Lohrmann et al. [33] assessed the incidence of TMA in patients with metastatic carcinomas at between 5 and 6%. In the present review, 60% of the patients with reported outcome died of tumour progression with a median survival time to 16 months (Figure 2); in two cases death was believed to be a direct consequence of HUS.

Treatments. Aspirin, dipyridamole and corticosteroids have been described as beneficial by some authors [34], but there is still a lack of convincing evidence on this point. Glucocorticoids and plasma infusion may be used in the initial management, but plasma exchange is the mainstay of treatment [35]. 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 TMA associated with malignancy itself or chemotherapy is less conclusive [36]. The role of plasma exchange therapy in such patients is unclear as the most important step is to discontinue the offending drug. There are no convincing data to support the efficacy of plasma exchange for syndromes that appear similar to TMA following cancer chemotherapy, such as mitomycin C. However, with certain other drugs such as quinine, the disease is so explosive that plasma exchange seems mandatory. More encouraging results for the treatment of chemotherapy-induced HUS have been reported for protein A immunoadsorption, with response rates of 45–75% observed in some studies [37]. In general, improvement of haematological parameters has been reported relatively frequently with plasma exchange therapy, whereas renal function only rarely responds. A number of case reports have indicated success employing the anti-CD20 antibody rituximab, with or without cyclophosphamide, in patients with primary refractory or relapsing TTP, with decrease or disappearance of the inhibitor to the von Willebrand factor (vWF)-cleaving protease, along with improvement of protease levels in some responders [38]. Recently, we reported a dramatical improvement on TMA only after doxycycline use [39], as in our case 2. Finally, several authors have described a dramatic escalating of HUS associated with blood and platelet transfusions.

Pathogenesis. The mechanism of action is still unclear, but it has been suggested that endothelial injury is the central feature. In endothelial cells, vWF is synthesized and assembled in larger multimers that are rapidly degraded in the circulation into the normal size range of vWF multimers by a specific vWF-cleaving protease (or ADAMTS13). ADAMTS13 activity is typically absent or severely deficient (i.e. <5% of normal) in patients with familial TTP. It is clear that absence of ADAMTS13 activity is a necessary but not sufficient condition to bring about this clinical syndrome. Furthermore, an inhibitory autoantibody to the ADAMTS13 metalloprotease has been found at varying titers among a high percentage of patients with the idiopathic form of this disease [40]. Based upon the previous reports, the underlying mechanism of HUS does not appear to be related to a deficiency in ADAMTS13 activity [41,42]. However, these data require confirmation in a prospective case series to validate the apparent distinction between TTP and HUS, in which the initial diagnosis was made clinically by the physicians providing the patient samples. Interestingly, patients with metastatic cancers, among other conditions, also have reduced serum ADAMTS13 activity [43]. Building on this, one might ask whether gemcitabine cause antibodies formation against the ADAMTS13 enzyme?
On the other hand, some authors propose direct drug-induced endothelial damage with concomitant activation of the clotting cascade as the inciting factor [44], and presume that direct endothelial injury is the initiating event in these settings. However, the onset of clinically evident disease is often delayed, frequently occurring months after chemotherapy has been discontinued [45]. Affected patients typically present with slowly progressive renal failure, new or exacerbated hypertension [3], and a relatively bland urine sediment, often occurring in the absence of a clinically apparent tumour. The syndromes resembling TMA, following mitomycin C and other chemotherapeutic agents such as cyclophosphamide appear to be a direct toxicity related to the cumulative dose of the drug.

Platelet activation in TMA may be a secondary response to endothelial injury [46]. The endothelial damage could be directly induced by a drug or indirectly via neutrophil or platelet activation [47]. The renal and cerebral vessels are commonly involved, while the pulmonary and hepatic microvasculature are usually spared. These differences in vascular endothelial damage might be explained by the anatomic restriction of CD36, the thrombospondin receptor (also known as GP IV when found on the platelet surface). CD36 is found on human microvascular endothelial cells, but not endothelial cells of large (umbilical) vessels.

Perspectives and practice

The incidence of gemcitabine-associated TMA may increase in coming years. Gemcitabine is being investigated in combination with a variety of other anticancer chemotherapeutic agents. As more patients respond to these combinations, patients may be exposed to the drug for extended times, potentially increasing the chance of developing TMA syndrome. Use with other renal toxins such as cisplatin, which is known to cause a TMA syndrome when administered as a single agent, could also increase TMA risk. Early intervention may improve the clinical impact of this highly fatal disease. Most importantly, the inciting agent should be discontinued immediately. Furthermore, earlier serological testing for TMA based on new or exacerbated hypertension would result in either earlier diagnosis or improved outcome. We would suggest looking specifically for clinical as well as biological markers of TMA before each cycle of Gemcitabine treatment as an integral part of surveillance protocols. Clinicians should be aware of de novo hypertension or destabilization of a previously controlled one. Pulmonary oedema should be particularly looked for. Biologically, each cycle should be preceded by a search for stigmata of mechanical haemolytic anaemia (complete blood count (CBC) with search for schistocytes, bilirubin, LDH and haptoglobin serum levels) and renal parameters (serum creatinine, proteinuria and haematuria).

Conclusion

The increasing number of patients treated with gemcitabine warrants a deeper understanding of this serious complication. Although it seems rare, this disorder is potentially fatal, and ancillary treatments or antidotes improving outcome have not been identified. A high index of suspicion for HUS is essential when cancer patients are treated with gemcitabine, especially with prolonged therapy. Any worsening of anaemia, thrombocytopenia, increments of LDH or serum creatinine, clinical deterioration with elevated blood pressure, dyspnoea, peripheral oedema, neurological signs or haematuria should prompt a careful evaluation and the timely discontinuation of gemcitabine.

Conflict of interest statement. None declared.

References

8. Flombaum CD. Gemcitabine nephrotoxicity and the Hemolytic Uremic Syndrome (HUS): report of 29 cases from a single institution. SA-PO1008. ASN 2005
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