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Gemcitabine and disseminated intravascular coagulation/ thrombotic microangiopathy

Summary

Gemcitabine a nucleoside analogue, is an anti-metabolite used for the treatment of various cancers including non-small cell lung cancer, pancreatic cancer, bladder cancer, breast cancer, ovarian cancer, and hepatobiliary cancer. Several cases of *disseminated intravascular coagulation* (DIC) with its subordinate Included Term (IT) *thrombotic microangiopathy* (TMA) have been reported in patients treated with gemcitabine through the Korean Adverse Event Reporting System. A few published studies support the hypothesis of an association between gemcitabine and DIC/TMA as well. Although DIC/TMA seem to be rare adverse events of gemcitabine, health care professionals should be aware of it due to its potentially life-threatening complication.

KIDS
Korea Institute of Drug Safety & Risk Management

Introduction

Gemcitabine, a cytosine analogue, is an antimetabolite that inhibits DNA synthesis by blocking the cellular progression at G1/S-phase boundary. It is indicated for non-small cell lung cancer, pancreatic cancer, bladder cancer, breast cancer, ovarian cancer, and hepatobiliary cancer in Republic of Korea.

Disseminated intravascular coagulation (DIC) is a hemorrhagic syndrome that occurs following the uncontrolled activation of clotting factors and fibrinolytic enzymes throughout small blood vessels. Fibrin is deposited and platelets and clotting factors are consumed, and fibrin degradation products inhibit fibrin polymerization, leading to tissue necrosis and bleeding [1]. Thrombotic microangiopathy (TMA) is a microvascular occlusive disorder characterized by the clinical manifestation of thrombocytopenia, microangiopathic haemolytic anaemia, and organ damage [2, 3].

Reports (in KAERS)

From 1989 until June 2017 the Korea Institute of Drug Safety and Risk Management (KIDS) received 41 reports of DIC/TMA (7 domestic cases, 34 foreign cases) associated with the use of gemcitabine through the Korean Adverse Event Reporting System (KAERS), the system for collecting post-marketing ICSRs in Korea.

Domestic cases which reported the WHO-ART preferred term (PT) “disseminated intravascular coagulation” or the included terms (ITs) “thrombotic microangiopathy”, and foreign cases which reported the MedDra PT “disseminated intravascular coagulation” were included in the assessment. After reviewing the reports, 5 duplicate reports (4 domestic duplicate cases, 1 foreign duplicate case) were excluded, and the remaining 36 reports underwent signal evaluation.

Three reports originated from Republic of Korea, whereas 33 reports were from 4 other countries including France (1 report), Italy (1), Japan (30), and Spain (1). Gemcitabine was the only suspected drug in 6 cases and it was the only reported drug in 1 case. The most frequently co-reported drugs were paclitaxel including nanoparticle albumin-bound paclitaxel (nab-paclitaxel) (29 cases), which may also cause DIC, followed by omeprazole including esomeprazole (11 cases) and oxycodone (6). Most co-reported events were septic shock (8 cases), neutrophil count decreased (7), pneumonia (7), and sepsis (7). These co-reported reactions may have contributed to DIC.

Well documented Individual Case Safety Reports (ICSRs) are summarized in Table 1. Case 1 presents a 45-year-old male who developed TMA after administration of gemcitabine plus nab-paclitaxel for treatment of pancreatic cancer. After his sixth cycle, he was hospitalized with fever, nausea, and abdominal pain. Admission laboratory data confirmed proteinuria, azotemia, hemolysis and aggravating renal function. Gemcitabine was withdrawn and his condition improved with active treatment including diuretics and calcium channel blockers. The reporting nephrologist considered TMA to be possibly related to gemcitabine as well as uncontrolled malignancy.

Case 2 describes a 55-year-old male with a single kidney who experienced elevation of the liver enzyme level, and elevated blood pressure 3 months after the start of palliative chemotherapy with gemcitabine for urothelial cancer. He was diagnosed with gemcitabine-induced TMA, which was confirmed by renal biopsy. Gemcitabine was withdrawn and started the second-line chemotherapy with weekly paclitaxel and he had recovered from TMA.

Case 3 concerns a 64-year-old female, a kidney transplant recipient, who developed simvastatin-induced rhabdomyolysis, acute kidney injury, urinary tract infection, DIC, and septic shock triggered by gemcitabine plus cisplatin combination chemotherapy for lung cancer in addition to sirolimus for prophylaxis of kidney transplant rejection. Two weeks after the first chemotherapy, she was hospitalized with general myalgia, and severe diarrhea. Although all suspected drugs were withdrawn and hemodialysis along with symptomatic treatment were performed, septic shock caused by the urinary tract infection and DIC did not improve, and the patient died 30 days after admission.

In Case 4 a 68-year-old male experienced DIC and anaemia 13 days after starting gemcitabine and vinorelbine for squamous cell carcinoma of lung. He intravenously received platelet transfusion for the DIC and red blood cell transfusion for the anaemia. The patient was recovering from DIC 6 weeks after gemcitabine had been withdrawn. The reporting pulmonologist considered DIC and anaemia were related to gemcitabine and stated that there was no other factor causing these events.

Case 5 concerns a 78-year-old male with unresectable cancer in the head of the pancreas developed haemolytic uraemic syndrome and DIC after starting gemcitabine. The patient received treatment including rehydration, diuretics and blood transfusion. At the time of reporting, haemolytic uraemic syndrome and DIC improved.

Table 1. Characteristics of well-documented ICSRs in KAERS of DIC associated with gemcitabine

Case	Age /Sex	Suspected drugs	Concomitant drugs	Adverse events* [Verbatim terms or Included terms]	Time to onset†	Action taken	Outcome
1	45/M	**Gemcitabine**	Nab-paclitaxel	· **Disseminated intravascular coagulation [Thrombotic microangiopathy]**	7.5 months	Unknown	Recovering
2	55/M	**Gemcitabine**	Cisplatin	· **Disseminated intravascular coagulation [Thrombotic microangiopathy]** · Hepatic enzymes increased · Hypertension	3 months	Drug withdrawn	Recovered

3	64/F	**Gemcitabine** Cisplatin Simvastatin Sirolimus	None	· **Disseminated intravascular coagulation** · Rhabdomyolysis [Simvastatin-induced rhabdomyolysis] · Sepsis [Septic shock] · Renal failure acute [Acute kidney injury] · Diarrhea [Severe diarrhea] · Urinary tract infection · Asthenia [Weakness] · Labeled drug-drug interaction medication error [Drug interaction]	Unknown	Drug withdrawn	Died
4	68/M	**Gemcitabine** Vinorelbine	None	· **Disseminated intravascular coagulation** · Granulocytopenia [Neutrophil count decreased] · Anaemia · Granulocytopenia [White blood cell count decreased] · Fever [Tumour associated fever]	13 days	Drug withdrawn	Recovering
5	78/M	**Gemcitabine**	Unknown	· **Disseminated intravascular coagulation** · Haemolytic uraemic syndrome · Pulmonary oedema	Unknown	Unknown	Recovering

* WHO-ART preferred terms (PTs) for domestic and MedDRA PTs for foreign cases.
† The duration of gemcitabine treatment prior to initial presentation of signs and symptoms of disseminated intravascular coagulation (thrombotic microangiopathy)

Literature and Labeling (Other sources of information)

At the time of the assessment in May 2018, hemolytic anaemia, thrombocytopenia, and petechiae which could indicate DIC or TMA were listed as adverse events but DIC and TMA were not listed in the product labels for gemcitabine in Republic of Korea. Furthermore, neither DIC nor TMA was mentioned in the UK, US, or Japanese labeling for gemcitabine products. In December 2018, the Ministry of Food and Drug Safety (MFDS) has announced that product information for gemcitabine should be revised to include DIC and TMA as adverse events based on the results of the KIDS's assessment. In 2019, the US [4] and UK [5] product label for gemcitabine were subsequently updated to include TMA in the section for an adverse reaction.

There were a few published studies on gemcitabine-associated TMA. A systematic review identified 85 cases of gemcitabine-associated TMA from 2001 to 2005 derived from case reports and Phase II/III trials, and reviewed retrospectively the clinical manifestations and outcomes of the cases. For 56 cases with enough patient information to analyze, the duration of gemcitabine treatment prior to initial presentations of signs and symptoms of TMA ranged from 0.5 to 19 months (mean 7.56 months). Signs and symptoms of TMA included worsening anemia, thrombocytopenia, increased serum creatinine and lactic dehydrogenase, hypertension, dyspnea, peripheral edema, proteinuria, hematuria, neurological signs, and fragmented red blood cells [6].

One case study reported that hemolytic uremic syndrome TMA developed in a 63-year-old Caucasian male with metastatic non-small cell lung cancer who received 3 cycles of gemcitabine and carboplatin, followed by 7 cycles of gemcitabine alone. A week after the seventh gemcitabine dose, the patient was admitted with hemolysis, thrombocytopenia, macroscopic hematuria, renal dysfunction and worsening high blood pressure. Hematological disorders quickly resolved after receiving antihypertensive agents, plasma infusion and hemodialysis. However, renal failure persisted, leading to continuation of hemodialysis for about 3 months until he died [7].

Although the pathophysiology related to gemcitabine-associated TMA remains unclear, it seems to involve endothelial injury [8, 9]. Both immune and non-immune mechanisms have been suggested by previous studies. Certain studies have suggested that gemcitabine induces formation of antibodies that interact with multiple cells including platelets, neutrophils and endothelial cells, thus resulting in microvascular damage and formation of platelet microthrombi, whereas other studies have been proposed a direct gemcitabine-induced endothelial injury promotes activation of the coagulation cascade as the inciting factor [10, 11].

Discussion and Conclusion

The majority of the reports have co-reported drugs such as other chemotherapeutic agents and/or adverse events that may have contributed to DIC/TMA. Moreover, patients treated with gemcitabine have thrombotic tendency due to the underlying carcinoma [12]. However, clinical improvements observed after gemcitabine cessation in some cases and physicians' causality assessment support the association between gemcitabine and DIC/TMA. Although DIC/TMA induced by gemcitabine occurs rarely, Health care professionals should be aware of its life-threatening complication.

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