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Time to Onset of Gemcitabine-induced Thrombotic Microangiopathy in a Japanese Population: A Case Series and Large-scale Pharmacovigilance Analysis

MASAKI TAKIGAWA[1,2,3], HIROYUKI TANAKA[3], HIROMI WASHIASHI[1], TOSHIHISA ONODA[3], AKIHITO ISHIGAMI[2] and TOSHIHIRO ISHII[3]

[1]*Department of Pharmacy, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan;*
[2]*Molecular Regulation of Aging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan;*
[3]*Department of Practical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, Funabashi, Japan*

Abstract. *Background/Aim: Gemcitabine-induced thrombotic microangiopathy (G-TMA) is associated with a high mortality rate. However, owing to its low incidence, data on G-TMA remain limited. Therefore, a detailed review of G-TMA cases is critical to understand this adverse event. In addition, reviewing literature and pharmacovigilance analytics may be useful to characterise G-TMA. Here, time to onset of G-TMA was analysed based on available data. Patients and Methods: We collected data for a case of TMA following gemcitabine administration at the Tokyo Metropolitan Geriatric Hospital. We also reviewed the literature on G-TMA cases in Japan from April 2000 to March 2022 to provide a case series. Moreover, we performed time-to-onset analysis of G-TMA using the data from the Japanese Adverse Drug Event Report (JADER) database. Results: Our case involved a patient with pancreatic cancer who developed thrombotic thrombocytopenic purpura 13 months after starting gemcitabine treatment. From the literature reviewed, in 14 out of 17 cases, G-TMA occurred 5-8 months after treatment initiation. The analysis of data from the JADER database showed that the median time to onset of G-TMA was 161 days. Weibull shape parameter analysis showed that the pattern of onset of G-TMA represented a random failure. Conclusion: This study elucidated the time to onset of G-TMA in a Japanese population. Weibull shape parameter analysis showed that G-TMA may not necessarily develop in a dose-dependent manner. These results may be useful for monitoring G-TMA in the clinical setting.*

Correspondence to: Hiroyuki Tanaka, Ph.D., Department of Practical Pharmacy, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi-shi, Chiba 274-8510, Japan. Tel/Fax: +81 474721633, e-mail: hiroyuki.tanaka@phar.toho-u.ac.jp

Key Words: Gemcitabine, thrombotic microangiopathy, Japanese Adverse Drug Event Report database, time to onset, Japan.

Gemcitabine is a metabolic antagonist of nucleotide analogues. Upon administration, gemcitabine is metabolised to active nucleotide diphosphate and triphosphate compounds by cells throughout the body; these compounds exert their cytocidal effects by inhibiting DNA synthesis (1). Gemcitabine is administered alone or in combination with other anticancer drugs to treat a range of diseases, including ovarian, bladder, non-small cell lung, pancreatic, and breast cancer (2-6). Frequently observed adverse events of gemcitabine include nausea, vomiting, and hepatic impairment, such as increased aspartate aminotransferase and alanine aminotransferase levels; more severe adverse events include myelosuppression, such as neutropenia (7).

Thrombotic microangiopathy (TMA) is a disease characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and organ damage due to platelet thrombus. The cranial nerves and kidneys are damaged due to microangiopathy (8). Typical diseases presenting with TMA include haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). The aetiology of TMA is a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, infection-associated TMA, complement-related TMA, coagulation-related TMA, and secondary TMA. Drug-induced TMA is classified as secondary TMA, and causative drugs include anticancer drugs such as gemcitabine (9), mitomycin C (10), and 5-fluorouracil (10); antiplatelet drugs such as ticlopidine (11) and clopidogrel (12); and immunosuppressive drugs such as cyclosporine and tacrolimus (13).

Gemcitabine is a leading cause of drug-induced TMA (8, 9). The pathogenesis of gemcitabine-induced TMA (G-TMA) is not clear; however, exposure of vascular sub-endothelium to gemcitabine, reduced prostacyclin, and secretion of the von Willebrand factor may be involved in thrombus formation (14, 15). A high mortality rate of 60% has also been reported in cases of G-TMA (15). The incidence of G-TMA has been reported to be as low as <1% (16, 17). Therefore, a detailed review of G-TMA cases is critical to understand this adverse event. In addition, a literature review and pharmacovigilance analysis may be useful to understand G-TMA further.

Gemcitabine is a drug often administered repeatedly over a prolonged period; however, the time of onset of G-TMA has not been conclusively established. G-TMA is more likely to occur when the cumulative dose of gemcitabine exceeds 20,000 mg/m^2 and at approximately 5-8 months after the start of treatment; case reports have corroborated the dose-dependent onset of G-TMA (9, 15). While dose-dependence of G-TMA has been reported, the dose-dependent onset of G-TMA has not yet been confirmed, and G-TMA onset reportedly occurs before the cumulative dose of gemcitabine exceeds 20,000 mg/m^2 (18, 19). As noted above, owing to the low incidence of G-TMA, few studies have focused on its time to onset using multiple patients. However, the time to onset of G-TMA must be considered because gemcitabine is a frequently used anticancer drug and G-TMA is associated with a high mortality rate. Therefore, in this study, we retrospectively analysed the time to onset of G-TMA from three real-world settings: Clinical data from one patient treated with gemcitabine at the Tokyo Metropolitan Geriatric Hospital; a G-TMA case series from Japan based on a literature review, and G-TMA cases recorded in the Japanese Adverse Drug Event Report database (JADER) of the Pharmaceuticals and Medical Devices Agency. To the best of our knowledge, this is the first study in Japan to examine the time to onset of G-TMA using multiple patient data.

Patients and Methods

Case report. Data of a case of TMA following gemcitabine administration at Tokyo Metropolitan Geriatric Hospital were collected. Written informed consent from the patient was not obtained as the data were collected retrospectively. The Ethics Committee of Tokyo Metropolitan Geriatric Hospital confirmed that ethical review was not required for this investigation (R22-041).

Literature review. A literature review was conducted using two databases, PubMed (https://pubmed.ncbi.nlm.nih.govh) and IgakuChuoZasshi (https://search.jamas.or.jp/search). We investigated case reports in English and Japanese published in Japan between April 2000 and March 2022 using the key words 'gemcitabine' and 'thrombotic microangiopathy', 'haemolytic uraemic syndrome', or 'thrombotic thrombocytopenic purpura'. Seventeen verifiable case reports were obtained.

	TMA cases	Non-TMA cases
Gemcitabine	A	B
Other drugs	C	D

$$\mathrm{ROR} = \frac{A/C}{B/D}$$

$$95\%\ \mathrm{CI} = \exp\left[\log(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}\ \right]$$

Figure 1. *Two-by-two contingency table for calculating reporting odds ratio (ROR) and 95% confidence interval (CI). TMA: Thrombotic microangiopathy.*

Case and exposure definition in pharmacovigilance analysis. We obtained data from the JADER database on the Pharmaceuticals and Medical Devices Agency website (https://www.pmda.go.jp/), from April 2004 to September 2021. In the JADER database, the adverse events are based on preferred terms in the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) (https://www.jmo.pmrj.jp). In this study, the following four preferred terms related to TMA in MedDRA/J version 24.0 were adopted: 'thrombotic microangiopathy', 'renal-limited thrombotic microangiopathy', 'thrombotic thrombocytopenic purpura', and 'haemolytic uraemic syndrome'. In the JADER database, 'drug involvement' is classified into three categories: 'suspected drug', 'concomitant drug', and 'interaction'. Only TMA cases with gemcitabine as a 'suspected drug' were included in the analysis.

Disproportionality analysis based on JADER and US Food and Drug Administration Adverse Event Reporting System (FAERS). To compare the reporting ratio of TMA between patients who were administered gemcitabine or other drugs, we calculated reporting odds ratios (ROR) and 95% confidence interval (CI) using a two-by-two table with data extracted from JADER (Figure 1). To support the results based on JADER, we calculated the ROR using data from the FAERS. Data registered in FAERS from April 2004 to September 2021 were analysed using OpenVigil (http://openvigil.sourceforge.net/), an open-access tool. In both analyses, a positive signal was defined when the lower limit of the 95% CI of ROR was >1.

Clinical characterisation and time-to-onset analysis of G-TMA in JADER. Using JADER, we analysed the time to onset of G-TMA in patients reported to have developed TMA with gemcitabine as the suspected drug. The exclusion criteria were as follows: Cases with missing data for the date of gemcitabine initiation or TMA onset, cases that could be considered duplicates (*i.e.*, cases considered to be duplicates based on the time of event onset, age, sex, and primary disease). The time to onset of G-TMA was defined as: TMA onset date − gemcitabine administration start date + 1. We also studied time to onset by sex, age group, cancer type, TMA classification, and clinical outcomes. As JADER reports age in 10-year increments, we defined 'younger' as those in their 50s or younger and 'older' as those in their 60s or older. Clinical outcomes were defined as 'good outcomes' for recovery or remission, and 'poor outcomes' for sequelae, no recovery, or death. Cases with unknown outcomes were excluded from the analysis. In addition, Weibull shape parameter tests, which are used for the statistical analysis of time to onset data and can express stationarity in the

Table I. *Data for Japanese cases of gemcitabine-induced thrombotic microangiopathy compiled from a case at Tokyo Metropolitan Geriatric Hospital and cases from a literature review. The case reported at Tokyo Metropolitan Geriatric Hospital and those reported in Japan between April 2000 and March 2022 in PubMed and IgakuChuoZasshi with key words 'gemcitabine' and 'thrombotic microangiopathy', 'haemolytic uraemic syndrome', or 'thrombotic thrombocytopenic purpura' are summarised.*

Patient no.	Study author (Ref)	Sex	Age, years	Primary disease	Gemcitabine administration			Concomitant medications	TMA classification	Time to onset of TMA, months	Clinical outcome
					Dosage	Cumulative dose	Duration, months				
1	Our case	Male	85	Pancreatic cancer	1,000 mg/m^2	39,520 mg/m^2	13	None	TTP	13	Death
2	Matsuo *et al*., 2003 (20)	Male	70	Pancreatic cancer	1,000 mg/m^2	21,000 mg/m^2	7	None	HUS	7	Death
3	Toyonaga *et al*., 2008 (21)	Male	71	Pancreatic cancer	1,600 mg	29,000 mg/m^2	8	None	HUS	8	Recovery
4	Hoshikawa *et al*., 2009 (22)	Male	42	Bile duct cancer	400 mg	14,400 mg	9	None	HUS	9	Death
5	Nasu *et al*., 2010 (23)	Male	70	Pancreatic cancer	1,000 mg/m^2	12,000 mg/m^2	4†	None	HUS	4†	Recovery
6	Wato *et al*., 2010 (24)	Male	63	Pancreatic cancer	1,000 mg/m^2	48,000 mg/m^2	14†	None	HUS	14†	Sequelae
7	Nishijima *et al*., 2013 (25)	Female	61	Lung cancer	700 mg/m^2	28,900 mg	12	Bevacizumab	TTP	12†	Recovery
8	Nishizawa *et al*., 2013 (26)	Female	54	Ovarian cancer	1,000 mg/m^2	24,000 mg/m$^{2\#}$	-	CBDCA	HUS	10$^{\#,\dagger}$	Sequelae
9	Yamada *et al*., 2014 (27)	Female	58	Gallbladder cancer	-	-	7	None	HUS	8$^{\#,\dagger}$	Sequelae
10	Katagiri and Hinoshita, 2018 (28)	Female	46	Pancreatic cancer	400-600 mg/m^2	11,000 mg	8	None	TMA	8$^{\#,\dagger}$	Recovery
11	Kobayashi *et al*., 2019 (29)	Male	60s	Pancreatic cancer	1,000 mg/m^2	15,000 mg/m$^{2\#}$	6†	Nab-PTX	TMA	7†	Recovery
12	Koshino *et al*., 2019 (30)	Male	70s	Pancreatic cancer	800 mg/m^2	53,600 mg/m^2	25	None	TMA	25	Death
13	Koshino *et al*., 2019 (30)	Female	80s	Bile duct cancer	800 mg/m^2	16,000 mg/m^2	9	None	TMA	9	Death
14	Suzuki *et al*., 2019 (31)	Male	66	Lung cancer	1,000 mg/m^2	2,000 mg/m^2	0.5†	CDDP	TTP	0.5†	Death
15	Shimokawa *et al*., 2020 (32)	Male	40s	Pancreatic cancer	750 mg/m^2	52,000 mg/m^2	37†	None	TMA	37†	Recovery
16	Shimokawa *et al*., 2020 (32)	Male	70s	Pancreatic cancer	820 mg/m^2	18,040 mg/m^2	11†	None	TMA	11†	Recovery
17	Nishikubo *et al*., 2021 (33)	Female	43	T-Cell lymphoma	1,000 mg/m^2	2,800 mg	0.8†	DEX, CDDP	TMA	0.9†	Recovery
18	Kashima *et al*., 2022 (34)	Male	57	Pancreatic cancer	1,000 mg/m^2	42,000 mg/m^2	12	Nab-PTX	TMA	12	Recovery

CBDCA: Carboplatin; CDDP: cisplatin; DEX: dexamethasone; HUS: haemolytic uraemic syndrome; Nab-PTX: nanoparticle albumin-bound paclitaxel; TMA: thrombotic microangiopathy; TTP: thrombotic thrombocytopenic purpura. #Estimation from the literature. †Approximately. -: Information cannot be verified from literature.

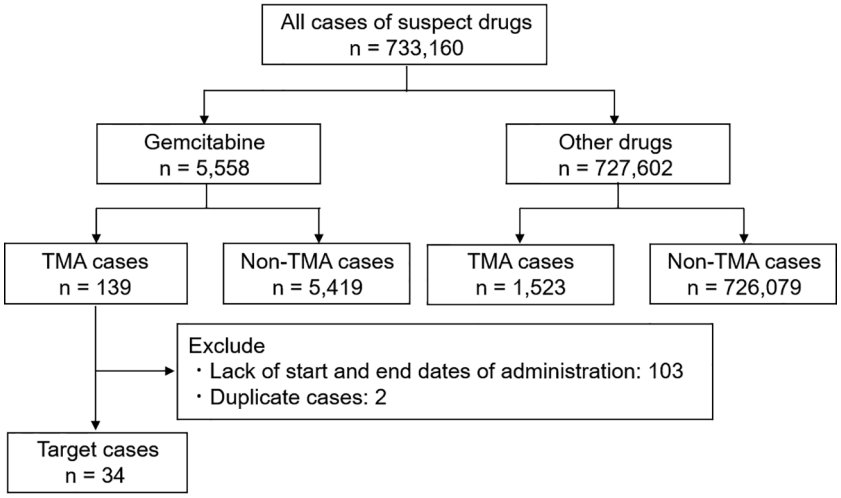


Figure 2. *Number of cases used to calculate the reporting odds ratio in the Japanese Adverse Drug Event Report database and flowchart of the indicated and excluded cases. Target cases were used for time-to-onset analysis. TMA: Thrombotic microangiopathy.*

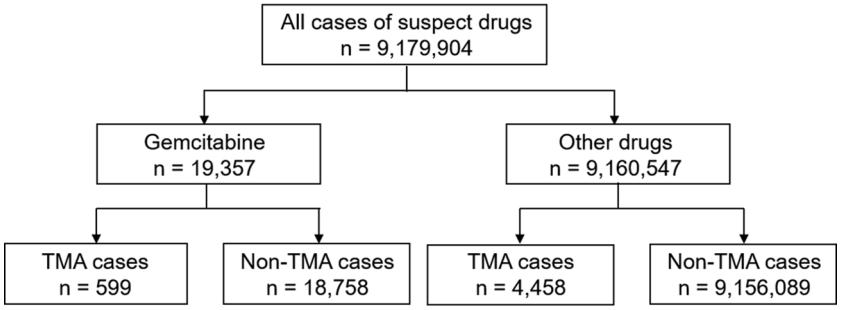


Figure 3. *Number of cases used to calculate reporting odds ratio in the Food and Drug Administration Adverse Event Reporting System database. TMA: Thrombotic microangiopathy.*

incidence of adverse effects, were performed to evaluate the time to TMA onset. Larger values of the scale parameter α indicate a wider distribution, whereas the shape parameter β indicates the hazard in the absence of a reference population. When β=1, the onset of adverse effects is presumed to be constant over time. When β>1 and the 95% CI for β does not include 1, the incidence of adverse effects is considered to increase over time. When β<1 and the 95% CI for β does not include 1, the incidence of adverse effects is considered to decrease over time.

Statistical analysis. Continuous data, such as time to onset of G-TMA, are presented as median (range). The time to onset of TMA among groups (sex, age group, cancer type, TMA classification, and clinical outcomes) were compared using Mann-Whitney *U*-test (comparison of two groups) and analysis of variance followed by post-hoc Bonferroni correction (multi-group comparison). Weibull shape parameters were calculated using JMP Pro, version 15.0.1 (SAS Institute Inc., Cary, NC, USA). SPSS Statistics 28 STANDARD (IBM Inc., Armonk, NY, USA) was used for all other statistical analyses.

Results

Case report. An 85-year-old man had been diagnosed with pancreatic cancer 2 years earlier. The patient had been administered one course of gemcitabine (1,000 mg/m^2: days 1, 8 and 15) 1 year earlier. Owing to thrombocytopenia, the gemcitabine dose was reduced by 80% from the 14th cycle, and further reduced by 80% in the 15th cycle. Thirteen months after the start of gemcitabine treatment (7 days after the last dose of gemcitabine), the patient was admitted to the hospital owing to a fever and dyspnoea. At this point, the cumulative dose of gemcitabine was 55,270 mg (39,520 mg/m^2). Upon admission, the patient's levels of platelets, haemoglobin, serum creatinine and blood urea nitrogen (BUN) were 116,000/μl, 7.5 g/dl, 1.51 mg/dl, and 27 mg/dl respectively, and the body temperature was 37.1˚C. From the time of admission, the patient was administered oxygen and

Table II. *Background data of cases with gemcitabine-induced thrombotic microangiopathy (TMA) in the Japanese Adverse Drug Event Report database.*

Characteristic		No. of patients (%)
Sex	Male	22 (64.7)
	Female	12 (35.3)
Age, years	10-19	2 (5.9)
	40-49	1 (2.9)
	50-59	5 (14.7)
	60-69	11 (32.4)
	70-79	15 (44.1)
Indication for gemcitabine	Pancreatic cancer	21 (61.8)
	Gallbladder cancer	4 (11.8)
	Ovarian cancer	2 (5.9)
	Kidney cancer	1 (2.9)
	Unknown	6 (17.6)
TMA classification	TMA[a]	15 (44.1)
	TTP	2 (5.9)
	HUS	17 (50.0)
Clinical outcomes of TMA	Recovery	5 (14.7)
	Remission	10 (29.4)
	Sequelae	8 (23.5)
	No recovery	6 (17.6)
	Death	3 (8.8)
	Unknown	2 (5.9)

HUS: Haemolytic uraemic syndrome; TTP: thrombotic thrombocytopenic purpura; [a]Included renal-limited TMA.

Table III. *Comparison of time to onset of gemcitabine-induced thrombotic microangiopathy (TMA) among different patient groups. Time to onset of TMA among groups (sex, age group, TMA classification, type of cancer, and clinical outcomes) were compared using Mann-Whitney U-test (comparison of the two groups) and analysis of variance followed by post-hoc Bonferroni correction (multi-group comparison).*

Characteristic	Median time to onset (range), days	*p*-Value
Total (n=34)	161 (7-1,219)	–
Sex		
Male (n=22)	156.5 (8-1,219)	0.631
Female (n=12)	246 (7-567)	
Age group		
≤59 years (n=8)	214.5 (32-567)	0.735
≥60 years (n=26)	161 (7-1,219)	
TMA classification		
TMA (n=15)	274 (7-1,219)	0.433
HUS (n=17)	108 (8-567)	
TTP (n=2)	209.5 (124-295)	
Type of cancer[a]		
Pancreatic (n=21)	158 (20-1,219)	0.911
Gallbladder (n=4)	305 (50-353)	
Ovarian (n=2)	171.5 (44-299)	
Kidney (n=1)	7	
Unknown (n=6)	184.5 (8-567)	
Clinical outcomes of TMA[b]		
Good (n=15)	194 (32-1,219)	0.278
Poor (n=17)	158 (7-575)	
Unknown (n=2)	222 (91-353)	

HUS: Haemolytic uraemic syndrome; TMA: thrombotic microangiopathy; TTP: thrombotic thrombocytopenic purpura. [a]Kidney cancer and Unknown were excluded from statistical analysis. [b]Unknown was excluded from statistical analysis.

antibiotics. On day 12 after admission, the renal function of the patient further deteriorated (serum creatinine: 1.94 mg/dl, BUN: 43 mg/dl). As renal failure persisted, haemodialysis was introduced 22 days after admission. At this point, TTP was suspected, as four out of the five required symptoms were present, namely, thrombocytopenia (platelets: 48,000/μl), haemolytic anaemia (haemoglobin 6.2 g/dl), agitated neuropsychiatric disturbance, and worsening renal function (serum creatinine: 2.78 mg/dl, BUN 96 mg/dl). On day 19 after admission, a decrease in ADAMTS13 activity was observed, leading to a confirmed diagnosis of TTP. The patient was subsequently treated with steroids and γ-globulin; however, the patient died 71 days after admission. A summary of this case study is given in Table I.

Case series from literature review. Table I also lists the cases reported in Japan between April 2000 and March 2022 using the key words 'gemcitabine' and 'thrombotic microangiopathy', 'haemolytic uraemic syndrome', or 'thrombotic thrombocytopenic purpura' in PubMed or IgakuChuoZasshi, and whose contents were confirmed. Of the 17 cases, 11 involved male patients, and six patients were older than 70 years. Pancreatic cancer was the most common type of cancer, with 10 cases. Fourteen patients developed TMA at 5-8 months after the start of gemcitabine administration or later. Alternatively, some cases developed TMA within 0.5 months, some within approximately 0.9 months, and some within 4 months after the start of treatment.

Disproportionality analysis based on data from JADER and FAERS. A flow chart of cases extracted from JADER is shown in Figure 2. Of the 733,160 cases registered on JADER between April 2004 and September 2021, adverse events due to gemcitabine administration were reported in 5,558 cases. Of these, TMA was reported in 139 cases. There were 727,602 adverse drug reaction reports for drugs other than gemcitabine, of which 1,523 were TMA cases. The ROR calculated from these data was 12.2 (95% CI=10.3-14.6) for patients in Japan.

A flow chart of cases extracted from FAERS is shown in Figure 3. Of the 9,179,904 cases registered in FAERS between April 2004 and September 2021, adverse events due to gemcitabine administration were reported in 19,357 cases. Of these, TMA was reported in 599 cases. There were

9,160,547 adverse drug reaction reports for drugs other than gemcitabine, of which 4,458 were TMA cases. The ROR calculated from these data was 65.6 (95% CI=60.2-71.5).

Background data of cases with G-TMA in JADER. To analyse the time to onset data of G-TMA, 34 out of 139 G-TMA cases were selected from JADER by excluding those with no data on the date of gemcitabine administration or onset of TMA, and duplicate cases (Figure 2). The background data of the analysed cases are shown in Table II. Elderly individuals, aged 60 years or older, accounted for 76.5% of the patients. Moreover, pancreatic cancer was the most common type of cancer. The most common TMA classification was reported as 'TMA'. The clinical outcome was good for 44.1% of patients and poor for 50.0%.

Time-to-onset analysis of G-TMA based on data from JADER. The time to onset of G-TMA is shown in Table III. The median time to onset of G-TMA considering all 34 eligible cases was 161 days. The time to onset did not vary significantly by sex or age (p=0.631 and p=0.735). By TMA classification, the median time to onset was the longest for 'TMA' at 274 days, whereas that for 'HUS' was the shortest at 108 days; however, these were not significantly different (p=0.433). Regarding cancer type, the median time to onset of TMA was 158 days for those with pancreatic cancer and 305 days for those with gallbladder cancer. When examining onset time according to clinical outcomes, the median time for patients with a good prognosis was 194 days, whereas the time to onset for patients with a poor prognosis was 158 days. The time to onset of G-TMA was profiled using Weibull shape parameter analysis (Figure 4). The value for the shape parameter β was 1.0 (95% CI=0.8-1.3) and the pattern was therefore classified as a random failure.

Discussion

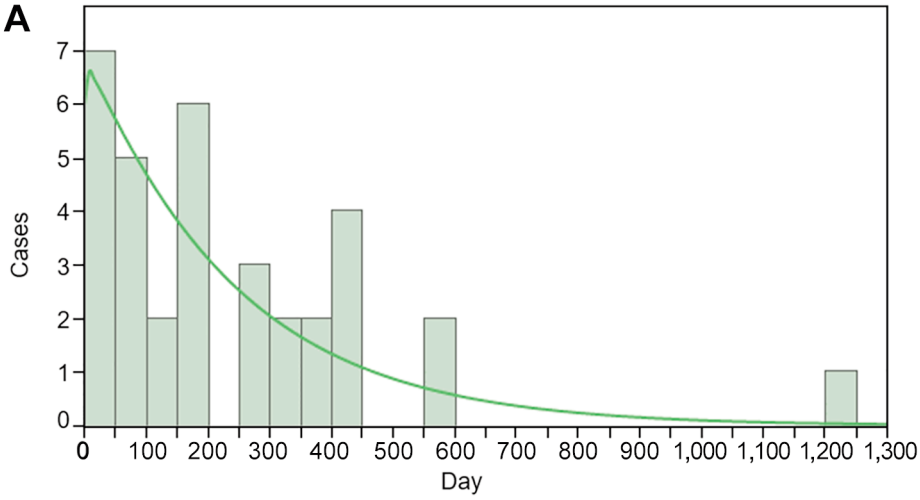
In this study, we analysed the time to onset of G-TMA in a Japanese population using a case at our hospital, a case series from a literature review, and data from JADER, a database of spontaneous adverse event reports. Some patients in the case series from the literature review developed G-TMA either in the same time frame or earlier than that previously reported in other countries. Analysis of data from JADER also showed that the median time to onset of G-TMA among Japanese patients was 161 days, suggesting that the disease may have an earlier onset that that reported outside Japan. In addition, the Weibull shape parameter analysis showed that the pattern of onset of G-TMA in Japanese was classified as a random failure, which means that the rate of onset was constant over time.

The patient at our hospital was treated with gemcitabine alone for pancreatic cancer. The time to onset of G-TMA in this patient was comparable to that in other reported cases of TMA due to gemcitabine-only administration for pancreatic cancer [patient numbers 2, 3, 5, 6, 10, 12, 15, and 16 (20-24, 28, 30, 32)]. In the case series, the majority of the cases developed G-TMA at 5-8 months after the start of treatment or later, similar to that in previous studies (9, 15). However, some cases reportedly developed G-TMA earlier. Suzuki *et al*. (31) reported that patients administered gemcitabine (1,000 mg/m^2 on days 1 and 8) with cisplatin (80 mg/m^2 on day 1) for the treatment of lung cancer showed symptoms suggestive of TTP 2 weeks after the first cycle of treatment. Nishikubo *et al*. (33) also reported that in patients with T-cell lymphomas treated with gemcitabine (1,000 mg/m^2 on days 1 and 8), cisplatin (75 mg/m^2 on day 1) and dexamethasone (33 mg on days 1-4), acute renal failure was observed from day 9 and a diagnosis of renal-limited TMA was made on day 25. One common feature of these two case reports was the use of cisplatin. Similar to gemcitabine, cisplatin can also cause TMA (35, 36). HUS caused by the combination of cisplatin and gemcitabine has been reported outside Japan (37). Cases of early G-TMA onset may have been influenced by concomitant medication, particularly cisplatin, which may hasten the onset of G-TMA, and this possibility requires further investigation.

Using data from JADER, the ROR for G-TMA was calculated to be 12.2 (95% CI=10.3-14.6) and a positive signal was detected. Although, the incidence of G-TMA was reportedly low (<1%) (16, 17), the results of our study confirm the possibility that TMA may develop following gemcitabine administration. Niinomi *et al*. (38) reported an ROR of 10.5 (95% CI=8.96-12.2) for G-TMA in their analysis using data from JADER, and our result is comparable to this. Additionally, the ROR calculated using data from FAERS was 65.6 (95% CI=60.2-71.5) and a positive signal was detected. The results support the detection of signals related to G-TMA in JADER. To our knowledge, this study is the first to investigate the association between gemcitabine and TMA using different databases.

The median time to onset of G-TMA was 161 days in cases retrieved from JADER. Owing to the low incidence of G-TMA, the time to onset analysis using Japanese patient populations is limited. Glezerman *et al*. reported a median duration of gemcitabine treatment of 8 months (range of 2-34 months) in 29 patients in whom HUS (worsening renal function, thrombocytopenia, and microangiopathic haemolytic anaemia) was observed after gemcitabine administration (39). In a retrospective study of 120 G-TMA cases enrolled in the French Pharmacovigilance Network and the French TMA Reference Centre, Daviet *et al*. reported a median duration of gemcitabine administration of 210 days (40). Compared with these findings, the median time to onset of G-TMA in our study was 161 days. Although previous studies did not examine the time to onset of G-TMA in a Japanese patient population, the results of our study suggest

A



B

Median (days)	Quartile (days)		Minimum (days)	Maximum (days)	Scale parameter		Shape parameter		Pattern
	Lower	Upper			α	95% CI	β	95% CI	
161.0	50.8	354.8	7	1219	239.4	165.7-340.1	1.0	0.8-1.3	Random failure

Figure 4. *Histogram of thrombotic microangiopathy onset time (A) and Weibull parameter (B). 95% CI: 95% Confidence interval.*

that G-TMA may occur relatively early in this population. Alternatively, the risk of developing G-TMA may be increased by concomitant medications and previous treatment (39, 41); however, these factors were not investigated in this study. Therefore, we realise that the results may not be directly comparable, owing to differences in patient backgrounds between this and previous studies. In the future, it is necessary to investigate the time to onset of G-TMA, considering patient backgrounds and risk factors.

The Weibull shape parameter analysis determined that the pattern of onset of G-TMA was a random failure. Therefore, the results of this study suggest that the incidence of G-TMA may be constant over time. Although there are various reports on the dose-dependence of G-TMA onset (9, 18, 19), the results of our study support the opinion that the onset of G-TMA is not dose-dependent.

This study has several limitations. Firstly, JADER lacks case details necessary for consideration, and under-reporting and reporting bias cannot be ruled out. Additionally, the quality of the data registered has not been verified. Secondly, in this study, we failed to examine the effect of pre-treatment and drug–drug interactions. The results of this study showed an earlier onset of G-TMA than in previous reports; however, the possibility that concomitant medication may have influenced the results cannot be ruled out. Thirdly, the case series from the literature reviewed and cases in JADER were small in number, and there was a large variation in data on the time of onset of G-TMA. Therefore, future studies must consider more cases and include cases from databases other than JADER. Increasing the number of cases will allow analysis with a history aligned with previous treatment, concomitant medications, and patient background.

As far as we are aware, this study is the first to examine the time to onset of G-TMA in Japan using multiple patient data. As G-TMA is associated with a high mortality rate, the results of this study may provide useful information for patients receiving gemcitabine treatment.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

MT, HT, AI, and HW: designed the study; MT and HW: conducted the study; MT, HT, and TI: analysed data; MT, HT, HW, TO, AI, and TI: wrote the article and had primary responsibility for the final content of the article. All Authors read and approved the final article.

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