HHS Public Access

Author manuscript

Am J Hematol. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Am J Hematol. 2023 December ; 98(12): E369–E372. doi:10.1002/ajh.27101.

Frequency and Characteristics of Chemotherapy-Associated Thrombotic Microangiopathy: Analysis from a Large Pharmacovigilance Database

Nattawat Klomjit, MD[1], **Richard Evans, PhD, PSTAT2**[2], **Thomas K. Le, MD**[3], **Sophia L. Wells, BS**[4], **Jessica Ortega, BS**[4], **Olivia Green-Lingren, BS**[4], **Marshall Mazepa, MD**[5], **Meghan E. Sise, MD, MS**[6], **Kenar D. Jhaveri, MD**[7], **Shruti Gupta, MD, MPH**[4,8]

[1]Division of Nephrology and Hypertension, Department of Medicine, University of Minnesota, MN, USA

[2]Masonic Cancer Center, University of Minnesota, MN, USA

[3]Department of Dermatology, University of Pittsburgh Medical Center, Pittsburgh, PA

[4]Division of Renal Medicine, Brigham and Women's Hospital, Boston, MA, USA

[5]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, MN, USA

[6]Department of Medicine, Division of Nephrology, Massachusetts General Hospital, Boston, MA, USA

[7]Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine, Great Neck, NY, USA

[8]Adult Survivorship Program, Dana-Farber Cancer Institute, Boston, MA, USA

Graphical Abstract

We used the information component (IC), a disproportionate Bayesian analysis comparing the number of observed versus expected adverse drug reactions, to determine the potential association between anti-neoplastic agents and TMA. The IC_{025} indicates the lower end of 95% of IC, in which a value >0 suggests a disproportionality signal between the drug of interest and the adverse drug reaction. Carfilzomib had the highest IC_{025} for TMA among all studied chemotherapies followed by gemcitabine, mitomycin, bevacizumab and bortezomib.

Tweetable Summary

Address correspondence to: Shruti Gupta, MD, MPH, 75 Francis St., MRB-4, Boston, MA 02115, United States of America, Sgupta21@bwh.harvard.edu, Phone: 617-732-7482, Twitter: @ShrutiGKidney.

AUTHOR CONTRIBUTIONS

NK and SG conceptualized the study, interpreted results, drafted manuscript and approved the final version of the manuscript. RE conducted the statistical analysis and approved the final version of the manuscript. TL conceptualized the study design, interpreted results, and approved the final version of the manuscript. SW, JO, OGL, MM, MES and KJ interpreted results, contributed to the manuscript and approved the final version of the manuscript.

PATIENT CONSENT

The patient consent is waived due to the nature of the study and the use of non-identifiable data from the VigiBase.

TMA was most commonly reported with gemcitabine/mitomycin, proteasome inhibitors, and anti-angiogenic agents. Time to TMA was shortest in patients receiving proteasome inhibitors, while immune checkpoint inhibitor-associated TMA had the highest mortality.

Keywords

thrombotic microangiopathy; TMA; drug-induced thrombotic microangiopathy; chemotherapy; VigiBase; pharmacovigilance

Thrombotic microangiopathies (TMA) are a heterogenous group of rare, yet life-threatening disorders that are characterized by hemolytic anemia, thrombocytopenia, and end-organ injury, including acute kidney injury (AKI).[1] TMA is associated with significant morbidity and mortality;[2] thus, early recognition is essential. Literature on TMA occurring after certain chemotherapies like gemcitabine and mitomycin,[3] and novel agents like targeted therapies (e.g., vascular endothelial growth factor inhibitors [VEGFi] and tyrosine kinase inhibitors [TKIs]), immune checkpoint inhibitors [ICPIs] and proteasome inhibitors [PIs]) are largely limited to case series.

Post-marketing, real-world surveillance data can help inform clinicians of the risk profile with different drugs. We used VigiBase, a large global pharmacovigilance database that contains over 20 million individual case safety reports,[4] to summarize and compare characteristics and outcomes of TMA after commonly-used anti-neoplastic agents.

We performed an observational, pharmacovigilance study using VigiBase (Supplemental Methods), which compiles data on medication safety through individual case safety reports that originate from various sources.[4] Each safety report represents one patient who has developed the adverse event of interest, and includes information on demographics, drug dosing and drug combinations, and outcomes related to the adverse drug reaction (ADR).

We included all reports of “thrombotic microangiopathy,” which could be biopsy-proven or cases for which there was a high index of suspicion for TMA. We then searched for anti-neoplastic therapies that have been associated with TMA in the literature.[1,3] These consisted of 38 distinct anti-neoplastic therapies, which were further classified as gemcitabine/mitomycin, PIs, platinum-based chemotherapies, VEGFi/TKIs, ICPIs, and others (bleomycin, docetaxel, doxorubicin and pentostatin) (Supplemental Methods; Supplemental Table 1). Gemcitabine and mitomycin were examined together as these are the most commonly-reported conventional chemotherapies associated with TMA.[3] The search also included combinations of any of these pre-specified medications. The query was run on de-duplicated data, whereby suspected duplicates were identified, flagged, and then removed. We hypothesized that certain drug classes, and exposure to a higher number of drug classes (e.g., 1 versus 2 versus ≥3), may impact characteristics or outcomes of TMA patients.

Drug safety was assessed using the information component (IC), a measure of the disproportionality between the observed and the expected reporting of a drug-ADR pair, to detect ADRs above baseline noise in VigiBase (Supplemental Methods). For this analysis,

drugs with a positive (>0) value for IC_{025} (the lower end of the 95% confidence interval of the IC) were identified as having a signal for TMA within VigiBase (Supplemental Methods).

Baseline characteristics, time to onset, indication for anti-neoplastic therapies and outcomes were reported as numbers (with percentages) for categorical variables and median (interquartile ranges) for continuous variables. Time to onset of TMA was examined by drug class if these data were available for at least 20 individuals. All comparisons were two-sided, with $p<0.05$ considered significant. All analyses were performed using R 4.1.2.

Between January 1, 2010 and January 15, 2023, there were 31,413 reports of TMA, atypical hemolytic uremic syndrome (aHUS), or thrombotic microangiopathy (TTP) (Supplemental Figure 1). After excluding non-TMA ADRs, there were 1712 TMA ADRs across 1099 unique individuals, of whom approximately half were female (n=498, 45.3%) and from North or South America (n=507, 46.1%). Most TMA cases (95.2%) were reported after 2014. TMA was most common in the 45–64 years age group (n=385, 35.3%), and among patients with gastrointestinal and hepatobiliary cancers (n=327, 29.8%) (Supplemental Table 2).

Most patients with TMA received only a single drug class (n=920, 83.7%) as opposed to 2 classes (n=152, 13.8%) or ≥3 drug classes (n=27, 2.5%) (Supplemental Table 2). Gastrointestinal and hepatobiliary cancers were the most common malignancies in TMA cases involving 1 or 2 drug classes, whereas gynecological cancer was most common among individuals receiving ≥3 drug classes.

When assessing the characteristics of TMA by drug class, we found that TMA was most often reported in the setting of treatment with gemcitabine/mitomycin (n=379, 41.2%) followed by PIs (n=228, 24.8%), VEGFi/TKIs (n=185, 20.1%), and platinum-based therapies (n=76, 8.3%) (Supplemental Figures 2 and 3A). Gemcitabine/mitomycin were the most frequent anti-neoplastic therapies in patients with gastrointestinal, hepatobiliary, gynecologic and lung cancers, while VEGFi/TKIs were most common in kidney and urological cancers (Supplemental Figure 3B). There were only adult cases (age ≥18 years) reported in the gemcitabine/mitomycin and ICPIs groups, whereas other drug classes reported cases among both pediatric and adult patients (Supplemental Figure 3C).

Additional characteristics and demographics by drug class are shown in Supplemental Table 3. Data on time to onset was available in 294 individuals (26.8%). Overall, the median time to onset of TMA was 122 days (interquartile range [IQR] 25–247). Median time to onset of TMA was shortest for PIs (median 35 days [IQR 8–178]), and longest for gemcitabine/mitomycin (median 156 days [IQR 91–245]) (Supplemental Figure 4).

There were 720 (65.5%) individuals with TMA with outcome data available. Of survivors, 519 (78.3%) were reported as “recovered” or “recovering.” TMA in the setting of other chemotherapies had the highest rate of recovery (e.g., either recovered/recovering; n=14/15; 93.3%), whereas ICPIs were associated with the lowest rate of recovery (n=3/7, 42.9%). The rates of recovery for PIs, platinums, gemcitabine/mitomycin, and VEGFi/TKIs were 85.8%, 85.3%, 74.4%, and 74.3%, respectively (Supplemental Figures 5A and 5B).

There were 57 (5.2%) reported fatalities in the entire cohort. ICPI-TMA had the highest fatality (n=9, 41.0%), while gemcitabine/mitomycin had the lowest fatality (n=13, 3.4%) (Supplemental Figure 5B).

Finally, we conducted a disproportionality assessment of the 38 anti-neoplastic agents, and found that 30 agents had TMA events reported in VigiBase and 22 agents had an IC_{025} >0. Carfilzomib had the highest IC_{025} at 5.92, followed by gemcitabine (5.52), mitomycin (4.21), bevacizumab (3.63) and bortezomib (3.33) (Figure 1; Supplemental Table 4).

In this large pharmacovigilance cohort, we describe the clinical features, timing, and outcomes of TMA after commonly used anti-neoplastic therapies. We used the $IC_{025,}$ which compares the number of observed versus expected adverse drug reactions, to determine the potential association between anti-neoplastic agents and TMA. We found that the drug classes with the highest disproportionality were PIs, gemcitabine/mitomycin, and VEGFi/TKIs.

Of all the drug classes that we examined, carfilzomib had the highest IC_{025}, and each of the PIs (carfilzomib, bortezomib and ixazomib) had a positive IC_{025}. TMA has been reported with gemcitabine and mitomycin in case series,[1,3] and these two drugs had the 2nd and 3rd highest IC_{025} among studied drugs, respectively. While most of the VEGFi/TKIs, all the platinums, and most of the other chemotherapies had a positive $IC_{025,}$ only 2 of 8 ICPIs with reported TMA in the VigiBase had positive IC_{025}. The reason for this is unclear, and may be due to a lower risk of TMA with these agents, or simply underreporting.

PIs have shown promise for the treatment of plasma cell disorders; however, TMA has been reported in case series of patients with multiple myeloma receiving PIs, particularly carfilzomib or ixazomib.[5] We found that carfilzomib had the highest IC_{025} of all studied drugs. Most cases of PI-associated TMA improve with drug discontinuation,[5] which was consistent with the relatively high rate of recovery observed in our study.

Gemcitabine and mitomycin are commonly associated with TMA[3] and had some of the highest IC_{025} among studied agents in our cohort. Though mitomycin is less commonly used, gemcitabine is still considered a first-line therapy for pancreatic cancer.[3] Despite the known association between gemcitabine and TMA, reports of TMA following gemcitabine are largely limited to case series. Patients with gemcitabine-associated TMA often have progressive kidney dysfunction;[3] thus, understanding characteristics and outcomes of TMA in patients receiving this drug is critical.

Time to anti-neoplastic drug-associated TMA is highly variable in case series.[1] Interestingly, we found that the median time to onset was only 70 days, perhaps reflecting earlier detection and recognition. Time to TMA onset was shortest among patients treated with PIs, and longest among patients receiving gemcitabine/mitomycin. This may be due in part to differences in the pathophysiology of TMA (e.g., immune-mediated versus dose-dependent toxicity).

ICPIs have transformed the landscape of cancer treatment but are also associated with kidney-related adverse events. While we found that 40% of TMA cases improved/recovered,

which is consistent with outcomes described in prior studies,[1] ICPI-TMA had the highest fatality rate. Case series of ICPI-TMA also suggest that these patients have poor outcomes,[6] possibly due to delayed recognition, longer half-life of the drugs, and patient-related factors.

Though this is the largest pharmacovigilance study of TMA to date, it has limitations. First, the IC does not imply causality between a particular drug and ADR. Second, granular clinical data are not available in the VigiBase. Third, reports are derived from a variety of sources, including from patients, pharmacists, and others. Fourth, there are no data on the number of patients exposed to the product or drug, and therefore inferences cannot be made with regards to prevalence. Fifth, there may be reporting bias (e.g., most cases originated from North and South America). Sixth, there are limited data on either time to recovery or nature of recovery (e.g., hematologic, renal, or both), or details about cause of death or time to death.

Despite these limitations, our study captured over 1000 cases of TMA among patients receiving common anti-neoplastic therapies used for a variety of cancers. Our findings suggest that clinicians should be aware of TMA as a potential complication of both older chemotherapies (e.g., gemcitabine/mitomycin) as well as novel agents like PIs, VEGFi/TKIs and ICPIs. Additionally, understanding the time to onset of TMA may allow clinicians to maintain a high index of suspicion for TMA and implement targeted preventative or therapeutic strategies. Future prospective studies are needed to better understand and characterize anti-neoplastic therapy-associated TMA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We would like to thank VigiBase for providing the data. VigiBase is the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre. The information does not represent the opinion of the UMC or the World Health Organization

FUNDING

This work was funded by NIH NIDDK K23DK125672 (to S. Gupta).

DISCLOSURES/CONFLICTS OF INTEREST

S. Gupta reports research support from the NIH, NIDDK K23DK125672. She also reports research funding from BTG International, GE Healthcare, and AstraZeneca outside the submitted work. She is a member of GlaxoSmithKline's (GSK) Global Anemia Council, a consultant for Secretome and Proletariat Therapeutics, and founder of the American Society of Onconephrology. M. Sise reports research support from the NIH, NIDDK R01DK140839. She also reports research funding from Gilead, Abbvie, EMD-Serono, Angion, and Otsuka outside of the submitted work. She has served on a scientific advisory board for Travere, Novartis, Vera Therapeutics, and Mallinckrodt and is a data monitoring committee member for Alpine Immunosciences. She is on the editorial board of the American Journal of Kidney Disease. K. Jhaveri reports consultancy agreements with Secretome, George Clinicals, PMV pharmaceuticals and Calliditas. KDJ serves as the USA co-national lead for the IgA Nephropathy trial- VISIONARY. KDJ reports honoraria from the American Society of Nephrology, Micromedex and UpToDate.com; reports serving on the editorial boards of American Journal of Kidney Diseases, CJASN, Clinical Kidney Journal, Journal of Onconephrology, Kidney International, and Nephrology Dialysis Transplantation; reports serving as Editor-in-Chief of ASN Kidney News and section editor for onconephrology for Nephrology Dialysis Transplantation.

DATA SHARING AND DATA AVAILABILITY

This data derived from VigiBase which is maintained by Uppsala Monitoring Center, Uppsala, Sweden.

REFERENCES:

1. Izzedine H, Perazella MA. Thrombotic microangiopathy, cancer, and cancer drugs. Am J Kidney Dis. 2015;66(5):857–868. [PubMed: 25943718]
2. Van de Louw A, Cohrs A, Leslie D. Clinical Features and Outcome of Thrombotic Microangiopathies: Comparison between Patients with and without Malignancy. Thromb Haemost. 2021;121(5):565–572. [PubMed: 33186993]
3. Aklilu AM, Shirali AC. Chemotherapy-Associated Thrombotic Microangiopathy. Kidney360. 2023;4(3):409–422. [PubMed: 36706238]
4. Lindquist M VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug information journal : DIJ / Drug Information Association. 2008;42(5):409–419.
5. Yui JC, Van Keer J, Weiss BM, et al. Proteasome inhibitor associated thrombotic microangiopathy. Am J Hematol. 2016;91(9):E348–352. [PubMed: 27286661]
6. Badra S, Ruchi R, Zeng X, Gordan L, Shah CV. Immune checkpoint inhibitor associated renally limited thrombotic microangiopathy - a clinical dilemma. Eur J Cancer. 2022;169:126–130. [PubMed: 35561455]

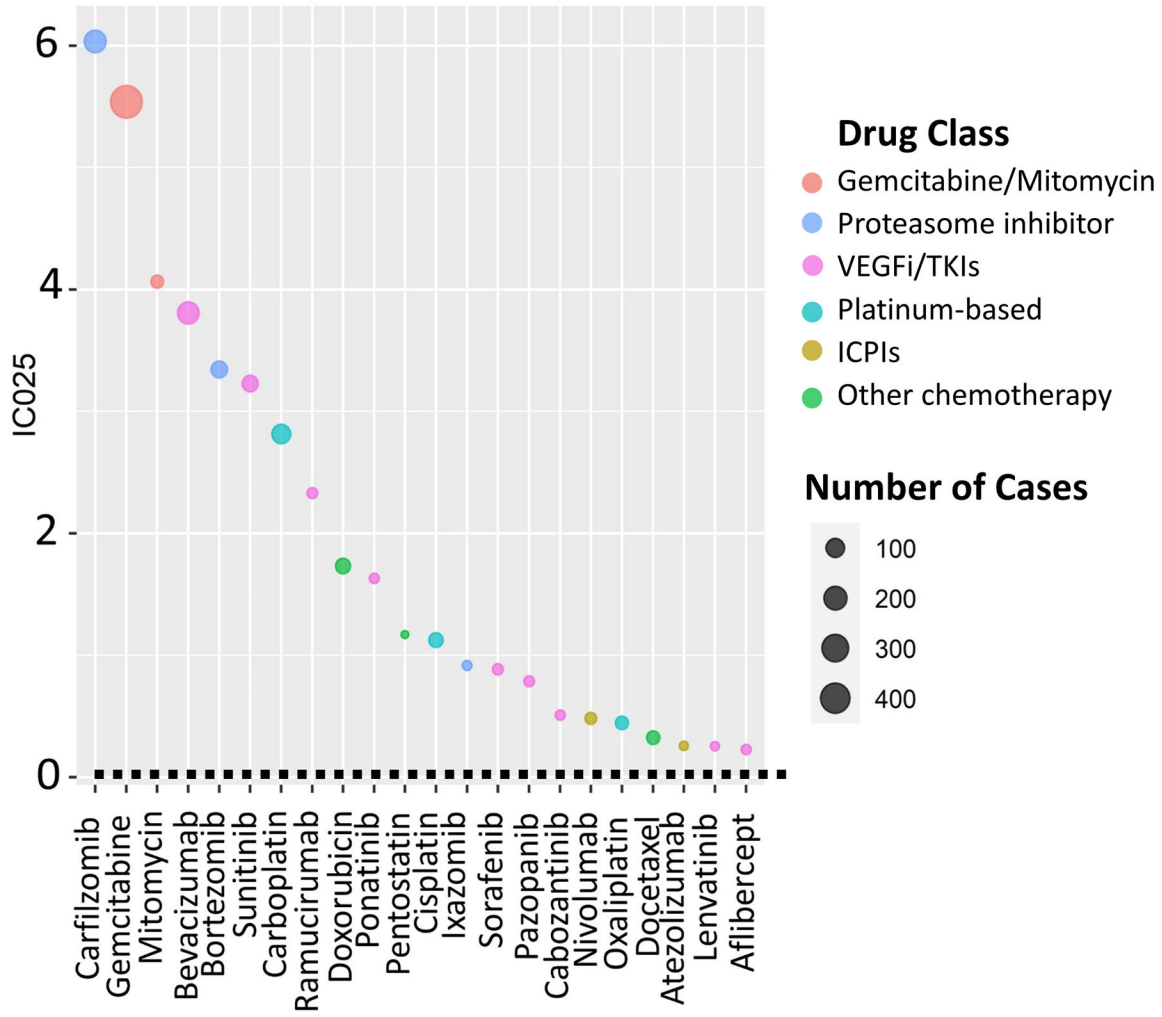

Figure 1: Number of Cases and IC_{025} for Each Drug Class

Information component (IC) is a disproportionate Bayesian analysis when using the full dataset as a comparator, which was developed and validated by Uppsala Monitoring Center. It compares observed and expected drug-adverse drug reaction to determine potential association. IC_{025} is the lower end of 95% of IC in which the value >0 suggests a disproportionality signal between the drug of interest and the adverse drug reaction. There were a total of 30 studied agents with available IC_{025}, and of these, 22 studied agents had IC_{025} >0. Carfilzomib has the highest IC_{025} among all studied chemotherapies followed by gemcitabine, mitomycin, bevacizumab and bortezomib. All drugs shown in this figure have a positive IC_{025}.

Abbreviations: VEGFi: vascular endothelial growth factor inhibitor, TKI: tyrosine kinase inhibitor, ICPI: immune-checkpoint inhibitor