Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura

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BACKGROUND: Reports of deterioration and death after platelet (PLT) transfusions in patients with thrombotic thrombocytopenic purpura (TTP) have led to recommendations that they should not be given except for life-threatening hemorrhage.

STUDY DESIGN AND METHODS: Published reports of PLT transfusions in patients with TTP were systematically reviewed and data from the Oklahoma TTP-HUS Registry, an inception cohort of 382 consecutive patients, 1989 through 2007, were analyzed.

RESULTS: A systematic review identified 34 publications describing outcomes of patients with TTP after PLT transfusions: 9 articles attributed complications to PLT transfusions, 4 suggested that they may be safe, and 21 articles did not comment about a relation between PLT transfusions and outcomes. Fifty-four consecutive patients from the Oklahoma TTP-HUS Registry were prospectively analyzed. ADAMTS13 activity was less than 10 percent in 47 patients; also included were 7 patients whose activity was not measured but who may have been deficient. Thirty-three (61%) patients received PLT transfusions. The frequency of death was not different between the two groups ($p = 0.971$): 8 (24%) patients who received PLT transfusions died (thrombosis, 5; hemorrhage, 1; sepsis, 2) and 5 (24%) patients who did not receive PLT transfusions died (thrombosis, 4; hemorrhage, 1). The frequency of severe neurologic events was also not different ($p = 0.190$): 17 (52%) patients who received PLT transfusions (in 5 of these 17 patients, neurologic events only occurred before PLT transfusions) and 7 (33%) patients who did not receive PLT transfusions.

CONCLUSION: Evidence for harm from PLT transfusions in patients with TTP is uncertain.

In 1981, Gottschall and colleagues[1] described "a close temporal relationship between infusion of platelets and development of coma" in three patients with thrombotic thrombocytopenic purpura (TTP). Also in 1981, Harkness and coworkers[2] and Byrnes[3] both reported the same 34-year-old woman with TTP who had sudden neurologic deterioration within 30 minutes after a platelet (PLT) transfusion and died 12 hours later. Her autopsy demonstrated microvascular thrombi typical of TTP in her heart, pancreas, adrenal glands, and kidneys. The thrombotic lesions in the brain were described as distinct from thrombi in other organs: "All vascular lesions in the brain were comprised chiefly of masses of platelets, with only occasional wisps of fibrin."[2] The authors concluded that these "fresh platelet aggregates" in the brain were the result of the PLT transfusion and the cause of her death.[2] The credibility of these observations was supported by previous reports that PLTs were the principal component of the thrombotic lesions in TTP.[4-6] These

ABBREVIATIONS: HUS = hemolytic-uremic syndrome; TTP = thrombocytopenic purpura.

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initial reports of complications after PLT transfusions,[1-3] because of their devastating outcomes and compelling rationale, provided the foundation for a belief that PLT transfusions are dangerous for patients with TTP and resulted in a widely accepted recommendation that PLT transfusions should not be given except for life-threatening bleeding.[7] However, this recommendation may create a dilemma for clinicians managing a patient with TTP and severe thrombocytopenia who needs surgery or an invasive procedure or who has severe, but not life-threatening, bleeding.

The experience of the Oklahoma TTP-HUS (hemolytic-uremic syndrome) Registry is that many patients with TTP receive PLT transfusions as part of their initial management without adverse effects. Therefore, the goal of this study was to investigate the apparent conflict between the widely accepted recommendation and the common community practice. First, to evaluate the published evidence on which the recommendation to avoid PLT transfusions in patients with TTP is based, we systematically reviewed patient reports to document data on patient outcomes after PLT transfusions. Next, we report the prospective analysis of the Oklahoma TTP-HUS Registry experience over the past 12 years to describe detailed outcomes of individual patients after PLT transfusions.

MATERIALS AND METHODS

Systematic literature review

Ovid software was used to search the Medline database on January 25, 2008. English language articles containing both a TTP-related key word or Medical Subject Heading (MeSH) in the title or available text (*thrombotic thrombocytopenic purpura, TTP, hemolytic-uremic syndrome, HUS, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, TTP-HUS, thrombotic microangiopathy, TMA, microangiopathy, intravascular hemolysis, plasma exchange*) and a PLT transfusion–related key word or Medical Subject Heading (MeSH) in the title or available text (*platelet transfusion, platelet transfusions, transfusion complications, platelet transfusion complications, blood transfusion, blood transfusion complications*) were identified. Retrieved articles were reviewed to identify data on patients described as having TTP, HUS, or thrombotic microangiopathy who were also described as having a PLT transfusion. The text and bibliographies of the reviewed articles were searched to identify additional relevant articles.

In addition we reviewed the titles and relevant abstracts of English language articles published since 1970 that were identified with the search terms *thrombotic thrombocytopenic purpura* and *TTP* to identify case series of 25 or more patients with TTP to document the frequency of reporting information about PLT transfusions. Limiting case series to those reporting 25 or more patients was arbitrary, a compromise between inclusiveness and practicality. 1970 was chosen as the earliest year for the selection of case series because the current practices of PLT transfusion[8,9] and plasma exchange treatment of TTP[10,11] were established soon after this year. During this search additional case reports that described patients with TTP who had received PLT transfusions were also identified.

In the literature review, we also excluded children less than 10 years old, because they may be at less risk for thrombotic complications; systemic microvascular thrombosis is uncommon in children with typical, diarrhea-associated HUS[12,13] and children's risk for thrombotic complications is inherently low.[14] We also excluded patients who had additional disorders that may have required PLT transfusions or that have a high risk for thrombosis: patients after hematopoietic stem cell or organ transplantation, patients receiving cancer chemotherapy, and patients who had systemic lupus erythematosus.[15] However, most articles did not report data on concurrent disorders. We did not exclude patients whose TTP occurred in association with pregnancy, a condition with physiologic hypercoagulability.

Article and patient selection and data extraction were performed independently by two of the authors (KKS, JNG). All articles were reviewed using a standardized format to record all relevant data. Differences of interpretation between the two reviewers were resolved by discussion and consensus.

The Oklahoma TTP-HUS Registry

The Registry includes all consecutive patients for whom the Oklahoma Blood Institute is requested to provide plasma exchange treatment for a diagnosis of TTP or HUS.[16-18] The Oklahoma Blood Institute is the sole provider of plasma exchange services for all hospitals in 58 of the 77 Oklahoma counties. Since standard practice in this region is to treat all adult patients who are diagnosed with either TTP or HUS with plasma exchange, the Registry is an inception cohort of consecutive patients in whom the diagnosis of TTP or HUS was established and a decision to initiate plasma exchange treatment was made. All relevant clinical and laboratory data were systematically collected on standard forms from the beginning of each patient's illness, including the time before TTP was suspected or diagnosed; data after diagnosis of TTP were collected prospectively; all data were entered into a computer database (Access, Microsoft Corp., Redmond, WA).[16] Severe neurologic abnormalities were defined as coma, stroke, grand mal seizure, or focal neurologic signs that occurred before presentation and during the course of illness.[16] Acute renal failure was defined as either 1) an increasing serum creatinine ($\geq$0.5 mg/dL) per day for 2 consecutive days or 2) a serum creatinine of 4.0 mg per dL or more plus

dialysis that began within 7 days of diagnosis.[16] Death was recorded as related to TTP if it occurred within 30 days of the last plasma exchange treatment.[16] Serum for ADAMTS13 assays was routinely collected immediately before the first plasma exchange procedure beginning on November 13, 1995. ADAMTS13 activity was measured by two methods, the quantitative immunoblotting of proteolyzed von Willebrand factor multimers[19,20] and a fluorogenic assay using the FRETS-VWF73 substrate.[21,22] Severe ADAMTS13 deficiency was defined as less than 10 percent activity identified by either assay method. A PLT transfusion was defined as one or more random- or single-donor units in a single physician order. PLT counts to document increments after transfusion were not systematically performed; typically patients had only routine daily PLT counts. The Oklahoma TTP-HUS Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Statistical analysis

The independent two-sample t test or Mann-Whitney test for interval/ratio data and the chi-square test or Fisher's exact test for categorical data were used to compare the two groups of patients, divided on the basis of whether or not they received a PLT transfusion. Computer software (SAS, Version 9.1, SAS Institute, Inc., Cary, NC) was used to perform all analyses. A p value of less than 0.05 was considered significant.

RESULTS

Systematic literature review

The initial key word search identified 396 articles. Nineteen articles were identified that reported outcomes of patients with TTP after a PLT transfusion; 1 additional article that reported outcomes of patients with TTP after a PLT transfusion was identified from searching the bibliographies of these 19 articles. During this search, 14 case series reporting 25 or more patients with TTP were identified; 5 of these case series were among the 20 articles that reported outcomes of patients with TTP after a PLT transfusion. The subsequent search, using only the terms *thrombotic thrombocytopenic purpura* and *TTP*, identified 3317 articles. Sixty-three additional case series were identified that reported 25 or more patients with TTP; 7 of these case series that had not been identified in the initial key word search reported outcomes of patients with TTP after a PLT transfusion. During this search, 7 additional articles reporting fewer that 25 patients were also identified that described outcomes of patients with TTP after a PLT transfusion. Therefore, altogether 34 articles were identified that described outcomes of patients with TTP after PLT transfusions (Table 1).[1-3,6,23-52] Altogether 77 case series reporting 25 or more patients with TTP published since 1970 were identified: 12 reported outcomes of patients with TTP after a PLT transfusion,[34-37,39,40,43,47-50] in 4 other case series[53-56] PLT transfusions were mentioned but no patient outcomes were described, and in the remaining 61 (79%) case series there was no mention of PLT transfusions.

Twenty-one articles reported outcomes of 1 to 13 (median, 1) patients who had received PLT transfusions without comparison to patients who had not received PLT transfusions. These articles are presented in the first section of Table 1, with detailed descriptions of individual patient data. Five articles described PLT transfusions as harmful.[2,32,36,38,47] In 4 of these articles, 14 patients were described in whom deterioration or death was attributed to a PLT transfusion;[2,32,36,38] individual patient data were not reported in the other article.[47] Plasma exchange treatment was described for 3 of these 14 patients and in each patient the PLT transfusions were given before treatment was begun.[2,32,38] Three other articles described 7 patients with no adverse effects of PLT transfusions and suggested that PLT transfusions may be safe if they are given after or immediately before plasma exchange treatment.[44,45,51] One article stated that no apparent clinical worsening was noted in the 13 patients who received PLT transfusions, but survival was not reported.[35] In 12 articles, PLT transfusions were incidentally described as part of the management for 16 patients but there was no comment about either risk or safety of PLT transfusions in the text.[6,23-25,28-30,37,42,46,49,52] Among these 16 patients, 6 died[30,42,49,52] and 10 survived.[6,23-25,28-30,37]

The second section of Table 1 describes 13 articles with data that allowed comparisons between patients who did or did not receive PLT transfusions. In all 13 articles, 103 (29%) of 358 patients were described as receiving PLT transfusions. Patient selection was described in 3 articles: 52 consecutive patients at University Hospitals of Cleveland over 7 years (dates not provided);[40] all 37 adult patients admitted to Hôpital Saint-Louis, Paris, 1989 through 1991;[48] and all 47 patients admitted to American University of Beirut Medical Center, 1980 through 2003.[50] In the Beirut study,[50] 4 of 47 patients were reported to have received PLT transfusions, all in other hospitals before referral to American University of Beirut Medical Center: 2 of the 4 and 7 of the other 43 patients died, and there was no comment about risk of PLT transfusions in the text. Neither of the other 2 articles[40,48] described PLT transfusions before admission to the hospital from which the patients were selected. The Cleveland study[40] reported that there was no difference in the number of PLT units transfused between patients who died and those who survived and concluded that PLT transfusion did not affect survival. In the Paris study,[48] 1 of 8 patients who received PLT transfusions died, the other 7 had no apparent

TABLE 1. Published reports describing outcomes of patients with TTP after PLT transfusions*

Year of publication (reference)	Number of patients reported	Number of patients who received PLT transfusion	Outcome	Original authors' comments and interpretation
Reports of patients who received PLT transfusions				
1973[23]	7	1	One patient described as having PLT transfusion before splenectomy with no adverse outcomes; subsequently recovered. No TPE. PLT transfusion not mentioned in the other 6 patients.	No comment about PLT transfusion in text.
1974[24]	1	1	Mental status initially improved after PLT transfusion; then coma 2 days later and no change with an additional PLT transfusion; subsequently recovered. No TPE.	No comment about PLT transfusion in text.
1977[25]	1	1	Twenty-two PLT transfusions over 18 days during pregnancy; 3 episodes of transient neurologic abnormalities; recovered after delivery. No TPE.	No comment about PLT transfusion in text.
1981[2]	1	1	Neurologic abnormalities 30 min after PLT transfusion; died 12 hr later, before TPE could be begun.	Death attributed to PLT transfusion. Same patient described below.[3]
1981[6]	25	1	One patient described as having PLT transfusion "with no observable effect"; subsequently recovered. No TPE. PLT transfusion not mentioned in the other 24 patients.	No comment about PLT transfusion in text.
1982[28]	1	1	Stroke 1 day after PLT transfusion (after TPE begun), complete recovery.	No comment about PLT transfusion in text.
1985[29]	1	1	Thirteen PLT transfusions before and after TPE begun. Possible seizure during anesthesia induction 6 hr after first PLT transfusion; complete recovery.	No comment about PLT transfusion in text.
1985[30]	4	4	PLT transfusion given to all patients as part of routine management before and during TPE. No adverse effects described.	No comment about PLT transfusion in text.
1987[32]	1	1	Death 2 hr after PLT transfusion, before TPE could be begun.	Death attributed to PLT transfusion.
1990[35]	25	13	Three patients died; not identified if they had received PLT transfusion. Patients received 1-12 PLT transfusions.	Comment about PLT transfusion: "No apparent clinical worsening was identified."
1991[36]	108	Not reported	Eleven patients had "precipitous decline in clinical status after a transfusion of PLTs." No description of treatment or outcomes of these 11 patients.	Adverse outcomes attributed to PLT transfusion.
1992[37]	27	Not reported	One patient described as having received PLT transfusion; complete recovery.	No comment about PLT transfusion in text.
1994[38]	1	1	PLT transfusion, before TPE, followed by somnolence and confusion. Died 4 days later.	Comment that PLT transfusion may be harmful.
1997[42]	2	2	Both patients died; one 6 hr after PLT transfusion, before TPE; in the other patient, sequence not described.	No comment about PLT transfusion in text.
2001[44]	2	2	PLT transfusion after TPE; no adverse effects.	Comment that PLT transfusion may be safe after TPE.
2002[45]	20	4	PLT transfusion after TPE; no adverse effects.	Comment that PLT transfusion may be safe after TPE.
2002[46]	1	1	PLT transfusion before TPE for cesarean delivery; no adverse effects.	No comment about PLT transfusion in text.
2003[47]	154	Not reported	Thirty-three patients died, 20 had received PLT transfusion. PLT transfusion not reported in the 121 survivors.	Comment that PLT transfusion is a strong risk factor for poor outcomes.
	35	Not reported	Three patients died, 1 had received PLT transfusion. PLT transfusion not reported in the 32 survivors.	
2003[49]	50	Not reported	One patient described as having received PLT transfusion; died, relation to PLT transfusion not described.	No comment about PLT transfusion in text.
2005[51]	1	1	PLT transfusion before TPE; no adverse effects.	Comment that PLT transfusion may be safe if followed promptly by TPE.
2006[52]	1	1	PLT transfusion for cesarean delivery; died 32 hr later. No TPE.	No comment about PLT transfusion in text.

Comparison of patients who did or did not receive PLT transfusions				
1978[26]	5	1 (20%)	PLT transfusion: unresponsive 1 day after PLT transfusion; recovery after splenectomy. No TPE. No PLT transfusion: all treated with splenectomy; 2 died. No TPE.	No comment about PLT transfusion in text.
1979[27]	4	3 (75%)	PLT transfusion: 1 patient died; 2 with no adverse effects. No PLT transfusion: patient recovered.	No comment about PLT transfusion in text.
1981[1]	11	8 (4, PLT transfusion; 4, fresh whole blood) (73%)	PLT transfusion (or FWB): 3 patients died. No PLT transfusion: all 3 patients recovered.	Deaths attributed to PLT transfusion.
1981[3]	18	1 (6%)	PLT transfusion: no adverse effects noted. No PLT transfusion: 5/17 died, 2 from hemorrhage.	The patient reported above[2] was also described, but not included in the 18 patients.
1986[31]	8	7 (88%)	PLT transfusion: all survived. No adverse effects noted. No PLT transfusion: 1 patient died, autopsy—disseminated thrombi.	No comment about PLT transfusion in text.
1987[33]	15	2 (13%)	PLT transfusion: 1 patient died 4 hr after PLT transfusion; 1 had mental status deterioration 24 hours after PLT transfusion, then recovered. No PLT transfusion: 3/12 died.	Death and deterioration attributed to the PLT transfusion.
1987[34]	38	13 (34%)	PLT transfusion: 5/13 patients died. No PLT transfusion: 1/25 patients died.	Greater frequency of PLT transfusion among patients who died ($p = 0.03$).
1994[39]	55	25 (45%)	PLT transfusion: 13/25 patients died. No PLT transfusion: 2/30 patients died.	Comment that PLT transfusion adversely affects survival.
1994[40]	39	22 (56%)	PLT transfusion: 10/22 patients died. No PLT transfusion: 3/17 patients died.	Comment that no difference in the total number of PLT units transfused between patients who survived or died.
1996[41]	11	5 (45%)	PLT transfusion: 1/5 patients died. No PLT transfusion: 1/6 patients died.	Comment that PLT transfusion should be used with caution because of risk for thrombosis.
1997[43]	70	4 (6%)	PLT transfusion: 0/4 patients died; no apparent adverse effects. No PLT transfusion: 10/66 patients died.	Comment that all 4 patients given PLT transfusion recovered completely with TPE.
2003[48]	37	8 (22%)	PLT transfusion: 1/8 patients died; 7 with no apparent side effects (2 previously reported[44]). No PLT transfusion: 6/29 patients died.	No comment about PLT transfusion in text.
2004[50]	47	4 (9%)	PLT transfusion: 2/4 patients died. No PLT transfusion: 7/43 patients died.	No comment about PLT transfusion in text.

* All 34 case reports describing outcomes of patients with TTP after PLT transfusions that were identified by our search are presented with individual patient data. Reports of patients who received PLT transfusions without a comparison group are described in the top section. Reports in which outcomes of patients who received PLT transfusions could be compared to patients who did not receive PLT transfusions are described in the following section. Within each section, articles are listed in chronological order.

FWB = transfusion of fresh whole blood containing viable PLTs; TPE = plasma exchange treatment.

adverse effects, and 6 of 29 patients who did not receive PLT transfusions died. There was no comment about risk of PLT transfusions in the text.[48] Six articles commented on potential risks from PLT transfusions,[1,3,33,34,39,41] 2 articles commented on the absence of apparent risk,[40,43] and in the other 5 articles there was no comment about PLT transfusions.[26,27,31,48,50]

The Oklahoma TTP-HUS Registry

From January 1, 1989, through December 31, 2007, the Oklahoma Registry enrolled 382 consecutive patients with a diagnosis of TTP or HUS. We focused our analysis on the first episode of patients with a clinical diagnosis of TTP to identify the pattern of community practice and outcomes in previously undiagnosed patients (Fig. 1). Therefore, 8 patients who were first seen for a relapsed episode, because their initial episode occurred before the Registry began or occurred outside of the Registry region and 12 patients initially diagnosed by renal biopsy, rather than by diagnostic clinical features of TTP, were excluded. We also excluded children less than 10 years old, because they may be at less risk for thrombotic complications; systemic microvascular thrombosis is uncommon in children with typical, diarrhea-associated HUS[12,13] and children's risk for thrombotic complications is inherently low.[14] In addition, we focused our analysis on patients whose diagnosis of TTP was supported by documentation of severe ADAMTS13 deficiency (activity less than 10% of normal) to avoid inclusion of patients who may have an uncertain diagnosis of TTP.

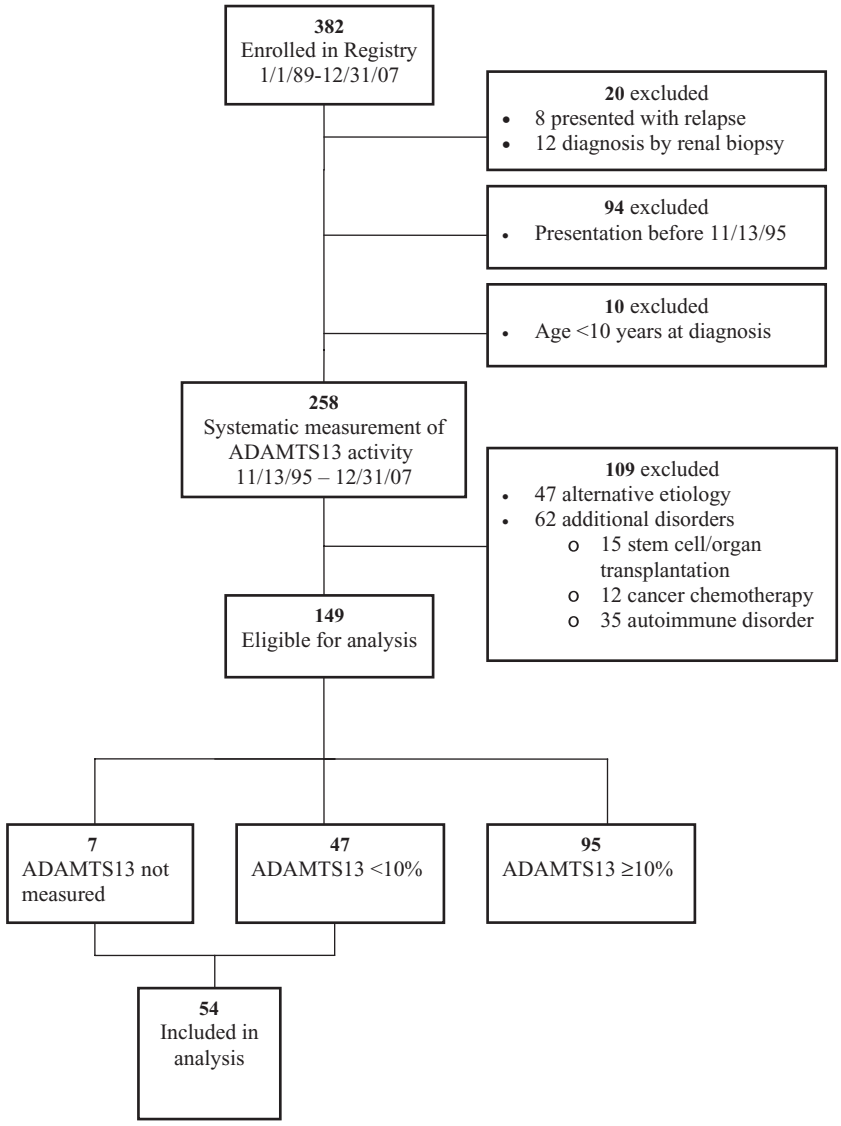

Fig. 1. Patient selection for the study. The rationale for exclusion of patient groups and inclusion of patients with ADAMTS13 deficiency and also patients who did not have ADAMTS13 activity measured is described in the text.

Therefore, we limited our analysis to the 258 consecutive patients who presented since November 13, 1995, the date when systematic collection of samples for measurement of ADAMTS13 activity began. From all 258 patients, we excluded 47 patients who were discovered to have an unsuspected alternative etiology for their acute disorder after plasma exchange for TTP was begun (sepsis, disseminated cancer, malignant hypertension, multiorgan failure). We also excluded 62 patients who had additional disorders that may have required PLT transfusions or may be associated with an increased risk for thrombosis: 1) 15 patients who had TTP after hematopoietic stem cell or organ transplantation, 2) 12 patients who had TTP associated with cancer chemotherapy, and 3) 35 patients who had an additional autoimmune disorder (such as systemic lupus erythematosus, polyarteritis nodosa, and antiphospholipid antibody syndrome).[15] Among the 149 patients eligible for analysis, ADAMTS13 was measured in 142 (97%) patients by both immunoblotting and the FRETS methods; 47 (32%) had ADAMTS13 activity less than 10 percent by either assay at the time of presentation with their first episode. Forty-two (89%) of the 47 patients had a demonstrable inhibitor of ADAMTS13 activity. The clinical categories[16] of these 47 patients were idiopathic in 42, postpartum in 3, and bloody diarrhea prodrome in 2. To avoid selection bias, we also included in our analysis the 7 patients who did not have ADAMTS13 activity

TABLE 2. Comparisons of presenting features and outcomes of patients with TTP who did or did not receive PLT transfusions*

Presenting feature or outcome	Received PLT transfusions (n = 33)	Did not receive PLT transfusions (n = 21)	p Value
Demographics			
Age (years; median, range)	40 (18-91)	41 (19-68)	0.672
Sex (female)	25 (76%)	19 (90%)	0.284
Race (black)	13 (39%)	7 (33%)	0.653
Presenting features			
Hematocrit (range)	21% (12%-26%)	22% (13%-30%)	0.193
PLT count, $\times 10^9$/L (range)	11 (2-27)	11 (4-101)	0.237
Creatinine, mg/dL (range)	1.6 (0.8-7.0)	1.4 (0.9-6.3)	0.710
Acute renal failure	2 (6%)	2 (10%)	0.638
LDH, U/L (range)	1668 (725-3423)	1363 (274-3909)	0.079
Management			
TPE treatments (range)†	19 (3-79)	17 (5-74)	0.790
Adverse outcomes			
Severe neurologic abnormalities	17 (52%)	7 (33%)	0.190
Coma	1	1	0.841
Coma, stroke	1	0	
Stroke	3	2	
Coma, seizure	3	0	
Seizure	3	2	
Transient focal abnormalities	6	2	
Death (total)	8 (24%)	5 (24%)	0.971
Death (cause)			
Thrombosis	5	4	0.739
Hemorrhage	1	1	
Sepsis	2	0	
Death and/or severe neurologic abnormalities	20 (61%)	11 (52%)	0.551

* Presenting clinical features and outcomes are described for patients in the Oklahoma TTP-HUS Registry who did or did not receive PLT transfusions. The 54 patients either had severe ADAMTS13 deficiency (<10% activity, 47 patients) or did not have ADAMTS13 measured but may have been severely deficient (7 patients). Laboratory data are the most abnormal values within 7 days before and after the day of diagnosis, designated as the day of the first plasma exchange treatment, to avoid transient effects of transfusions and to document the frequent worsening of anemia and renal function after diagnosis. Severe neurologic abnormalities and acute renal failure are defined under Materials and Methods. LDH (lactate dehydrogenase) values were normalized to an upper limit of 200 U per L to compare data across different hospital laboratories. Deaths occurred within 30 days of stopping plasma exchange treatment and were therefore attributed to TTP.[16]

† Numbers of TPE treatments are reported only for surviving patients: 25 patients who received PLT transfusions and 16 patients who did not.

measured. Of the 7 patients, 5 died after plasma exchange was requested but before treatment could be initiated and a sample for ADAMTS13 was not obtained; a sample was not obtained in 2 other patients. The clinical categories[16] of these 7 patients were idiopathic in 5 and drug-associated in 2. These 54 patients were managed by 26 different physicians at 10 different hospitals; these 10 hospitals accounted for 97 percent of all 258 Registry patients during this time period. One of the authors (JNG) saw and evaluated 50 (93%) of the 54 patients at the time of their initial diagnosis.

Thirty-three (61%) of the 54 patients received PLT transfusions; there was no trend in the proportion of patients receiving PLT transfusions across the duration of the study. Nineteen (58%) received only one transfusion, 5 received two transfusions, 8 received three transfusions, and 1 patient received four PLT transfusions. Thirty-two of the 33 patients received PLT transfusions before treatment with plasma exchange was begun. In 10 of these patients the only PLT transfusion was for the central venous catheter insertion, immediately before the initial plasma exchange treatment. Among the other 22 patients, 17 were for asymptomatic thrombocytopenia, often before the diagnosis for TTP was suspected; 3 were for overt bleeding; and 2 were for cesarean section. Seven of these 32 patients also received PLT transfusions after plasma exchange was begun: 1 for asymptomatic thrombocytopenia, 1 for overt bleeding, and 5 for insertion of a new central venous catheter; 1 patient only received a PLT transfusion after plasma exchange was begun, for severe thrombocytopenia associated with *Staphylococcus aureus* sepsis.

Table 2 compares the presenting features and clinical outcomes of the 33 patients who received PLT transfusions to the 21 patients who did not receive a PLT transfusion. There were no significant differences between the two groups of patients in demographics, clinical features, or outcomes. The frequency of death, the causes of death, the frequency of severe neurologic abnormalities, and the type of neurologic abnormalities were not different between the two groups of patients. Thrombotic deaths occurred in both groups, 5 (15%) of 33 patients who received PLT transfusions and 4 (19%) of the 21 patients who did not receive a PLT transfusion. Among surviving

patients, there was no difference in the number of PLT transfusions required to achieve a remission.

The occurrence of deaths and severe neurologic abnormalities related to the time of PLT transfusions and the time of initiation of plasma exchange treatment for the 20 patients who received PLT transfusions and who died and/or had severe neurologic abnormalities are illustrated in Fig. 2. Five (26%) of the 19 patients who received only one PLT transfusion died and 3 (21%) of the 14 patients who received more than one PLT transfusion died ($p = 1.00$). Six (24%) of the 25 patients who only received PLT transfusions before plasma exchange was begun died and 2 (25%) of the 8 patients who received PLT transfusions after (7 both before and after, 1 only after) plasma exchange had begun died ($p = 1.00$). Table 3 summarizes the clinical course for each of the 8 patients who received PLT transfusions and died and describes their cause of death. Two patients (Patients 2 and 3) died before plasma exchange was begun. Death was attributed to thrombosis in 5 patients: 2 patients who died 33 and 58 hours after PLT transfusions had autopsies demonstrating disseminated microvascular thrombi (Patients 4 and 5); 2 patients (Patients 2 and 3) died with clinically diagnosed acute myocardial infarction but did not have autopsies. One patient (Patient 7) who had responded to plasma exchange treatment died 10 days after plasma exchange was discontinued from pulmonary emboli, 18 days after her PLT transfusion. One patient (Patient 1) died from hemorrhage. She had initially responded to plasma exchange treatment and then developed *S. aureus* sepsis, requiring removal of her central venous catheter. Two days later a new central venous catheter was required for exacerbation of TTP. A PLT transfusion given before the procedure increased her PLT count from 39×10^9 to 67×10^9 per L; she died in the surgical operating room immediately after insertion of a left internal jugular central venous catheter. Sepsis may have contributed to her fatal hemorrhage even though she had had 2 days of appropriate antibiotic treatment. Two patients (Patients 6 and 8) died of staphylococcal sepsis, attributed to a complication of the central venous catheter, 14 and 26 days after their last PLT transfusion (Fig. 2, Table 3).

Among the 12 patients who received PLT transfusions and had severe neurologic abnormalities but who survived, 2 patients (Patients 10 and 20; Fig. 2) had neurologic abnormalities only before the PLT transfusions were given. In 2 patients neurologic abnormalities occurred both before and after PLT transfusions (Patients 15 and 19, Fig. 2). In the other 8 patients neurologic abnormalities occurred only after PLT transfusions. Among the 10 patients whose neurologic abnormalities occurred after PLT transfusions, they occurred within 24 hours in 3 patients (Patients 15, 18, and 19), 32 to 48 hours in 4 patients (Patients 11, 14, 16, and 17), and 4 to 11 days in 3 patients (Patients 9, 12, and 13; Fig. 2).

The occurrence of deaths and severe neurologic abnormalities related to the time of initiation of plasma exchange treatment for the 11 patients who died and/or had severe neurologic abnormalities but who did not have PLT transfusions are illustrated in Fig. 3. Table 4 summarizes the clinical course for each of the 5 patients who died and describes their cause of death. In 4 patients, death was attributed to thrombosis (Patients 1-4). Systemic microvascular thrombosis was documented at autopsy in 3 patients (Patients 1-3). The fourth patient had an acute myocardial infarction with cardiac arrest 4 days after coronary artery bypass graft surgery and remained comatose until her death 9 days later (Patient 4). One patient died suddenly from hemorrhage and/or pneumothorax after placement of a right subclavian venous catheter before her initial planned plasma exchange treatment when her PLT count was 13×10^9 per L (Patient 5; Fig. 3, Table 4).

Forty-one (76%) of the 54 patients survived their episode of TTP; 12 (29%) of the 41 surviving patients have had 17 subsequent episodes of TTP. Single PLT transfusions were given in only 3 (18%) episodes. One patient received a PLT transfusion for asymptomatic thrombocytopenia in a community hospital emergency department before transfer to an Oklahoma City hospital for plasma exchange treatment; he had focal neurologic abnormalities before but not after his PLT transfusion. One other patient received a PLT transfusion during each of two subsequent episodes before central venous catheter insertion; she had no neurologic abnormalities or other adverse events after the PLT transfusions. One patient died of a myocardial infarction and two other patients had severe neurologic abnormalities (transient focal abnormalities) during subsequent episodes; they did not receive PLT transfusions.

DISCUSSION

After effective treatment became available for patients with TTP in 1977[10,11] and survival was expected, interventions that may adversely affect recovery were recognized. The first reports describing patients' deterioration and death after PLT transfusions were published in 1981.[1-3] These reports gained attention because of the dramatic nature of the critical outcomes and they achieved credibility because of the biologic basis for potential harm from PLT transfusions. Subsequent reports[32,33,36,38,39] supported these observations and led to the standard of practice to avoid PLT transfusions in patients with TTP except for management of life-threatening hemorrhage.[7]

However, our comprehensive search identified few published descriptions of patients with TTP who had adverse effects attributed to PLT transfusions. Because PLT transfusions are assumed to be harmful in patients with TTP, three recent reports have been published to describe the absence of any adverse effects in seven

TABLE 3. Patients who died after receiving a PLT transfusion*

Patient	Age, race, sex	Time (last PLT transfusion to death)	Clinical course	Autopsy	Cause of death
1	25, white, female	6 hr	Admitted for abdominal pain and hematuria; diagnosis sepsis; no neurologic abnormalities. Two PLT transfusions for asymptomatic PLT counts of 6×10^9 and 17×10^9/L on Days 1 and 2. TTP diagnosed on Day 5. PLT count 195×10^9/L after 6th TPE; skip 1 day TPE; exacerbation; PLT count 61×10^9/L→132×10^9/L after 14th TPE; *S. aureus* cultured from CVC; CVC withdrawn. PLT count→39×10^9/L; PLT transfusion given for CVC placement; PLT count→67×10^9/L. Died during CVC placement.	No	Hemorrhage
2	91, black, female	8 hr	Unresponsive, left hemiparesis on admission; diagnosis AMI, stroke. PLT transfusion for asymptomatic PLT count of 6×10^9/L 7 hr after admission; PLT count→23×10^9/L. TTP diagnosed 22 hr after admission; CVC inserted but died before start of TPE.	No	Probable thrombosis (AMI, stroke)
3	72, Native American, female	12 hr	Admitted for chest pain; AMI diagnosed. PLT count 12×10^9/L; no neurologic abnormalities; PLT transfusion for gross hematemesis 4 hr after admission; PLT count→54×10^9/L; hematemesis stopped. TTP diagnosed 7 hr after PLT transfusion. Became hypotensive with bradycardia and died 12 hr after PLT transfusion, before CVC insertion and TPE.	No	Probable thrombosis (AMI)
4	37, black, female	33 hr	Admitted for abdominal pain; diagnosis ITP with mild hematemesis and vaginal bleeding; no neurologic abnormalities. PLT count 10×10^9/L; PLT transfusion for mild bleeding on Days 1, 3, and 4; PLT count→20×10^9/L. TTP diagnosed on Day 5; died 21 hr after 1st TPE.	Yes	Thrombosis (systemic microvascular)
5	30, black, male	58 hr	Disoriented, combative on admission; diagnosis TTP. PLT count $<11 \times 10^9$/L; PLT transfusion before CVC insertion; PLT count→16×10^9/L. Improved mental status after 2 days of TPE. 43 hr after PLT transfusion, multiple grand mal seizures; PLT count $<11 \times 10^9$/L; 3rd TPE performed; died 58 hr after PLT transfusion.	Yes	Thrombosis (systemic microvascular)
6	41, black, female	14 days	Admitted for hematemesis, rectal and vaginal bleeding; diagnosis sepsis. Confused but without other neurologic abnormalities. Urine positive for cocaine. PLT count 13×10^9/L. Cardiac arrest 5 hr after admission, intubated, remained unresponsive throughout hospitalization. PLT transfusion for bleeding on Days 1, 3, 4, and 6. TTP diagnosed on Day 4; no response to 12 TPEs and steroids. On Day 16, temperature 107°F, blood cultures—*S. epidermidis*, attributed to the CVC. TPE discontinued, died on Day 20.	No	Infection (*S. epidermidis* sepsis)
7	51, white, female	18 days	Admitted for seizure, hyponatremia, obtunded; diagnosis sepsis; PLT count 851×10^9/L. PLTs→17×10^9/L on Day 8; PLT transfusion for asymptomatic thrombocytopenia. TTP diagnosed on Day 9; PLT count 161×10^9/L after 7th TPE; TPE stopped. Day 21, PLT count 437×10^9/L, ARDS, lung biopsy-multiple emboli. Died on Day 26.	No	Thrombosis (pulmonary emboli)
8	66, white, female	26 days	Admitted for purpura, dizziness; PLT count 13×10^9/L; diagnosis ITP. TTP diagnosed on Day 3. PLT transfusion for CVC insertion; PLT count 13×10^9/L. Response to 13 TPEs, steroids, rituximab. PE discontinued, PLT count 205×10^9/L→107×10^9/L on Day 19; TPE resumed; PLT count→29×10^9/L on Day 24; cerebral hemorrhage; blood cultures—MRSA, attributed to the CVC; died on Day 28.	No	Infection (MRSA sepsis)

* The clinical course and cause of death of the eight patients of the Oklahoma TTP-HUS Registry who died after receiving PLT transfusions are described. The patient numbers correspond to the numbers in Fig. 2. Attribution of death to thrombosis was only considered probable in the absence of an autopsy. ADAMTS13 activity was less than 10 percent in all patients except in Patients 2 and 3 in whom ADAMTS13 was not measured.

AMI = acute myocardial infarction; ARDS = adult respiratory distress syndrome; CVC = central venous catheter; MRSA = methicillin-resistant *S. aureus*; TIA = transient cerebral ischemic attack; TPE = plasma exchange treatment.

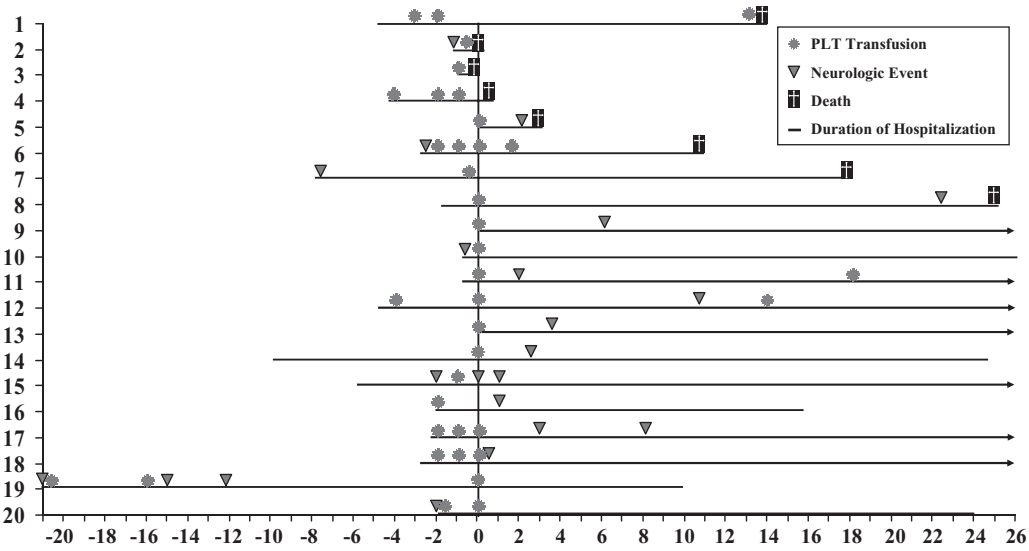

Fig. 2. The clinical course of each of the 20 patients of the Oklahoma TTP-HUS Registry who received PLT transfusions and had a severe neurologic abnormality or died is illustrated. ADAMTS13 activity was less than 10 percent in all patients except in Patients 2 and 3 in whom ADAMTS13 was not measured. Day 0 is the day of diagnosis of TTP and the first plasma exchange treatment. Arrowheads on the lines indicate continued hospitalization beyond the chart margins. The stars indicate each PLT transfusion. The triangles indicate severe neurologic events: focal neurologic abnormalities, seizure, stroke, or coma. The crosses indicate death. Patients 1 through 8 correspond to Patients 1 through 8 in Table 3.

TABLE 4. Patients who died and who had not received a PLT transfusion*

Patient	Age, race, sex	Clinical course	Autopsy	Cause of death
1	28, black, female	Admitted for headache, dyspnea, abdominal pain; PLT count 11×10^9/L; diagnosis SLE. TTP considered on Day 3 but diagnosis deferred because of DIC (PT, 14.5 sec; fibrinogen, 135 mg/dL). Day 4—confused, combative; TTP diagnosed; CVC inserted; died before TPE.	Yes	Thrombosis (systemic microvascular)
2	46, white, male	Admitted for headache, fatigue; diagnosis TTP. Became confused, hypotensive; died before CVC inserted 13 hr after admission.	Yes	Thrombosis (systemic microvascular)
3	50, white, female	Arrived in emergency room for purpura, nausea, vomiting; diagnosis TTP. Became lethargic, hypotensive with bradycardia; died 3 hr after arrival before CVC inserted.	Yes	Thrombosis (systemic microvascular)
4	68, white, female	Admitted for abdominal, back pain; diagnosis abdominal aortic aneurysm; PLT count 330×10^9/L. Cardiac catheterization, severe coronary disease, coronary artery bypass graft surgery on Day 6; PLT count 215×10^9/L. Day 10, cardiac arrest, coma; AMI; PLT count 101×10^9/L. Day 11, TTP diagnosed, TPE begun. PLT count increased to 327×10^9/L after fifth TPE, but remained hypotensive, unresponsive. Treatment stopped, died on Day 19.	No	Probable thrombosis (AMI)
5	61, white, female	Admitted for abdominal pain, nausea, vomiting, hypotension; diagnosis sepsis. Day 3, quinine-associated TTP diagnosed; PLT count 13×10^9/L; died immediately after insertion of subclavian CVC.	No	Hemorrhage, pneumothorax

* The clinical course and cause of death of the five patients of the Oklahoma TTP-HUS Registry who died and who did not receive PLT transfusions are described. The patient numbers correspond to the numbers in Fig. 2. Attribution of death to thrombosis was only considered probable in the absence of an autopsy. ADAMTS13 activity was less than 10 percent in Patients 3 and 4; ADAMTS13 activity was not measured in Patients 1, 2, and 5.

AMI = acute myocardial infarction; DIC = disseminated intravascular coagulation; PT = prothrombin time; CVC, central venous catheter; SLE = systemic lupus erythematosus; TIA = transient cerebral ischemic; TPE = plasma exchange treatment.

patients.[44,45,51] These reports suggested that PLT transfusions may be safe if they are given immediately before or after plasma exchange treatment begins,[44,45,51] in contrast to the initial reports of deterioration and death after PLT transfusions that occurred in patients who had not been treated with plasma exchange.[2,32,38] Most case reports in which PLT transfusions were noted and patient outcomes were described did not comment about a relation

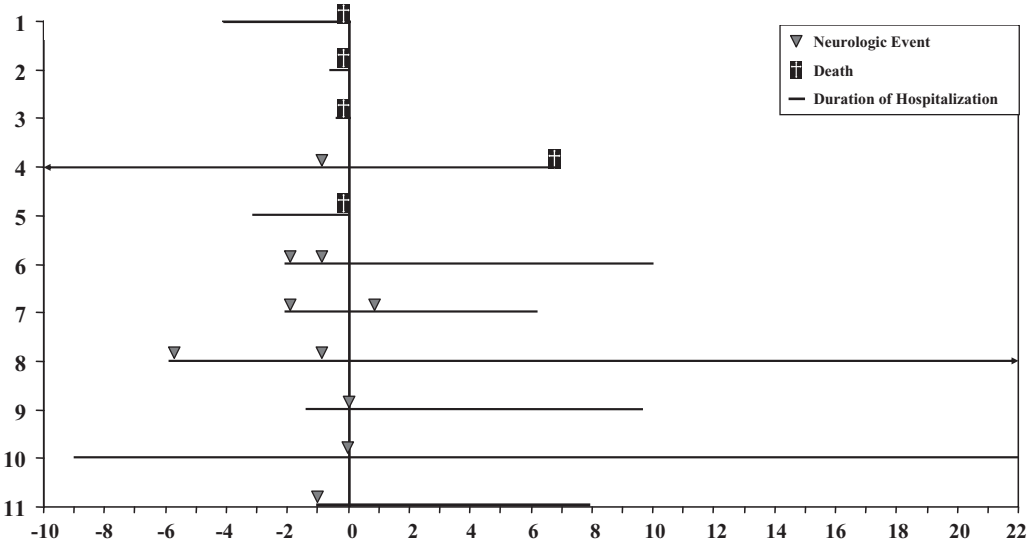

Fig. 3. The clinical course of each of the 11 patients of the Oklahoma TTP-HUS Registry who had a severe neurologic abnormality or died but who did not receive a PLT transfusion is illustrated. ADAMTS13 activity was less than 10 percent in all patients except in Patients 1, 2, and 5 in whom ADAMTS13 activity was not measured. Day 0 is the day of diagnosis of TTP and the first plasma exchange treatment. Attribution of death to thrombosis was only considered probable in the absence of an autopsy. The triangles indicate severe neurologic events: focal neurologic abnormalities, seizure, stroke, or coma. The crosses indicate death. Patients 1 through 5 correspond to the Patients 1 through 5 in Table 4.

between PLT transfusions and outcomes. For all 13 studies with a comparison group of patients who did not receive PLT transfusion, the mortality rates were 36 percent (37 of 103) for patients who received PLT transfusions and 16 percent (41 of 255) for patients who had not received PLT transfusions. Although a statistical comparison of patients who did or did not receive PLT transfusions suggests a difference, the comparison is not valid because 1) patients are aggregated across multiple studies and 2) these studies were retrospective, observational, and diverse regarding patient selection, documentation of management, and description of outcomes. In these reports, patients who did or did not receive PLT transfusions may have been different; patients who received PLT transfusions may have had more severe disease; not all PLT transfusions may have been documented.

A search for patient outcomes after PLT transfusions in 77 case series of 25 or more patients with TTP published since 1970, the era of effective treatment[10,11,57] and available PLT transfusions,[8,9] identified only 12 (16%) case series that described patient outcomes after PLT transfusions.[6,34-37,39,40,43,47-50] The silent majority of case series suggests that dramatic occurrences of acute deterioration promptly after PLT transfusions were uncommon or if deterioration occurred, it was not attributed to the PLT transfusion. The minimal amount of anecdotal observations does not support the recommendation that PLT transfusions must be avoided in patients with TTP except for life-threatening hemorrhage. However, the absence of data cannot refute the possibility that PLT transfusions may be harmful in some patients.

In spite of the common belief among physicians that transfusions are potentially harmful for patients with TTP, our experience demonstrates that patients with TTP commonly receive PLT transfusions. PLT transfusions are a common component of initial empiric management for thrombocytopenia in acutely ill patients with severe anemia in whom bleeding and sepsis are initially suspected in an emergency department or during initial hours in the hospital. The high frequency of PLT transfusions in our patients (61%), higher than in any previously reported case series of 25 or more patients, may be related to our collection of all data from all hospitals beginning with the onset of the patient's illness. In 32 of 33 patients who received PLT transfusions, transfusions were given before plasma exchange treatment was begun. In 10 patients, PLT transfusions were only given for placement of the central venous catheter, immediately before plasma exchange treatment. Although central venous catheter insertion may be performed without complications in patients with severe thrombocytopenia,[58,59] hemorrhage can occur[60] related either to the thrombocytopenia or technical complications of the procedure. Among the 54 patients in this report, 2 patients died as a result of hemorrhage from central venous catheter insertion, accounting for 15 percent of the 13 deaths.

In our analysis, there was no difference in the frequency of death or severe neurologic abnormalities

between patients who did or did not receive PLT transfusions. Among the 33 patients who received PLT transfusions, death was attributed to thrombosis in 5 (15%) patients, but 1 of these deaths was caused by multiple pulmonary emboli 18 days after her PLT transfusion. Deaths from thrombosis also occurred in 4 (19%) of the 21 patients who did not receive PLT transfusions. Among the 33 patients who received PLT transfusions, severe neurologic abnormalities occurred in 12 of the surviving patients. However, in 2 of these patients the neurologic abnormalities only occurred before the PLT transfusion was given; in 2 patients, neurologic abnormalities occurred both before and after PLT transfusions; and in 3 patients the neurologic abnormalities only occurred 4 to 11 days after the PLT transfusion. Therefore, it is difficult to document a causal relation between the transfusion of PLTs and complications since severe neurologic abnormalities occurred both before and after PLT transfusions and thrombotic deaths occurred in both patients who did not receive PLT transfusions as well as those who did. Also there was no apparent difference among patients who received PLT transfusions before or after the initiation of plasma exchange.

The analysis of our patients has several limitations. 1) If PLT transfusions do cause death in patients with TTP, this may prevent some patients from being diagnosed with TTP and referred for plasma exchange treatment, resulting in a selection bias of our patients. We attempted to minimize selection bias by including patients who died very soon after the diagnosis of TTP was established, before plasma exchange was begun and a sample for ADAMTS13 measurements could be obtained. 2) We limited our analysis to patients with documented or possible ADAMTS13 deficiency, to analyze only patients with a confirmed diagnosis of TTP and to avoid potential bias of including patients whose diagnosis of TTP was less certain and therefore whose risk from PLT transfusions may be different. However, this criterion excludes the large majority of patients who were treated with plasma exchange for TTP in our community but who did not have severe ADAMTS deficiency.[16] 3) Although the demographic data, presenting features and clinical outcomes of the patients who received PLT transfusions were not different from the patients who did not receive PLT transfusions, the two groups could have had fundamental differences since they were not randomly allocated, as in a clinical trial. 4) Our analysis of complications after PLT transfusions was limited to severe neurologic abnormalities and death. Minor complications may have occurred that were not recorded in our data, especially after PLT transfusions that preceded the diagnosis of TTP and the beginning of our prospective data collection. 5) A benefit from PLT transfusions cannot be documented from our data. A suggestion that PLT transfusions could be beneficial was the observation that many of the patients had substantial PLT count increments after PLT transfusions. 6) Finally, although the patients were managed by 26 different physicians at 10 different hospitals, these data are from a single state and will need to be confirmed by observations from different locations.

However, our study also has several strengths for the analysis of clinical outcomes after PLT transfusions in patients with TTP. 1) A prospective cohort of all 258 consecutive patients across 12 years from a defined geographic region for whom plasma exchange was requested for a diagnosis of TTP or HUS was initially included; ADAMTS13 activity was measured in 239 (93%) patients. 2) From these 258 patients, all 47 consecutive patients in whom the diagnosis of TTP was supported by ADAMTS13 deficiency, and the 7 patients in whom ADAMTS13 activity could not be measured, were included in the analysis. 3) Patients were prospectively enrolled at time of their TTP diagnosis and all preceding data since the onset of illness were systematically collected on standard forms at that time; all future data were collected prospectively. 4) All PLT transfusions throughout the entire clinical course of each of the 54 patients were analyzed, including transfusions before the diagnosis of TTP was considered. 5) These data represent the complete community experience from 58 of Oklahoma's 77 counties.

PLT transfusions may be harmful for patients with TTP, but the evidence supporting this belief is limited. Our prospective cohort study of consecutive TTP patients documenting detailed individual patient data cannot determine whether PLT transfusions do or do not contribute to poor outcomes in patients with TTP. However, our experience, as well as experience from previous publications, documents that PLT transfusions are commonly given and may be uncommonly, or not at all, associated with adverse events. However, because of the important role of PLTs in microvascular thrombus formation in patients with TTP, our practice is to avoid or minimize PLT transfusions. This standard of practice among physicians in our community was confirmed by the fewer PLT transfusions given to patients with an established diagnosis of TTP during relapsed episodes. PLT transfusions are not often required, since bleeding is an uncommon problem[61,62] but severe bleeding can occur.[60,61] PLT transfusions should not be withheld from patients who have appropriate indications for management of overt bleeding, surgery, or invasive procedures in the presence of severe thrombocytopenia.

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