

Frequently relapsing thrombotic thrombocytopenic purpura treated with cytotoxic immunosuppressive therapy

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Background and Objectives. Treatment of thrombotic thrombocytopenic purpura (TTP) with plasma exchange has reduced mortality rates from 90% in untreated cases to less than 20%. Despite plasma exchange, relapses may occur in as many as 40% of cases. Multiple relapses occur in a minority but pose a significant therapeutic challenge. Recent evidence supports the presence of an autoantibody which inhibits proteolysis of von Willebrand factor (vWF) in active TTP, allowing large multimers of vWF to form and promote platelet aggregation. Additional evidence suggests autoantibodies activate capillary endothelium and promote platelet aggregation in the microcirculation. Immunosuppression, thus, has a biologically plausible role in TTP. We describe three consecutive cases of relapsing TTP treated with cytotoxic therapy to highlight the potential role of immunosuppression.

Design and Methods. Cytotoxic immunosuppressive therapy with either cyclophosphamide or azathioprine was used in three consecutive patients with frequently relapsing TTP.

Results. All three patients have maintained remissions of 8 to 10 months without recurrence.

Interpretation and Conclusions. Cytotoxic immunosuppressive therapy may have a role in inducing long-term remissions in recurrent TTP.

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Key words: TTP, relapse, cyclophosphamide, azathioprine, case series.

Thrombotic thrombocytopenic purpura (TTP) is a microangiopathic disease characterized by schistocytic hemolytic anemia, thrombocytopenia, neurologic deficits, fever and renal failure. A recent review summarizes our current knowledge and treatment of TTP.¹ Plasma exchange has evolved as the mainstay of therapy for acute episodes of TTP and has reduced the 30-day mortality rate from 90% in untreated cases² to less than 20%.³⁻⁶

Improved survival has allowed rates of relapse to approach 40% despite additional therapies with prednisone, intravenous immune globulin, anti-platelet agents or splenectomy.⁶⁻⁹ Early relapse while patients continue to receive daily plasma exchange is frequent, being reported in nearly 50% of patients in one series of 318 patients with either TTP or hemolytic uremic syndrome (HUS).¹⁰ Others have argued that failing to differentiate TTP relapses from recurrences caused by premature termination of treatment leads to overestimating rates of relapse.¹¹ According to data from Bell,¹⁰ 10% of all patients with either TTP or HUS have multiple relapses. Controversy exists regarding our ability to separate TTP from HUS clinically and the risk of relapse may vary accordingly. Early death from refractory disease still occurs in 5-18%.^{10,12} Precipitating factors and predictors of relapse are largely unknown.

Relapses in TTP may lead to increased thrombotic events including neurologic and renal deterioration, exposure to large quantities of scarce blood products, and unknown effects on long-term survival. Treatments that decrease relapse frequency or shorten time to remission are needed to reduce patient morbidity further in recurrent TTP as well as to ease the burden on blood product supplies.

Large multimers of von Willebrand Factor (vWF) have been isolated in plasma from patients with

TTP¹³ and diminished activity of vWF protease was recently observed during acute episodes.¹⁴ An IgG autoantibody is purported to act as an inhibitor of the vWF protease, allowing the large multimers to exist and promote excessive platelet aggregation.^{15,16} Reducing plasma levels of inhibitory anti-protease IgG or replenishing levels of active protease are likely mechanisms of successful treatments in TTP. Plasma exchange with cryosupernatant containing active protease may not yield a lasting therapeutic effect if production of the anti-protease IgG is not suppressed. Additionally, autoantibodies found against capillary endothelial CD36 have been reported in TTP and are believed to cause platelet aggregation.¹⁷⁻¹⁹

Cytotoxic immunosuppressive drugs, therefore, have a biologically plausible role in treating TTP by diminishing production of antibody inhibitor against the vWF protease or by reducing antibodies that promote platelet aggregation. Cytotoxic immunosuppressive agents may play an important role in cases of multiple relapses. In this report, we discuss three consecutive cases of frequently relapsing TTP treated with cytotoxic immunosuppressive therapy.

Design and Methods

Consecutive patients who presented with their second or greater relapse of TTP from July 1999 to July 2000 were considered for cytotoxic immunosuppressive therapy at our institution. Relapse was defined as the recurrence of any of the following:

recurrence of initial symptoms; presence of microangiopathic hemolytic anemia; abrupt thrombocytopenia (platelet count $<100 \times 10^9/L$); acute deterioration of renal parameters; or sudden rise of lactate dehydrogenase (LDH). All patients received daily plasma exchange until their platelet count was greater than $150 \times 10^9/L$ and LDH normalized. Prednisone or methylprednisolone was administered initially at 1 mg/kg and then tapered over 8-12 weeks. Either cyclophosphamide, administered at 1.5 mg/kg orally per day for 6-12 months and tapered over 6 months, or azathioprine, given at 1.5 mg/kg and administered for 6-12 months, was started at the time of relapse. Hospital and clinic charts and plasmapheresis records were reviewed for each patient. Previous experience with cytotoxic therapy was reviewed by searching Medline using Advanced PubMed (1966-2000) and by scanning bibliographies.

Results

Case Reports

Case #1 (Figure 1).

A female, aged 46, presented in November 1993 with a 1-week history of dysarthria, confusion, disorientation, and right-sided weakness. On initial examination she was febrile, had diffuse purpura, was dysarthric, and had right-sided weakness. Initial laboratory investigations showed a platelet count of $27 \times 10^9/L$, hemoglobin (Hb) 155 g/L, leukocytes $10.2 \times 10^9/L$, LDH 647 units/L (normal 91-180), creatinine (Cr) $96 \mu\text{mol/L}$, normal INR and aPTT, and a peripheral blood film demonstrated schistocytes. Computed tomography (CT) of her head confirmed an ischemic infarct in the territory of the left middle cerebral artery. She was treated with daily plasmapheresis (4L exchanges) for TTP. Attempts at lengthening the period between exchanges led to prompt relapses. Oral prednisone therapy was initiated at 100 mg daily on day 18 and tapered slowly over 7 months. After 5 months (70 plasma exchange sessions), with no sustained remission, intravenous immune globulin (IVIG) therapy was administered at 1.2 g/kg over 3 days. A partial remission was achieved after 7 months with monthly IVIG and two courses of dexamethasone 40 mg daily for 4 days. Her platelet counts ranged from $125-300 \times 10^9/L$ until 1996. She remained in a state of chronic thrombocytopenia for several years from 1996 onwards. Between January and July 1997, her platelet counts remained less than $150 \times 10^9/L$. In July 1997 her platelet count fell to $32 \times 10^9/L$ and she received IVIG 60g. After July 1997 her platelet counts remained less than $100 \times 10^9/L$ on most mea-

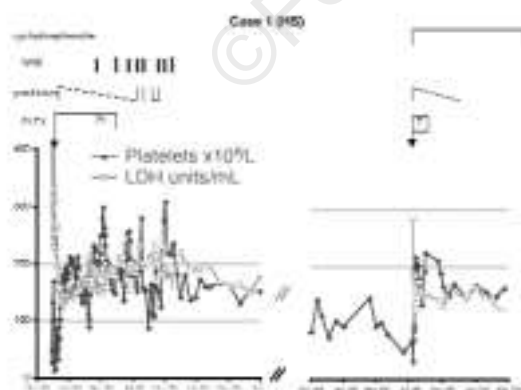


Figure 1. Case #1 (see text). Platelet and LDH values are plotted against time with treatment modalities depicted above using the same time axis. (PLEX – plasma exchange with number of sessions in box; IVIG – intravenous immune globulin).

surements until 1999. In July 1999 she developed symptoms of headache and aphasia accompanied by a platelet count of $37 \times 10^9/L$, LDH 261 units/L, Hb 128 mg/L, normal renal function and schistocytes on a peripheral blood film. CT of the head demonstrated a new left frontal lobe ischemic infarct. She was treated with daily plasma exchange for 7 days, prednisone 60 mg daily and oral cyclophosphamide 100 mg daily starting on day 8. Her platelet count was greater than $150 \times 10^9/L$ on day 4 with a normal LDH and partial resolution of her speech deficits. Her platelet count has remained greater than $100 \times 10^9/L$ and she remains in clinical remission after 8 months of follow-up and her dose of cyclophosphamide has been reduced to 50 mg daily.

Case #2 (Figure 2).

A female, aged 25, presented in July 1999 with a 3-day history of easy bruising, fever, fatigue, and pleuritic chest pain. She was febrile, had purpura on her legs and multiple bruises on her upper extremities. Laboratory investigations: Hb 77 g/L, platelets $<10 \times 10^9/L$, Cr $94 \mu\text{mol/L}$, bilirubin $39 \mu\text{mol/L}$, LDH 1136 units/L, normal INR and aPTT and schistocytes on a peripheral blood film. She was treated with daily plasma exchange and prednisone 60 mg daily with gradual tapering. She relapsed after 6 days but sustained a remission after 13 plasma exchange sessions. She relapsed 10 weeks

after her initial presentation, 2 weeks after completing her tapering course of prednisone, with platelets $40 \times 10^9/L$ and LDH 264 units/L. She achieved remission with 6 plasma exchange sessions, prednisone 60 mg daily, and oral cyclophosphamide 100 mg daily was initiated. She has remained in remission for 8 months and is currently off all therapies after choosing to become pregnant.

Case #3 (Figure 3).

A female, aged 56, presented in December 1997 with a 1-week history of upper respiratory tract infection, nausea, vomiting, jaundice, and abdominal pain with an elevated serum lipase. She then developed right arm weakness, headache, and progressive drowsiness. Her Hb was 106 g/L with schistocytes on a peripheral blood film, platelets $6 \times 10^9/L$, LDH 985 units/L, Cr $92 \mu\text{mol/L}$ and she had a normal coagulation profile. She developed fever the day following admission. CT head and abdominal ultrasound were unremarkable. She was diagnosed as having TTP and started on daily plasma exchange therapy. She required 30 sessions of plasma exchange over 34 days to achieve remission. Prednisone 60 mg daily was started on day 27 and weaned over 12 weeks.

She relapsed 6 months later and required 13 additional plasma exchange sessions to reach a second remission. She was restarted on prednisone 60 mg

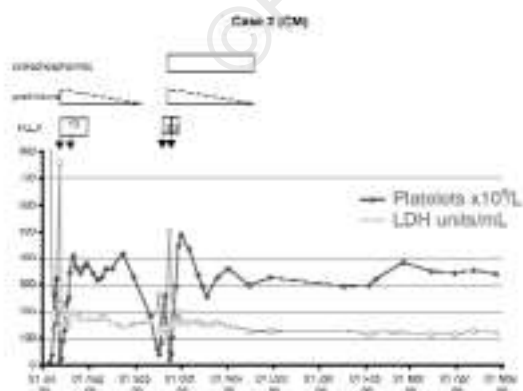


Figure 2. Case #2 (see text). Platelet and LDH values are plotted against time with treatment modalities depicted above using the same time axis (PLEX – plasma exchange with number of sessions in box).

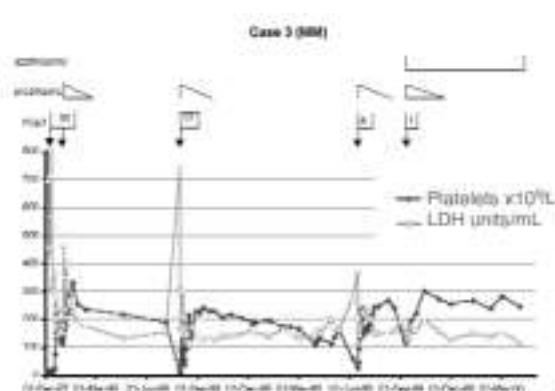


Figure 3. Case #3 (see text). Platelet and LDH values are plotted against time with treatment modalities depicted above using the same time axis (PLEX – plasma exchange with number of sessions in box).

daily and this treatment was tapered over 12 weeks. She relapsed again 10 months later and a third relapse occurred 2 months after achieving remission from the second relapse. At the final relapse she was treated with a single plasma exchange, started on prednisone 60 mg daily and azathioprine 100 mg daily. She has been tapered off steroids and remains on azathioprine 50 mg daily in remission 8 months later.

Discussion

Our three cases of idiopathic relapsing TTP demonstrated early benefit from immunosuppressive therapy with sustained remissions lasting 8-10 months. All three patients exhibited frequent relapses of TTP prior to initiating immunosuppression. One patient (case #1) had a clinical course of chronic TTP spanning several years. The second

patient had 4 relapses in 2 years and the third case had 3 relapses in 18 months. Treatment was well tolerated by all three patients.

Multiple strategies aimed at suppressing immune function have been used to treat relapses of TTP; such strategies include intravenous immunoglobulins, splenectomy, glucocorticoids, and cytotoxic immunosuppressive drugs. Evidence supporting the effectiveness of these strategies exists in the form of case series and institutional reviews. No dominant strategy is widely accepted.

A case series of 6 patients treated with splenectomy while in remission reported a significant reduction in relapse frequency.²⁰ Morbidity associated with splenectomy and long-term infectious risks has limited the widespread acceptance of splenectomy. Several published protocols have incorporated regular use of glucocorticoids^{10,12,21}

Table 1. Previous reports of cyclophosphamide in treatment of TTP.

Ref.	Year	No. of pts	Age/sex	No. of relapses	Underlying condition	Concomitant/prior treatments	Cyclophosphamide	Outcome	Follow-up
(33)	1999	1	49, F	refractory over 15 d	nil	plasma exchange	iv, total 2600 mg	remission	6 mos
(34)	1999	2	19, F	1 st episode	SLE	prednisone	iv, 500 mg/month	remission	18 mos
			32, F	1 st episode	SLE ITP	plasma exchange methylprednisolone plasma exchange protein A column	iv, 500 mg/month	remission	3 mos
(29)	1998	1	48, F	5 in 8 wks	nil	plasma exchange prednisone	iv, 1 g × 2	remission	18 mos
(27)	1997	2	28, F	relapsing	nil	plasma exchange vincristine	po, 100 mg/d	remission	47 mos
			56, F	chronic	nil	plasma exchange prednisone vincristine	po, 100 mg/d	remission	30 mos
(32)	1995	1	23, M	4 in 29 d	common cold	plasma exchange prednisone vincristine	iv, 1 g × 2	remission	n/a
(26)	1990	1	26, F	8 in 38 mos	nil	plasma exchange methylprednisolone vincristine IVIg ASA, dipyridamole	po, 50 mg/d	remission	19 mos
(30)	1990	1	53, F	relapsing	lymphoma	plasma exchange splenectomy ASA vincristine corticosteroids	iv, 800 mg	relapses × 5	n/a
(28)	1985	1	36, F	multiple	carcinoma	plasma exchange corticosteroids	po, 100 mg/d	death	2 wks
(31)	1979	1	22, F	3 in 7 wks	infectious cerebritis	methylprednisolone splenectomy plasma infusion (day 5) ASA, dipyridamole, sulfinpyrazone	po, 100 mg/d	remission	3 mos

Table 2. Previous reports of azathioprine in treatment of TTP.

Ref	Year	No. of pts	Age/sex	No. of relapses	Underlying condition	Treatments	Azathioprine	Outcome	Follow-up
(35)	1985	1	51, F	multiple over 6 mos	nil	prednisone	po, 100 mg/d	remission	17 mos
(10)	1997	2	n/a	4-6 over 2 yrs	n/a	n/a	po, 100 mg/d	remission	1 yr

but at varying dosages. Although there is currently no data from prospective randomized studies, the use of glucocorticoids is likely to increase in light of increasing evidence for an immunologic basis of TTP. Likewise, there are no randomized trials using IVIG. There are case reports of both success^{22,23} and ineffectiveness²⁴ of this modality and in one case series of 17 patients, only 4 patients had a response attributed to IVIG.²⁵

Previous experience with cytotoxic agents in TTP includes the use of cyclophosphamide, azathioprine, and vincristine. Eleven patients in 9 anecdotal case reports received oral or intravenous cyclophosphamide²⁶⁻³⁴ (see Table 1). Nine patients had frequent relapses over weeks to months or had chronic relapsing TTP. All but one had received prior plasma exchange. Five patients had failed prior treatment with vincristine and 6 had received glucocorticoids previously. Nine of the 11 patients had a lasting remission over a median of 18 months of follow-up. However, four summaries of clinical experience in TTP, involving over 400 patients, report no use of cyclophosphamide and only 2 cases of refractory TTP responding to azathioprine⁶⁻⁹ (see Table 2). Anecdotal experience suggests more widespread usage. Azathioprine was associated with long-term remission in a single case report of recurrent TTP associated with large vWF multimers.³⁵ The large multimers were noted during several relapses and remissions and disappeared after treatment with steroids and azathioprine. Combined treatment with CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) has been reported in a single case of resistant TTP.³⁶

The use of vincristine for both initial therapy^{37,38} and for relapsed TTP has been reported in several case series^{39,40} and in 2-15% of almost 200 relapsed TTP episodes from summaries of single institutional experiences.^{3,6,8} Lack of outcome data in these patients, use of concomitant treatment modalities, and reported relapses after treatment with vincristine make it difficult to draw conclusions regarding this drug's effectiveness.

Cyclophosphamide and azathioprine are commonly used to diminish immune-mediated tissue injury in inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, and vasculitis. In our view, complications of bladder toxicity, infertility, and teratogenic effects during pregnancy in this largely female population make azathioprine a safer and more reasonable choice for immunosuppression. Co-operative efforts to study the best treatment choice in relapsed TTP will be needed to assess the efficacy of the various therapeutic choices.

Various definitions of relapse in TTP exist in the literature. The *Canadian Apheresis Group* have defined episodes of relapsed TTP as meeting the same criteria specified in their study of plasma exchange⁴ on a second or subsequent occasion without specific mention of a minimum interval of time from the last plasma exchange session.⁹ The *Italian Cooperative Group* has argued that relapses need to be differentiated from premature termination of therapy. Included in their definition of relapse is maintenance of platelets above $100 \times 10^9/L$ without plasma exchange for 4 weeks.¹¹ Consensus regarding apparent relapses despite ongoing therapy or relapses following very short durations of remission is needed. The issue of defining relapse is a source of ongoing debate.

In conclusion, relapsing TTP remains a problem in terms of management. Given recent evidence that this disease is antibody-mediated, therapies aimed at immune suppression seem logical. Our small series shows promise for cyclophosphamide and azathioprine. Further study in a larger series is recommended to define the optimal treatment in relapsing TTP.

Contributions and Acknowledgments

All authors contributed to the management of the patients described in our article, participated in discussions regarding the analysis and interpretation of data, and were involved in drafting or revising the article for intellectual content. All authors approved the submitted version of the article.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlap with previous papers.

Manuscript processing

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Potential implications for clinical practice

Cytotoxic immunosuppressive therapy should be considered in addition to plasma exchange in the treatment of patients with multiple relapses of TTP in order to maintain durable remissions.

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