Therapeutic plasmapheresis for the treatment of the thrombotic thrombocytopenic purpura-haemolytic uraemic syndromes

WY K Hwang, L Y A Chai, H J Ng, Y T Goh, P H C Tan

ABSTRACT

Introduction: The thrombotic thrombocytopenic purpura-haemolytic uraemic syndromes (TTP-HUS) are uncommon disorders that are fatal if untreated. Therapeutic plasma exchange has resulted in excellent remission and survival rates in this patient population.

Methods: We reviewed our experience of therapeutic plasmapheresis for TTP-HUS syndromes for 11 patients who presented in the last five years. Parameters captured included haemoglobin and platelet counts at presentation as well as the number of plasmapheresis sessions and adjunctive treatment given.

Results: We found a response rate of 82 percent to plasma exchange, of whom 55 percent attained complete remission. Responses were excellent in the five patients who presented with primary or idiopathic TTP (100 percent response) among whom 80 percent had sustained long term responses. Responses were poor and often unsustained (only one out of six survived) in patients who presented with thrombotic microangiopathies secondary to underlying disorders such as bone marrow transplantation and metastatic carcinoma.

Conclusion: Plasmapheresis is mandatory and extremely effective for primary TTP. However, it is at most an adjunct for patients who developed it secondary to an underlying disorder until and if the primary disorder can be successfully treated.

Keywords: therapeutic plasmapheresis, thrombotic thrombocytopenic purpura

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INTRODUCTION

Thrombotic microangiopathies are a spectrum of disorders characterised by widespread microcirculatory microthrombi with consequential red cell fragmentation. The rarest, and yet most representative, of these disorders is thrombotic thrombocytopenic purpura (TTP). TTP is a syndrome of Coomb's negative microangiopathic haemolytic anaemia and thrombocytopenia in the absence of any other possible causes for these manifestations[1,2]. It is characterised by a clinical pentad of thrombocytopenia, microangiopathic haemolytic anaemia (MAHA), fever, renal dysfunction and fluctuating neurological deficit. TTP may be idopathic (primary TTP), but it may also occur secondary to drugs, autoimmune disease, cancer and infections linked with the human immunodeficiency virus[3]. Secondary TTP may be harder to treat unless the primary disorder can be controlled.

Thrombotic microangiopathy may also be seen in disseminated intravascular coagulation, the haemolytic uraemic syndrome (HUS), the HELLP syndrome, and severe pre-eclampsia. They may be differentiated from each other, and from TTP by their predominant clinical manifestations and by the setting in which they occur[4]. However, the lines are sometimes blurred and overlap syndromes with features of several of the above are not uncommon. Hence, the term TTP-HUS is often used. The mainstay of therapy for TTP is therapeutic plasmapheresis; otherwise known as plasma exchange[2,5]. For the other thrombotic microangiopathies, plasma infusions are often employed and the role of plasma exchange is less certain. This paper traces the experience of therapeutic plasmapheresis for the treatment of TTP-HUS syndromes in our hospital for the last five years. We will discuss the role of plasma exchange and adjunctive therapies in the treatment of this group of disorders. There is currently no published local data on therapeutic plasmapheresis for TTP-HUS and TTP-HUS-like syndromes. We hope to improve the awareness and understanding of the presenting characteristics and treatment outcome of these conditions in our local Asian population.

METHODS

We performed an analysis of the patients presenting to Singapore General Hospital (SGH) between 1997 to 2002 with TTP and TTP-like syndromes who required plasma exchange. The list of patients was obtained from the plasmapheresis log-book of the plasmapheresis facility of the SGH Haematology

Department of Haematology Singapore General Hospital Outram Road Singapore 169608

W Y K Hwang, MRCP, MMed, FAMS
Consultant and Clinical Scientist, SingHealth Research Facilities

L Y A Chai, MBBS, MRCP
Registrar

H J Ng, MBBS, MRCP, FAMS
Associate Consultant

Y T Goh, MBBS, MMed, FAMS
Senior Consultant

P H C Tan, MBBS, MMed, FAMS
Senior Consultant

Correspondence to:
Dr William Hwang Ying Khee
Tel: (65) 6321 4855
Fax: (65) 6225 0210
Email: ghehyk@sgh.com.sg

Table I. Profile of patients with TTP/HUS.

Patient initials	Sex	Triggering factors	Age (in years)	Platelet counts (x 10^9/L) on starting plasma exchange	Hb (g/dL) on starting plasma exchange	Fever	Other renal manifestations	Creatinine (μmol/L)	Neurological manifestations	Number of sessions of plasma exchange	Outcome	Other treatment given
TGC	F	None	50	34	7.3	None	None	102	Slurring of speech	7	CR, survived	FFP infusions, aspirin, dipyridamole, vincristine, and cyclophosphamide
ASR	F	None	17	6	6.9	Yes	None	71	Seizure	9	CR, survived	FFP infusions and aspirin
GAL	F	SLE	50	98	7.5	Yes	None	219	Seizure and confusion	13	CR, survived	FFP + cryosupernatan infusion and aspirin
IBG	F	SLE	19	15	5.6	Yes	Micro-haematuria	821	Seizure	14	PR, died of underlying disease	FFP + cryosupernatant infusions, cyclophosphamide, and IV immunoglobulins
TSC	M	None	60	82	9.4	Yes	Proteinuria & micro-haematuria	295	Seizure	17	CR survived	FFP infusions, aspirin, and vincristine
TKF	F	Disse-minated adeno-carcinoma	27	14	5.1	Yes	Proteinuria & micro-haematuria	76	Seizure and confusion	9	PR, died of cardio-respiratory failure	FFP infusions, vincristine, and IV immunoglobulins
HPH	M	None	70	27	9.3	Yes	Micro-haematuria	100	Seizure and confusion	22	CR, multiple relapses and died	FFP infusions, aspirin, vincristine, and splenectomy
YMC	F	None	43	7	9.9	Yes	Micro-haematuria	70	Seizure and confusion	28	CR, survived	FFP infusions, aspirin, cyclophos-phamide, vincristine, and dipyridamole
ABG	F	BMT on cyclos-porin	46	6	8.0	Yes	Micro-haematuria	237	Confusion	3	NR, died of infection	FFP infusions
CH	F	BMT on cyclos-porin	18	4	8.7	None	Proteinuria & micro-haematuria	346	Seizure and confusion	8	NR, died of liver failure	FFP infusions

SLE: systemic lupus erythematosus; Hb: haemoglobin; CR: complete response; PR: partial response; NR: no response; BMT: bone marrow transplantation; FFP: fresh frozen plasma; IV: intravenous.

Centre. Patients were included if they had a diagnosis of TTP or HUS on the basis of red cell fragmentation in the presence of markers of haemolysis (as evidenced by low haemoglobin, decreased platelets, elevated indirect bilirubin and elevated lactate dehydrogenase [LDH] levels). Plasma exchange was initiated as soon as possible (given the need for line insertion in the presence of coagulopathy) once a clinical diagnosis of TTP/HUS was made by a haematologist. Plasma exchange was stopped upon normalisation of the serum LDH and recovery of platelet counts to >100,000/uL.

A total of 10 cases were captured during the period of study (Table I). An eleventh patient with poor response to plasma exchange was excluded from our analysis as she was subsequently found to have microangiopathy secondary to disseminated intravascular coagulation, and was likely a misdiagnosed case. Parameters captured included haemoglobin and platelet counts at presentation, as well as the number of plasmapheresis sessions and adjunctive treatment given. Normalisation of LDH and a recovery of platelet counts to the normal range defined complete

response. Partial responders were those who exhibited some degree of recovery of platelet counts but not into the normal range.

RESULTS

Of the 10 cases that could be analysed, there were two men and eight women. The mean age of the patients was 46.7 (range 17 - 70) years. The average serum haemoglobin and platelet count on initiation of plasmapheresis were 7.7 g/dL (range 5.1 - 9.9) and 29.5 x 10^9/L (range 4 - 98), respectively. Fever was present in nine of the 10 patients and the highest temperature at presentation was 39.2ºC. Renal impairment with a raised serum creatinine was detected in five of the 10 patients, of whom three subsequently required acute dialysis support. Interestingly, three out of five of the patients who had a normal serum creatinine had either microscopic haematuria or proteinuria. Eight of the patients developed seizures, though this may not be the initial presentation. Five of those with seizures had a prodrome of confusion as well. One patient without seizures had confusion as a neurological manifestation, while the others presented with slurring of speech.

The patients underwent an average of 13 (range 3 - 28) sessions of plasmapheresis. All were supported with fresh frozen plasma (FFP) or cryosupernatant before initiation of plasma exchange when a tentative diagnosis of TTP/HUS was made, during episodes when plasma exchange could not be immediately available, and again as an overlap for a variable period upon cessation of plasma exchange. Only one session was carried out each day, and each session involved the exchange of 1 to 1.5 times of the patient's calculated plasma volume. Six patients were also initiated on aspirin anti-platelet therapy, two of whom were given dipyridamole as well. Immunosuppressive agents have been used in treatment of TTP and 10 of the patients were given steroids. Intravenous (IV) vincristine was administered to three patients who had inadequate response (one of whom finally attained complete remission). Adjuvant therapy with cyclophosphamide was also attempted in two of the patients.

Eight out of 10 patients demonstrated response to plasmapheresis (response rate of 80%). Six patients (60%) had complete remission (platelet count of >150 x 10^9/L independent of further intervention, excluding steroid therapy, with associated clinical resolution). A further two patients had partial remission (partial response 20% – defined as an improvement in platelet count but less than 150 x 10^9/L or not sustainable without intervention). One patient with complete remission had subsequent relapses before succumbing at the fourth relapse.

The partial responders (n=2) and those with no response to plasmapheresis (n=2) all died. Both partial responders had thrombotic microangiopathies secondary to underlying disorders. One was secondary to systemic lupus erythematosus, while another had previously-undiagnosed disseminated adenocarcinoma of the stomach. The two non-responders were patients who developed a TTP-HUS syndrome secondary to cyclosporine and bone marrow transplantation.

There were five patients who presented with primary or idiopathic TTP. All of them had complete response to treatment and were able to be discharged from hospital in a good clinical state. However, one of these patients was a 70-year-old man who had a chronic relapsing form of TTP. Despite splenectomy, vincristine, cyclophosphamide and IV immunoglobulins, and repeated plasma exchanges, he had three more relapses in the next two years. He finally succumbed to acute renal failure during his third relapse. The other four patients continued to be in complete remission (80% sustained complete remissions) though one suffered a mild unilateral weakness from an episode of cerebrovascular ischaemia during her acute presentation.

DISCUSSION

Primary TTP is very rare. In our local population, the annual incidence is only about one to two new cases presenting to our institution a year. This figure is comparable to that quoted in the West, which is estimated to occur in about one case per million people[6], with a predilection for young women in their thirties. The high incidence of neurological symptoms (in particular, seizures) and renal disease in our local patients with TTP and TTP-like syndromes is notable; as compared to 84% and 76% for neurological and renal manifestation, respectively, in published literature[6].

Attainment of the full classical textbook pentad of clinical manifestation is not a pre-requisite for the diagnosis of TTP. It is described to be seen in only 40% of TTP patients[6], though interestingly in our small series, all but two patients developed the classic pentad. When patients present with the full pentad of manifestations, the clinical outcome tends to be poorer. This has led to the definition of TTP as a syndrome of Coomb's negative microangiopathic haemolytic anaemia and thrombocytopenia in the absence of any other possible causes for these manifestations. In fact, the detection of (1) MAHA (defined as red cell fragmentation/destruction in the presence of a negative Direct Coomb's test) and (2) thrombocytopenia is currently sufficient as the two primary diagnostic criteria for TTP and for

consideration of early initiation of plasma exchange therapy. Treatment is now strongly advocated, even when patients present with only the aforementioned dyad of mainifestations[1-2,7]. As such, many of the patients with thrombotic microangiopathies were treated as for TTP, even though they may not have had the classical manifestations of this disorder.

It is believed that the formation of occlusive platelet aggregates in the terminal arterioles and capillaries leads to ischaemic organ dysfunction, platelet consumption, shearing of erythrocytes. Abnormalities of plasma von Willebrand factor (VWF) have been linked to TTP and there is an excess of unusually large VWF multimers[8-10]. Recent studies suggest that deficiency of a VWF-cleaving protease (termed ADAMTS13) may be responsible for the presence of these multimers. Multiple mutations of the ADAMTS13 gene can result in ADAMTS13 deficiency and cause congenital TTP, while acquired TTP may be linked to autoantibodies neutralising ADAMTS13 protease activity[11,12]. Plasma exchange has, to date, been the only established mainstay of therapy for the past 20 years. This recent hypothesis explains why plasma exchange may be so effective; it removes antibodies against VWF – cleaving proteases and replaces fresh proteases. An immunological aetiology may also account for the observation that immunosuppressive therapy may further ameliorate the disease course of TTP[13].

Plasma exchange has dramatically improved survival in TTP. Before the introduction of plasma manipulation as a therapeutic measure, only 10% of patients survived. With the introduction of plasma infusions, and later, plasmapheresis utilising either fresh frozen plasma or cryosupernatant, survival has improved to 79% in the acute phase[1,5,14]. This figure is almost comparable to our local response rate of 80% with plasma exchange. Not unexpectedly, responses were best among the patients with primary TTP who all had complete responses. There was an 80% rate of sustained remission in this group with primary TTP, and only one of the five patients with primary TTP had the chronic relapsing form.

There was only one complete response among the patients who presented with secondary thrombotic microangiopathy. This complete response was sustained, but the rest had at most only a partial response. None of the two patients who presented with the TTP-HUS syndrome secondary to cyclosporine and bone marrow transplantation were assessed to have any significant response. This is consistent with the experience of plasma exchange in this group where the utility of plasmapheresis is questionable[15]. The use of anti-platelet agents and corticosteroids have been anecdotal in the absence of well-conducted randomised trials, though a recent study did suggest that when combined with plasma exchange, antiplatelet agents did not increase response rates but may prevent further relapses or deaths[16]. Cytotoxic immunosuppressive agents, such as vincristine and cyclophosphamide, have been used in anecdotal cases refractory to plasmapheresis. The use of cyclophosphamide or azathioprine in patients with frequently relapsing TTP has led to sustained long term remissions[17].

Prompt and aggressive plasmapheresis is vital in the treatment of patients with TTP. When TTP is secondary to some other underlying disorder, the responses may be minimal and unsustainable, especially if the causative ailment or agent cannot be eradicated. Local patients have a greater propensity in manifesting the classical TTP pentad as compared to their Western counterparts. This may be due to a different spectrum of disease here or a greater hesitancy to label patients with this diagnosis. We hope that this article has served to urge primary physicians to make an early diagnosis and prompt referral of patients suspected of having this disorder.

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