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Thrombotic Thrombocytopenic Purpura is Associated with a High Relapse Rate after Plasma Exchange : A Single Centre Experience

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Running Title : Neurologic features predict treatment failure in TTP

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Abstract

Thrombotic Thrombocytopenic Purpura (TTP) is a rare condition characterized by micro-angiopathic haemolytic anaemia, thrombocytopenia, renal and/or neurological dysfunction secondary to micro-vascular or macro-vascular thrombosis. Despite advances in treatment, TTP remains a serious condition with significant morbidity and mortality. We undertook an audit of patients with TTP over fourteen years to assess remission, relapse, survival and factors predictive of outcome using current therapy based on plasma exchange with fresh frozen plasma.

Forty patients were identified between January 1992 and December 2005. Thirty one (82%) achieved complete response (CR) to therapy using plasma exchange with fresh frozen plasma (median 11 exchanges) and steroids. Twelve (37%) relapsed a median of 14 days following cessation of therapy, with multiple relapses occurring in two patients. TTP related death occurred in four patients during their initial presentation and in two during subsequent relapse. Four patients were only partially responsive to first-line therapy. The absence of neurological features at presentation was the only factor predicting a sustained CR to first-line therapy (p=0.027, log-rank analysis).

The mean duration of inpatient treatment was 18 days (range 4-38) with 30% of patients requiring intensive care admission. 34% of patients acquired central venous line infection, with a median of two episodes of line sepsis per patient.

Our results indicate the need for better treatments to reduce the high early relapse rate and significant mortality associated with current therapy.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare condition with a standardized annual incidence of up to 11.3 per million. It is characterized by microangiopathic haemolysis, thrombocytopenia, fever, renal and neurological dysfunction, and micro- and macro-vascular thrombosis (1). Mortality approaches 90% in untreated patients (2).

Current therapy for TTP incorporating the early institution of plasma exchange (PE) with fresh frozen plasma (FFP) has been associated with a reduction in the early mortality rate to 10-30% (3). However, a significant minority of patients treated with PE and FFP remain refractory to therapy, and up to one third of patients who survive an acute episode will experience at least one relapse over the next ten years (4) (5) (6).

We undertook an audit of all patients with non-transplant related TTP over 14 years to evaluate response to therapy, incidence of relapse, survival and factors predictive of outcome

Methods

A retrospective single-institution analysis of patients with TTP treated between January 1992 and December 2005 was performed. Patients were identified from an institutional database and plasma exchange records. Eligible patients were defined by the presence of a microangiopathic haemolytic anaemia, thrombocytopenia ± renal impairment, neurological features and/or fever. Patients who had undergone solid organ or stem cell transplant were excluded.

Patients were treated under a recommended clinical protocol incorporating daily single volume PE with FFP. PE was ceased when platelet count had normalised and was tapered or ceased abruptly according to physician discretion. Steroids, other immunosuppression agents, chemotherapy and splenectomy were used according to physician discretion.

Clinical and laboratory features of TTP were assessed from case and pathology records. Specific neurological features of TTP noted included altered conscious state, focal neurological symptoms and/or signs, decreased vision or seizures. Headache was not included due the non-specific nature of the symptom.

Response Criteria. The primary endpoint of this study was failure to achieve a sustained completed response including relapse after complete response, partial response, refractory disease or death during an episode of TTP. Complete response (CR) was defined as normalisation of platelet count and LDH, rising haemoglobin and resolution of microangiopathy and neurologic features, other than those secondary to a documented stroke. Sustained complete response (sustained CR) was defined as those patients who achieved a CR with no documented relapse on follow-up for a minimum of 12 months. Refractory disease was defined as at least one of: persistent neurological features unrelated to a documented cerebrovascular accident, thrombocytopenia < $75x10^9$/L and/or microangiopathic haemolysis despite at least one week of ongoing therapy or TTP related death within one week of therapy. Partial response (PR) was defined as clinical, biochemical and haematological improvement with a platelet count > $75x10^9$/L, but not achieving CR within two weeks of therapy.

Factors evaluated for prediction of sustained CR included clinical and laboratory parameters at presentation (fever, neurological features, haemoglobin, LDH, renal function), infection and number of plasma exchanges received, were assessed from case notes and pathology records.

Statistical Methods.

Time to treatment failure curves were generated using the Kaplan-Meier method and compared using log-rank analyses. Predictive factors for sustained CR underwent univariate analysis using paired t-test for laboratory parameters and Fischer's exact test for clinical parameters. All statistical analyses were two-sided and performed with GraphPad Prism 4 (GraphPad software Inc, San Diego CA, USA).

Results

Forty patients were identified, with characteristics as detailed in Table 1. The majority of patients had idiopathic TTP.

Primary Treatment

Two patients who were treated with plasma infusion with a palliative intent only were excluded from further statistical analysis. Thirty-eight patients (95%) received corticosteroids, 77% with the commencement of PE, the remainder during their initial course of treatment after failing to achieve CR with PE alone, with a mean cumulative prednisolone equivalent dose of 1235mg per patient, received over a median of 6.5 days (range 1-720 days).

Twenty patients (50%) received an interim plasma infusion with FFP prior to facilitating PE by central venous access insertion. The remaining thirty eight patients underwent PE with FFP with a median volume of 3 litres, which was on average 95% of the patient's calculated plasma volume. The median number of exchanges received per patient was 11 (range 3-38).

Treatment Outcomes

Response to first-line therapy. Treatment outcome is outlined in Figure 1. CR was achieved in thirty one patients (82%). The time to normalisation of key laboratory parameters in patients achieving CR is shown in figure 2. The median time to platelet normalisation was six treatment days (range 1-17 days), LDH normalisation 11.5 days (range 3-41 days in 26 evaluable patients) and haemoglobin normalisation 14 days (range 0-46 days). Ten patients achieving CR remained anaemic up until last follow up of laboratory indices at day 50.

Sustained CR was achieved in nineteen patients (50%) of patients receiving PE with FFP. The absence of neurological features at presentation was the only statistically significant clinical or laboratory parameter that predicted for a sustained CR ($p = 0.027$, log-rank analysis, Table 1, Figure 3).

Renal function, haemoglobin, LDH, platelet count at presentation, number of plasma-exchanges received, abrupt versus weaning cessation of PE, infectious complications (line- and non-line related) occurring during treatment did not predict for sustained CR (data not shown).

Relapse following CR

Twelve of thirty one patients achieving CR (37%) relapsed at a median of 14 days after cessation of therapy. One patient with underlying systemic lupus erythematosus, developed a late relapse more than 5 years from initial presentation. Two died from TTP-related complications; ten patients were able to achieve a second CR following the re-institution of PE together with additional therapy (Table 2). One patient died after achieving second CR from unrelated causes. Two patients experienced more than one relapse (median 4.5 episodes, range 3-6).

Partial response to first-line therapy.

Four patients obtained a PR to first-line therapy. Two patients were diagnosed with concurrent prostate cancer, of whom one died from progressive malignancy and one responded to hormonal therapy. One patient developed progressive TTP after premature cessation of therapy and died despite treatment intensification, and the other patient achieved a sustained CR with further treatment intensification including splenectomy.

Secondary Therapy

Additional treatment for patients with refractory or relapsed disease is shown in Table 2. Of the six patients who underwent splenectomy two died subsequently from TTP-related complications and four remain in sustained CR (median 43 months follow up, range 3-135 months). Of the three patients who received rituximab, one remained treatment refractory and died and two remain in sustained CR (at 16 and 18 months of follow up).

Mortality from TTP complications

Acute mortality secondary to TTP complications

Four patients died from an acute TTP-related complication during the first TTP-episode, a median of seven days from presentation (range 1-32). Two patients subsequently died of a TTP-related complication during relapse (Figure 1). The causes of death are detailed in Table 3.

Non-TTP related mortality

Two other patients who underwent PE died within 18 months of first presentation with TTP, one from prostate cancer and one from a cardiac arrhythmia.

Comparison over Time

Comparison of patients treated during the first seven years of analysis (1992–1998 inclusive) with the patient cohort in the last seven years of analysis (1999-2005 inclusive), did not determine any significant differences in rate of diagnosis, time to commencement of treatment, number of PE received or patient outcome (Data not shown).

End-Organ Complications of TTP

Neurological complications. Fifteen patients exhibited neurologic features at presentation, with deficits being transient in twelve patients and catastrophic stroke occurring in three.

Renal complications. The mean glomerular filtration rate (Cockroft-Gault) at presentation was 54ml/min (range 5-183, normal > 60mL/min). Sixteen patients (42%) required acute dialysis for renal failure for a median four weeks. *End-stage renal failure* occurred in six patients, of whom five underwent renal biopsy. Four biopsies revealed glomerulonephritis associated with an underlying connective tissue disease, and TTP-related microangiopathy as the sole process in the remaining patient.

Complications of therapy

Treatment-related complications

Thirteen of 38 patients (34%) who underwent central venous access acquired a line-related infection at 3-19 days following insertion of a central venous catheter with a median number of two episodes of line sepsis per patient (range 1–7). Hospital-acquired non-line related infection occurred in ten patients (26%) and transfusion related events in four patients (11%) (Table 4).

Duration of hospitalisation

The mean number of treatment days for the initial episode of TTP was 18 days (range 4-38). Intensive care admission was required in twelve patients (30%) with a median duration of stay of 5 days.

Discussion

This study demonstrates the continuing difficulty in treating TTP, with only 50% of patients achieving a sustained CR despite a high initial CR rate of 82%. Failure was due to early acute complications during initial therapy and for those achieved CR, relapse in one-third of patients following treatment cessation. The study confirms that although patient outcomes have been improved with plasma exchange using fresh frozen plasma as de novo therapy, further progress is required for those patients who do not achieve a CR with initial therapy and for patients who relapse following successful de novo therapy.

Although we found the absence of neurological features to be predictive for sustained CR, the presence or absence of neurological features at presentation in the cohort of patients who achieved CR did not discriminate patients who would relapse. In particular, given the relatively high early relapse rate in patients achieving CR, and the absence of clearly predictive clinical or laboratory parameters for relapse, careful post-therapeutic monitoring of all patients is recommended to enable re-institution of therapy in early relapse.

The demonstration of low levels of ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin-1-like domains) in inherited and acquired forms of TTP (7) (8), with antibodies against ADAMTS-13 in acquired disease, provides a pathologic model and immunologic basis for treatment intensification in patients at high risk of treatment failure (9). Indeed, future strategies to predict patients who may relapse following initial therapy may include sequential post therapeutic monitoring of ADAMTS-13 activity, antigen levels and auto-antibodies to ADAMTS-13 (10).

Second line therapies for refractory or relapsing TTP, include splenectomy, vincristine, azathioprine, and novel agents such as the anti-CD20 antibody, rituximab (11) (12) (13) (14). Rituximab has been described in several small uncontrolled case-series to have therapeutic efficacy in patients with refractory or relapsing TTP (15) (16) (17) (18) (19) (20). The effectiveness of targeting B-cells with rituximab in autoimmune conditions has been proven in one randomized controlled trial with rheumatoid arthritis (21). Rituximab is an attractive de novo therapy with plasma-exchange for TTP with the intent of increasing the proportion of patients achieving CR, reducing the time to CR, decreasing early death, end-organ complications and treatment associated morbidity. A randomized control trial using rituximab in this setting has been recently proposed (20). An alternative strategy is the addition of rituximab early after achieving CR to reduce the high rate of early relapse. This avoids the potential issue of rituximab clearance by concomitant PE, which may minimize the efficacy of rituximab therapy.

To this end, a phase I/II trial has been commenced at the Royal Melbourne Hospital to assess the efficacy of therapeutic intensification using rituximab for those patients with TTP who have not responded after a week of PE, those who have relapsed, and pre-emptively in all patients at completion of PE after achieving CR. Given the relatively rare incidence of TTP, multi-centre enrolment into clinical trials is clearly desirable, and the establishment of a national Australian TTP registry is recommended.

Table 1. Patient characteristics and initial presenting features

Number of Patients	40
Age (median years, range)	47 (18-77)
Sex (male/female)	14/26
Aetiology	
Idiopathic	70% (n=28)
Connective tissue disease	12.5% (n=5)
Pregnancy	7% (n=3)
Malignancy (prostate, pancreas)	5% (n=2)
Immunodeficiency (HIV, CVID)	5% (n=2)
Clinical Features at presentation	
Altered conscious state/focal symptoms • focal symptoms/signs • decreased vision • seizure • headache	37.5% (n=15) 27.5% (n=11) 5% (n=2) 7.5% (n=3) 32.5% (n=13)
Renal impairment GFR<60ml/min (mean creatinine ± 2SD)	95% (n=38) (0.38 mmol/L ± 0.35)
Fever > 38^{o}C	25% (n=10)
Laboratory Features at presentation	
Haemoglobin (mean) Lactate dehydrogenase (mean) Platelet count (mean)	93g/L 2384U/L 42x109/L

Table 2. Secondary therapy for relapsed or refractory disease

	Number of patients
Steroids (resumption or increased dose)	13
Plasma Exchange (intensification) • increased plasma exchange volume (>1 plasma volume) • change to cryodeplete FFP	10 6 4
Vincristine	7
Splenectomy	6
Intravenous immunoglobulin	5
Aspirin and/or Vitamin E	4
Cyclophosphamide	3
Rituximab	3
Azathioprine	1

Table 3: Causes of death

Patient group	Cause of Death
PR	TTP related (n=1) • cerebrovascular ischaemia non-TTP related (n=1) • prostate cancer
Refractory	TTP related (n=3) • acute myocardial infarction • cerebrovascular ischaemia • acute respiratory failure secondary to myocardial ischaemia
Relapse	TTP related (n=2) • intracerebral haemorrhage • acute myocardial infarction non-TTP related (n=1) • cardiac arrhythmia (1.5 years following TTP episode)

Table 4: Complications of Treatment

Complication	Number of Patients (%)
Line related infections	13 (34%)
Hospital Acquired non-line related infections • urinary tract infection • pneumonia	10 (26%) 5 (13%) 5 (13%)
Transfusion related complications • pulmonary oedema • anaphylaxis	4 (11%) 3 (8%) 1 (3%)

Figure Titles and Legends

Figure 1. Treatment outcome

Figure 1 Legend: Deaths attributable to TTP-related causes (See Table 3).

Figure 2. Time to normalization of laboratory parameters in patients achieving CR

Figure 2. Legend: Normalisation platelets > $140x10^9$/L (normal range 140-$400x10^9$/L), LDH < 420U/L (normal range 210-420U/L), Haemoglobin > 120g/L (normal range 120-170g/L)

Figure 3. Kaplan-Meier plot of sustained CR > 12 months to first-line therapy according to the presence or absence of neurological features at diagnosis

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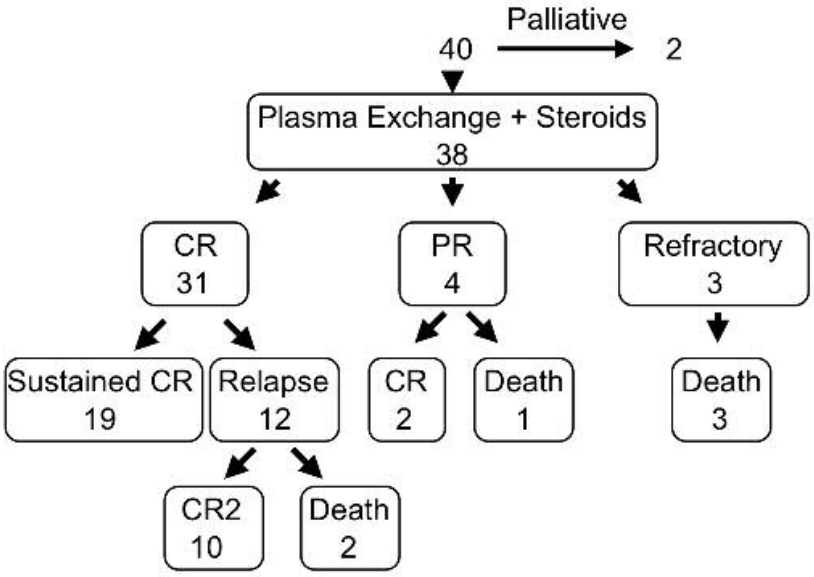
Figure Titles and Legends

Figure 1. Treatment outcome

Figure 2. Time to normalization of laboratory parameters in patients achieving CR

Figure 2. Legend: Normalisation platelets > $140x10^9$/L, LDH < 420U/L, Haemoglobin > 120g/L

Figure 3. Kaplan-Meier plot of sustained CR > 12 months to first-line therapy according to the presence or absence of neurological features at diagnosis



Deaths attributable to TTP-related causes (See Table 3)
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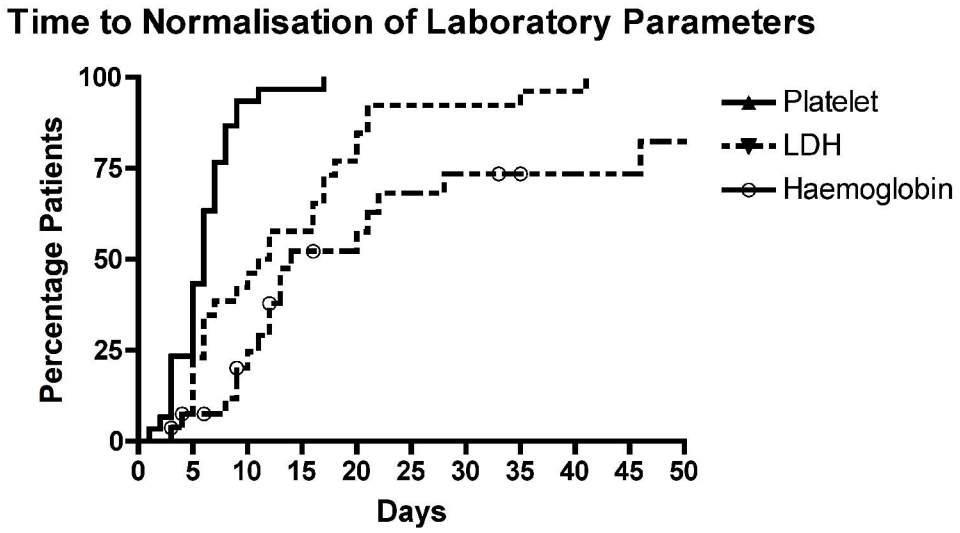

Normalisation platelets >140x10^9/L, LDH <420U/L, Haemoglobin >120G/L.
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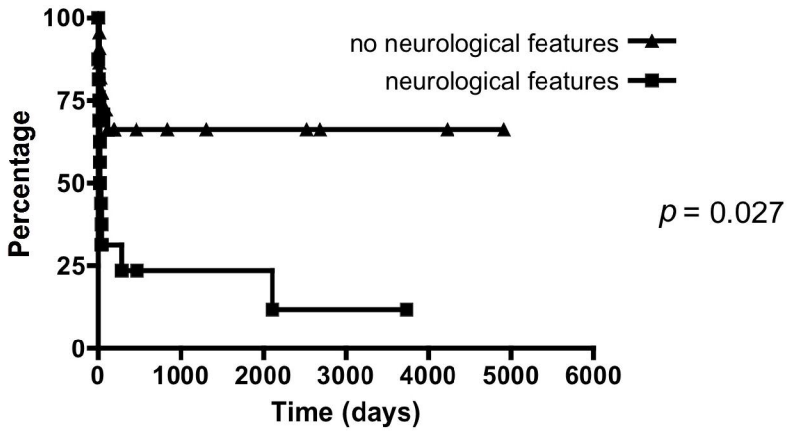

Kaplan-Meier plot of sustained CR > 12 months to first-line therapy according to the presence or absence of neurological features at diagnosis
268x207mm (150 x 150 DPI)

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