Transfusion and Apheresis Science 43 (2010) 159–162

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Thrombotic thrombocytopenic purpura: A single – Centre experience

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ARTICLE INFO

Keywords:
Thrombotic thrombocytopenic purpura
Total plasma exchange
Organ damage
Mortality

ABSTRACT

We aimed to describe the characteristics, treatment regime, and 6-month all-cause mortality of thrombotic thrombocytopenic purpura (TTP) patients treated with total plasma exchange in the our clinic. Thirteen patients were included in the study. Mortality rates of TTP have improved over the last three decades but they are still too high according to modern therapy expectations. Etiology directed treatment should be added to total plasma exchange in secondary TTP cases. Based on TTPs' immunologic etiology, immune modulator and immune suppressor agents have been applied together with total plasma exchange, but mostly in anecdotal case reports or with questionable responses.

1. Introduction

Thrombotic thrombocytopenic purpura (TTP), first described by Moschcowitz in 1924, has long been known as a generally fatal acute disease occurring in previously healthy subjects [1–3]. TTP is characterized by platelet aggregation and thrombosis in the microvasculature. It results in thrombocytopenia, hemolytic anemia, organ ischemia and unless treated, a mortality rate higher than 90%. Causes of this condition include pregnancy, HIV and Escherichia coli infections, pancreatitis, collagen vascular disease, cancer, bone marrow transplantation, and drugs such as cyclosporine-A, antineoplastic agents, ticlopidine, and quinidine [3]. It is more commonly seen in women and the peak incidence is between the ages of 30 and 40 years. TTP is proposed to be initiated by endothelial injury and release of abnormally large von-Willebrand Factor multimers. Von-Willebrand Factor cleaving protease (a disintegrin and metalloprotease with thrombospondin type 1 repeats; ADAMTS13) deficiency has been shown in most patients. This disorder may be inherited in an autosomal recessive pattern or acquired during life. Antibodies against ADAMTS13 have been demonstrated in 59–100% of acquired TTP. Complete deficiency of VWF-cleaving protease (ADAMTS13) activity was reported by Furlan et al. in four patients, including two brothers, with chronic relapsing TTP in 1997 [4]. Other suggested mechanisms include endothelial damage, platelet activation, and clotting alterations [3,5].

Because of the high fatality rate in untreated TTP patients, the diagnosis is urgent. However, diagnosis may be difficult if the patient does not have a complete pentad of symptoms. The presence of hemolytic anemia with schistocytes, thrombocytopenia, and markedly increased LDH that is unexplained by another condition allows a tentative diagnosis. It is better to start treatment than to wait for the appearance of additional symptoms which may be lethal. Notably, the three other features of the classic pentad renal involvement, neurologic symptoms, and fever are not necessary to make the diagnosis. These signs of end organ damage are considered to be relatively late events that should be avoided if possible by prompt diagnosis and treatment [6,7].

Current standard treatment for TTP includes plasma exchange at 40–60 mL/kg daily until the patient has a normal

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doi:10.1016/j.transci.2010.07.007

platelet count and a normal LDH, and any nonfocal neurologic deficits have resolved. If plasma exchange cannot be performed for some reason, patients may be treated instead with plasma infusion at up to 30 mL/kg daily, provided they can tolerate the fluid load. Patients are often treated with corticosteroids or antiplatelet drugs during plasmapheresis. The benefit of these therapies is unclear in-patients receiving plasma exchange but probably minimal [8].

The main objective of the present study were to describe the presenting characteristics, treatment regime, and 6-month all-cause mortality of TTP patients treated with total plasma exchange (TPE) at our institution.

2. Patients and methods

This study was a retrospective review of 13 adults patients with TTP-HUS treated with TPE at our institution from January 2004 to December 2007. The in-patient records of all patients referred for plasma exchange were identified through records from the Department of Internal Medicine. Data was collected by a trained research assistant. Inclusion criteria required the detection of unexplained hemolytic anemia (haemoglobin <12 g/dL) with schistocytes and thrombocytopenia (platelet count $<100 \times 10^9$/L). Exclusion criteria consisted of age <18 years, International Normalized Ratio (INR) > 1.39, chart review detecting a cause for this syndrome that was not due to a microangiopathy (e.g. malaria, severe sepsis, valvular heart disease, endocarditis) or was due to a microangiopathy of another cause (e.g. haemolysis elevated liver enzymes-low platelet (HELLP) syndrome, malignant hypertension or disseminated intravascular coagulopathy). The clinical information at presentation including: age (years), sex, weight (kg), hemoglobin (g/dL), platelet count (10^9/L), creatinine (mg/dL), dialysis at presentation, INR, lactate dehydrogenase (LDH; U/L), presence of fever (>38.0 °C) and presence of neurological dysfunction (focal deficit, seizure, coma) were collected from AUMF records via the review charts. The following treatment information was obtained: frequency of exchange during the first cycle of therapy (exchange/day), mean exchange volume during the first cycle of therapy (mL/kg per day). In our practice, we treated the patients with methylprednisolone.

According to retrospectively collected data, daily plasmapheresis with one total plasma volume of the patients for each plasmapheresis applied to all patients with presh forzen plasma as initial therapy. Daily plasmapheresis went on until thrombocytopenia, reticulosis elevated LDH levels and other signs of persistence of hemolysis ameliorated. Hb levels were also followed. Frequency of plasmapheresis reduced gradually after remission of laboratory and clinical findings. Before cessation of therapy, weekly and after than twice in a month plasmapheresis applied. Prednisolone (1 mg/kg, daily) added to daily plasmapheresis in two patients due to lack of improvement of laboratory and clinical findings of TTP at the 4th day of daily plasmapheresis.

Patients with TTP were grouped into two categories according to etiological factors such as; idiopathic or secondary TTP. The idiopathic group was defined as unexplained hemolytic anemia and thrombocytopenia with no established trigger or associated disease. Secondary TTP was defined as hemolytic anemia and thrombocytopenia with an identified trigger (e.g. gastric carcinoma) or associated disease (e.g. brucellosis). The definition of a response was restoration of platelet count above 150×10^9/L and LDH below 360 U/L leading to cessation of plasma exchange [9,10].

3. Results

We identified 13 patients with plasma exchange for suspected TTP after eliminating patients who did not meet our inclusion criteria and patients with incomplete records treated from January 2004 to December 2007.

Diagnostic categories and clinical features at presentation are presented in Table 1. Patients received an average of 42 mL/kg per day of plasma exchange during their treatment. The overall all-cause mortality rate was 31% ($n = 4$). The 6-month all-cause mortality rate for patients with idiopathic versus secondary TTP was 30% and 33%, respectively. There were no relapsed patients among the survivors during period of the study.

Average LDH values were found to be significantly higher in the unresponsive TTP patients group 2314 U/L and 1070 U/L correspondingly. Increased age was also shown to be a significant risk factor in our study. The average ages of the unresponsive and responsive patients groups were 43 and 62, respectively.

High creatinine levels at presentation were also identified as a risk factor in our retrospective study. Average creatinine values were 4.25 mg/dl in the unresponsive group and 2.9 mg/dl in the responsive group.

Laboratory findings such as low platelet counts and reticulocytosis improved at the end of first week of total plasma exchange therapy. One of the patients' high LDH levels continued until the end of the 2nd month. This existence of high LDH levels improved after 54 courses of TPE. The late recovery of this patient may be explained by the presence of two risk factors; high creatinine levels and high LDH levels.

The etiologic factors of our three secondary TTP patients were brucellosis infection, gastric malignancy and post-transplantation calsineurin inhibitor agent usage. Except from gastric malignancy, other two secondary TTP patients were responding to plasma exchange therapy successfully. The gastric malignancy patient was treated with calcium leucovorin and 5-flourouracil. Methylprednisolone and vincristine were added to the plasma exchange in this patient but he died after 12 courses of total plasma exchange during the 18 day follow-up period.

It was not possible to test patients for the presence of ADAMTS13 deficiency due to the limitations of our laboratory.

4. Discussion

In this 4 year retrospective analysis of TTP patients at our institution, we observed four unresponsive fatal events