

## Thrombotic Thrombocytopenic Purpura Refractory to Plasmapheresis Treated Successfully with Vincristine: A Case Report

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### Abstract

#### Introduction:

TTP is a life-threatening clinicopathologic disorder involving multiple organ systems, which remains a management challenge to physicians. If not treated promptly, TTP typically follows a progressive deteriorating course with irreversible renal failure, progressive neurologic deterioration, cardiac ischemia, and death. The immediate administration of plasma exchange has been the essential and urgent treatment for patients with a clinical diagnosis of TTP. The reported incidence of patients who do not respond to plasma exchange (PE) [refractory TTP] and require additional therapy varies between 10% and 42%.

#### Case report:

We have described a 24 year female patient of TTP who remained refractory after 27 sessions of PE combined with corticosteroids. We added a slow infusion of 2mg Vincristine (VCR) and followed by another 2 doses of 1 mg with 6 days between each dose resulting in successful clinical and laboratory improvement.

#### Conclusion:

We conclude that, VCR is a safe, inexpensive, readily available and rapidly acting agent and should be used from the start together with PE.

### Keywords:

Thrombotic thrombocytopenic purpura, Plasmapheresis, Vincristine, Refractory TTP

### Introduction

Thrombotic Thrombocytopenic Purpura (TTP) has a specific pathogenetic defect characterized by the inability to cleave ultralarge vWF (ULvWF) [1]. They are normally cleaved by a metalloprotease, ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 domain 13) [2]. Low ADAMTS13 activity can result from a constitutive deficiency or circulating acquired IgG autoantibodies to different antigenic regions of the ADAMTS13 molecule in patients with acute TTP. The pathogenetic role of this autoantibody is supported by its disappearance from the circulation when remission is achieved by effective treatment [3]. The classic clinical pentad: fever, thrombocytopenia, hemolytic anemia, neurologic symptoms, and renal failure were described in a review of 271 published cases in 1964. Mortality is ~ 90% in untreated cases [4]. After the introduction of plasma exchange (PE) in the 1980s, TTP patient survival rates increased to 70-90% [5]. About 20% of TTP are resistant to plasma exchange [6-9].

We describe a patient presenting with a first episode of acute refractory TTP in whom remission was not achieved by PE & steroids who was successfully treated with vincristine (VCR).

### Case Report

A 24-year old female, presented to our department with pallor, fatigue, and headache. She had no past medical history, except she was on diet regimen to decrease her weight one year ago and stopped after 2 months only ( her weight on presentation was 110 kg, BMI: 38.2kg/m<sup>2</sup>). No any abnormality observed by examination, except pallor and ecchymotic rash on her lower limbs. Laboratory investigations revealed severe anemia Hb: 7.5 gm/dl, thrombocytopenia PLT: 9,000 /mm<sup>3</sup> and WBC: 11,800 /mm<sup>3</sup>. A peripheral blood smear was showing schistocytes, fragmented red blood cells and anisopoikilocytosis. Reticulocytes were 21%, ESR was 24/62, LDH: 3000 U/L, total bilirubin: 2.5 mg/dl and the indirect: 1.5 mg/dl. Direct Coomb's test was negative, and coagulation profile was normal. Urine analysis revealed microscopic hematuria but no proteinuria. Serum creatinine and liver function tests were within normal limits and HIV, HbsAg, HCV were negative. Lupus anticoagulant, ANA and anti-dsDNA antibodies and were negative.

A diagnosis of TTP was established and we started Therapeutic Plasma Exchange of one plasma volume with fresh frozen plasma daily for 7 days together with oral administration of prednisolone (60mg/

day), until the platelets count reached  $>150,000$ . The plasma exchange regimen changed to one plasma volume every other day instead of daily with daily CBC follow up. We found that the platelets count started to decrease again reaching  $47,000/\text{mm}^3$  then  $9,000/\text{mm}^3$ . So we restarted PE again daily and pulse steroids were given (methylprednisolone 500 mg/day for 3 days) followed by oral prednisolone 80 mg/day. But, unfortunately after another sixteen PE sessions the platelets count didn't exceed  $30,000/\text{mm}^3$ , Hb: 8.7gm/dl and LDH rose to reach 5000 u/l.

After exclusion of other causes associated with poor response to PE like infection and after a total 27 sessions of PE, the patient's hemolysis and thrombocytopenia did not resolve, we have considered it as Thrombotic Thrombocytopenic Purpura refractory to steroids & plasmapheresis.

So, vincristine (VCR) treatment was started in addition to PE. The VCR was given as follows: a slow infusion over 6 h of 2 mg on day 1 followed by 1 mg on days 7 and 13. After three doses of VCR with continuation of the PE therapy, the hemolysis and thrombocytopenia resolved. The platelets count reached  $175,000/\text{mm}^3$  after the second dose of VCR and clinically the patient improved with tapering of PE twice /week. After the third dose of VCR the platelets count increased to  $233,000/\text{mm}^3$ . We have discharged patient and on follow up after one month, platelet counts were  $251,000/\text{mm}^3$ .

## Discussion

TTP is a life-threatening clinicopathologic disorder involving multiple organ systems, which remains a management challenge to physicians. If not treated promptly, TTP typically follows a progressive deteriorating course with irreversible renal failure, progressive neurologic deterioration, cardiac ischemia, and death [10, 11]. The immediate administration of plasma exchange has been the essential and urgent treatment for patients with a clinical diagnosis of TTP since the publication of the randomized clinical trial by the Canadian Apheresis Group in 1991[12]. The reported incidence of patients who do not respond to PE (refractory TTP) and require additional therapy varies between 10% and 42 % [13-16]. In much of that literature, refractory TTP is defined as a failure of platelet response after 4 to 7 days of PE, or a clinical deterioration in a patient receiving standard therapy [17]. Treatment of these refractory TTP patients poses therapeutic dilemma as most evidence in this setting is limited to case reports and case series. Salvage options include high-dose immunoglobulin [18], rituximab [19], immunosuppressive agents [e.g. cyclophosphamide [20], cyclosporine [21], autologous stem cell transplantation [22] and splenectomy [23].

Successful vincristine use has been described in various small studies and case reports, usually as a rescue therapy in refractory TTP [17, 24-33].

Vincristine, a vinca alkaloid generally used as chemotherapy. Evidence of the efficacy of VCR in treating TTP first became available in the late 1970s [35]. VCR prevents the interaction between damaging immunoglobulin G antibodies and endothelial cells. Furthermore, VCR is known to alter PLT membrane glycoprotein receptors preventing their up regulation and binding of von Willebrand factor (VWF) multimers, thereby reducing PLT aggregation [36].

Our patient received VCR after 27 sessions of PE. The platelet count began to increase reaching  $65,000/\text{mm}^3$  after 3 days of starting VCR and  $175,000/\text{mm}^3$  after 8 days. The total dose of VCR given to the

patient was 4 mg without apparent side effects and this agrees with some studies using doses ranging from 2 mg up to 14 mg (24-34). Ziman et al, reported 100 percent survival in their retrospective data of 12 TTP patients (PLT counts ranging  $4,000/\text{mm}^3$  to  $36,000/\text{mm}^3$ ) treated with standardized protocol of PE and VCR without side effects. This report is also parallel with their valuable review of literature that demonstrated a significant advantage in durable remission rates in patients treated with combination TPE and VCR as initial therapy compared to patients treated with TPE without VCR. In a literature review that involved 56 studies and 105 patients, stable remission was obtained in 73% of patients receiving vincristine as secondary or salvage therapy (ie,  $>3$  days following diagnosis), with adverse events in only 5.7% of patients[36]. These studies were retrospective and uncontrolled, but provided the historical evidence that vincristine is an effective salvage therapy in patients with acquired TTP who do not respond optimally to standard treatment.

We conclude that, on the basis of the literature review VCR is a safe, inexpensive, readily available and rapidly acting agent. Further large prospective studies need to be done to confirm the benefit of its use from the start either alone or as a second line with TPE. We suggest that it should be used from the start together with PE.

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