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Case Report

Caplacizumab-Related Bleeding in a Cancer Patient Affected by Thrombotic Thrombocytopenic Purpura: Case Report and Literature Analysis

Marco Bardetta[1-3*], Carola Sella[1-3], Federica Valeri[1,2], Cristina Dainese[1,2], Benedetto Bruno[2,3], Alessandra Borchiellini[1,2]

[1]Regional Centre for Hemorrhagic and Thrombotic Diseases, AOU City of Health and Science, Turin, Italy

[2]Division of Hematology, AOU City of Health and Science and University of Turin, Turin, Italy

[3]Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy

***Corresponding author**: Marco Bardetta, Regional Centre for Hemorrhagic and Thrombotic Diseases, AOU City of Health and Science, Turin, Italy

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare disease characterized by the triad microangiopathic hemolytic anaemia, thrombocytopenia and multiorgan failure. Its origin lies in the lack of a metalloprotease known as ADAMTS13 which is useful to lyse the high molecular weight multimers of von Willebrand factor (vWF), thus causing the development of multiple thrombotic occlusions which consume the platelets and mechanically break the circulating red blood cells. Caplacizumab is a new monoclonal antibody approved in 2018 as first line treatment of the disease, alongside plasma exchange and immunosuppression. It prevents the excessive platelet consumption by blocking vWF and allows a faster complete response achievement. Given its mechanism of action, the principal adverse event is an increased bleeding risk, which is mostly mild. Nevertheless, some life-threatening bleedings requiring specific treatments have been described. Here, we report a case of a patient who, after treatment with a checkpoint inhibitor for a lung cancer, developed a TTP but the treatment with Caplacizumab was complicated by an abdominal bleeding. This brought to a premature suspension of the treatment and the necessity to infuse a von Willebrand factor/factor VIII (vWF/FVIII) concentrate. Further, a literature review upon bleeding during Caplacizumab and relationship between immune-therapy and TTP is reported.

Keywords: Thrombotic Thrombocytopenic Purpura; Caplacizumab; Bleeding, Von Willebrand Factor/Factor VIII Concentrate; Checkpoint Inhibitors

Introduction

Thrombotic Thrombocytopenic Purpura (TTP), or Moschowitz syndrome, is a rare thrombotic microangiopathy characterized by the simultaneous presence of microangiopathic hemolytic anaemia, thrombocytopenia and multiorgan ischemic damage [1]. Two main forms are distinguished: a rare congenital form (representing almost 5% of all the new diagnoses) and a more frequent acquired one [2]. Almost half cases are idiopathic, whilst the remaining part is secondary to miscellaneous causes (some of which being cancer-associated as a paraneoplastic effect and some being iatrogenic or drug-related) [3]. The pathogenetic mechanism lies in the unsuccessful degradation of the high molecular weight multimers of von Willebrand factor (vWF) because of a deficiency in ADAMTS13, a metalloprotease aiming to prevent an excessive linkage and consumption of platelets when adherent to sub endothelium through the vWF. This leads to the intravascular formation of micro thrombi sequestering the circulating thrombocytes. As a consequence, platelet number decreases, red blood cells break when passing through and a state of hypoxia in the affected organs arises after the occlusion of the smallest capillaries [4]. The mechanism of the acquired deficiency is predominantly autoimmune, because of the presence of circulating antibodies of the IgG family directed against the cysteine-rich spacer catalytic domain of the metalloprotease [5]. Together with the rise of the hemolytic indexes, an ADAMTS13 plasmatic activity < 0,10 IU/mL (10%) and the dosage of circulating inhibitors are mandatory to validate the diagnosis. These tests are also useful during follow-up to monitor the course of the disease and guide the treatment, which lies on three main cornerstones: plasmapheresis or plasma-exchange (PEX) to quickly remove the high burden of circulating antibodies and the vWF multimers, immunosuppression to prevent further production of inhibitors and supportive care for the possible organ damage [6]. Mortality of TTP is still high despite the clear improvement of our capacity to promptly diagnose and treat it, with a rate of 10 to 20% depending on the casuistries [7]. In 2018, EMA approved a new nanobody (Caplacizumab, Cablivi®) that has become predominant in the first-line treatment of TTP. By binding the A1 domain of vWF, it blocks its interaction with thrombocytes preventing their removal from blood flow. Efficacy and safety have been demonstrated in the randomized controlled trials HERCULES and TITAN, respectively phase III and phase II trials [8,9]. Given its mechanism of action, an increased but not significant bleeding risk has been described, independently from the treatment duration, with a bleeding rate in the phase III trial of 65% in the experimental arm versus 48% in the placebo one. Few data are still available on bleeding reverse strategy. In this regard, we describe a case of a patient with a newly diagnosed TTP, who needed rescue therapy for an abdominal bleeding during Caplacizumab therapy.

Case Presentation

In September 2021, a 58-year-old man was transferred to our Hospital for a new diagnosis of Moschowitz syndrome. The patient was even affected by a small cell lung cancer (SCLC), which had been previously treated with cycles of chemo immunotherapy with Carboplatin, Etoposide and Atezolizumab, followed by a maintenance therapy with Atezolizumab single agent after obtaining a partial response. In summer 2021, for a mediastinum nodal progression, he stopped immunotherapy and underwent radiotherapy sessions. He was then admitted to the Emergency Department for an upper limb motor clumsiness and a diagnosis of transient ischemic attack. During hospitalization, a severe thrombocytopenia (5.000/uL) accompanied by a non-immune hemolytic anemia with schistocytes at 7% were found. In suspicion of a thrombotic microangiopathy, PLASMIC score was performed and, with a result of 5 out of 7, the patient resulted at an intermediate risk for TTP. Diagnosis was then confirmed when ADAMTS13 activity resulted 0,007 IU/mL (0,7%). Therefore, corticosteroid treatment and transfusion support were started in addition to daily PEX and Caplacizumab. The day after, an antiepileptic, therapy was also necessary because of the onset of a seizure crisis. Hemoglobin levels initially rose (up to 9 g/dL) and platelets almost reached a normality range; but after 16 days of therapy, he developed deep asthenia and a progressively rapid reduction of hemoglobin levels (down to 5.3 g/dL) was observed with absent hemolytic indexes, new reduction of platelet counts and a positive research for faecal occult blood. Eventually, he referred an episode of melena. In the suspicion of bleeding, Caplacizumab was immediately interrupted and an urgent esophagogastroduodenoscopy (EGD) was performed. No active bleeding was found in the explored tract, so a contrast full-body CT scan was executed and a hemorrhagic spot in the left hypochondrium (jejunum) was suspected. The following arteriography did not confirm any bleedings requiring embolization. Therefore, conscious of the recovery times of vWF activity after suspension of Caplacizumab and because of the unknown exact site of bleeding, in order to stop it, we decided to administer von Willebrand factor/factor VIII (vWF/FVIII) concentrate (Fanhdi®) 40 U/Kg to counterbalance the effect of the drug [10]. An immediate clinical and laboratory benefit was observed and, because of the progressive amelioration of the platelet counts and ADAMTS13 activity with a contemporary decrease of the inhibitors, we opted to definitely hold the drug ahead of time and last PEX was executed after 20 days since diagnosis. A clear clinical improvement followed; the disease progressively shut down and the corticosteroid treatment was slowly tapered but low doses were maintained for oncological indications. Figure 1 summarizes the management of this case.

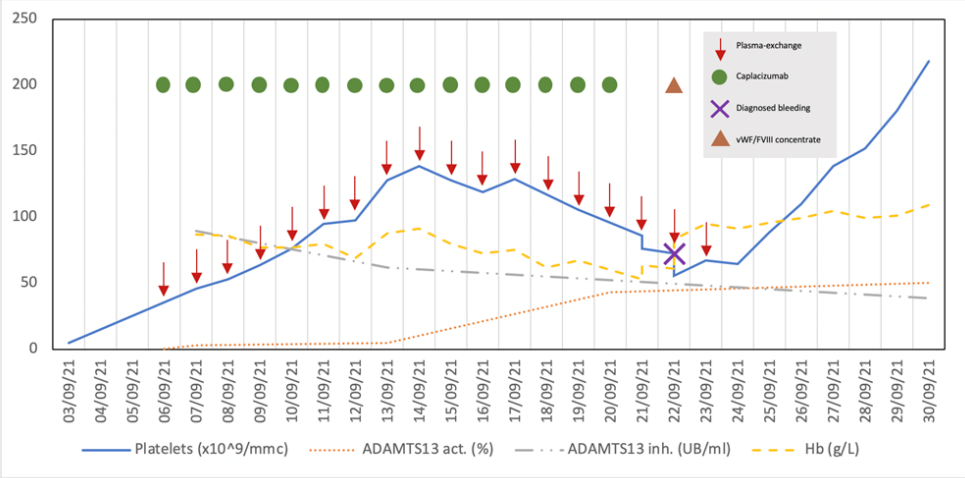

Figure 1. Clinical management of TTP and bleeding. Corticosteroid treatment was continued throughout all the period.

Discussion

As mentioned above, Caplacizumab-induced bleeding risk is very mild. An integrated analysis of the two pivotal trials, conducted to increase statistical power, confirmed mild mucocutaneous bleeding as the main safety finding [11]. In the pivotal phase III HERCULES trial, among those patients who experienced bleedings under Caplacizumab, only 3 of them (6%) had severe but self-limiting bleedings versus only 1 (2%) in the control group who died after a hemorrhagic transformation stroke. Instead, serious adverse events of bleeding were reported in 8 patients (11%) in the Caplacizumab group and in 1 patient in the placebo group. Half of the cases of bleeding under Caplacizumab were epistaxis and only one of them was treated with vWF concentrate, while among the others, two non-fatal cases of hemorrhagic cerebral infarct and subarachnoid haemorrhage resolved after discontinuation of the drug [8,9]. In a Japanese open-label phase II/III study, safety of Caplacizumab was also guaranteed but some cases of severe therapy-related adverse events were reported (e.g. gastrointestinal bleedings or pulmonary alveolar hemorrhage). Even in this trial, a discontinuation of Caplacizumab, with no need to start anti-hemorrhagic treatment, was enough [12]. Despite this, life-threatening bleeding risk exists, but how to manage with it is still unclear: major bleedings management under Caplacizumab is mostly relegated to clinical trials and cases of real-life experience are still very exiguous. A case series published in 2021 reported three cases of intracranial hemorrhages in which Caplacizumab discontinuation didn't avoid death, while in another case the patient survived after holding the treatment [13]. Literature about the use of vWF/FVIII concentrate is scant. In one case, Haemate P® was unsuccessfully used as a rescue therapy for a cerebral hemorrhage occurred under Caplacizumab in a 50-year-old woman with TTP who died after this [14]. Alongside treatment of TTP, we also focused on cancer history and treatment. Several cases of autoimmune and hematological complications following immune check-point inhibitors (ICIs) have been described in literature. Severe immune-related adverse events (irAEs) have been reported to be approximately 13% during ICIs [15,16]. As regards thrombotic microangiopathies, ICIs can be a trigger of an acquired thrombotic thrombocytopenic purpura. In a restrospective observational analysis, 7 patients (out of a total of 35 presenting with a new diagnosis of TTP after treatment with ICIs) had been treated with Atezolizumab but, unlikely other drugs (i.e. Ipilimumab, Pembrolizumab or Nivolumab), these data were only derived from the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and no clinical case reports have been published [17]. So, this is the first case that relates TTP to a previous therapy with Atezolizumab. The correct management of such cases is still unknown. According to ASCO guidelines, ICIs should be continued with close monitoring for grade 1 toxicities, while discontinuation should be considered with more severe toxicities and it is strongly recommended with grade 4 irAEs [18].

Conclusions

Thrombotic microangiopathies, like Moschowitz syndrome, are complex and rare diseases where the physiological hemostatic balance breaks up with a contemporary higher risk of ischemic events and hemorrhages. At the time of this paper, alongside plasmapheresis and immunosuppression, as well as the removal of the underlying cause (whenever possible), Caplacizumab is one

of the cornerstones of the treatment. Pivotal studies have shown its safety but some cases of major/life-threatening bleedings from retrospective real-life data collections have been described [19]. In these cases, treatment with Caplacizumab must be stopped promptly and a cure with hemostatic agents (e.g. von Willebrand factor concentrates) could be useful. To our knowledge, apart from the Hercules pivotal study, this is the first case in literature where a major bleeding under Caplacizumab was successfully and safely treated with anti-hemorrhagic rescue therapy. More real-life experiences are necessary to better understand the management of such adverse events. Also, deeper knowledge on new oncologic drugs, like ICIs, is important to prevent the multiple potential side effects. Eventually, with regard to the onset of anemia under Caplacizumab, our clinical case shows the importance of an accurate differential diagnosis which can completely subvert the clinical scenario, inducing to modify the therapeutic options and improve the expected outcomes.

Conflicts of interest: The authors declare that there are no conflicts of interest regarding the publication of this article.

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