Case Report

High-dose Continuous Infusion of Tranexamic Acid for Controlling Life-threatening Bleed in Advanced Cancer Patients

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Abstract

Life-threatening bleeding although uncommon in palliative care is associated with significant distress among patients and family. The current guidelines emphasize the need for identification of a patient with early signs of bleeding and providing assurance and comfort care to patients and family in case of an event. There is very little known about the role of high dose of tranexamic acid, a lysine analog in controlling the bleeding irrespective of the underlying pathophysiology of the bleed. Tranexamic acid is known to competitively block the lysine-binding site of plasminogen and thus inhibit the activation of plasminogen to plasmin and at high-concentration tranexamic acid noncompetitively blocks plasmin, thus inhibiting the dissolution and degradation of fibrin clots by plasmin. Here, we discuss two case studies of patients who presented with massive bleed from the tumor site. With a high dose of continuous intravenous infusion of tranexamic acid, there was a complete arrest of the bleed with a reduction in the requirement for blood transfusion.

Keywords: Life threatening bleed, palliative care, tranexamic acid

Introduction

Life-threatening bleeding is uncommon in palliative care, although there is no clear consensus definition on life-threatening bleeding. The distress associated with such exsanguination is immeasurable for both patient and family and is often manifest with emotional outburst due to fear of impending death and helplessness. The current published literature suggests that bleeding is likely to occur in 6%–10% of patients with advanced cancer.[1] Terminal hemorrhage – bleeding which is considered to be "major, from an artery, which is likely to result in death within a period of minutes" – has a reported incidence of 3%–12%.[2] Multiple putative mechanisms for bleeding in advanced cancer patients include tumor invasion into the blood vessels, treatment-related complication such as radiotherapy, hematological complications, and anticoagulant drugs and nonsteroidal anti-inflammatory drugs (NSAIDs).[1] The current BMJ guidelines emphasize the need for identification of a patient with early signs of bleeding and providing assurance and comfort care to patients and family in case of an event.[3] There is very little known about the use of antifibrinolytic agents such as tranexamic acid at a high dose as a continuous intravenous infusion (CIVI) in patients with terminal bleeding. Most results are from studies in the perioperative periods. Here, we attempt to discuss the case of patients who presented with massive bleeding who responded well to a high dose of tranexamic acid infusion.

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Case Reports

Case 1

A 65-year-old elderly gentleman, retired senior manager of a reputed bank, was a known case of metastatic spindle cell sarcoma of the medial aspect of the right thigh. He underwent surgical excision of the tumor in March 2018. He was apparently well for 6 months postsurgery when he developed recurrence at the original site of treatment and oligometastasis to the lungs. He was advised amputation by the plastic surgeon as a treatment for pain control which the

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patient refused. On January 21, 2019, he presented to the emergency department with a history of massive bleed from the tumor site followed by drowsiness since the preceding 2 days. He was apparently well 2 days prior to the incident, when he noticed that his pajama was stained with blood. He consulted a local physician who advised him to apply pressure over the area. This helped to arrest the bleed, and the rest of the day was uneventful. Next day morning, his family members found him soaked in blood with sluggish response to verbal calling thus rushed him to the emergency department. On examining him, he had a blood pressure of 90/60 mmHg, pulse rate of 125/min, and respiratory rate of 24/min. He had severe pallor and edema of the right lower limb. Other general and systemic examinations were unremarkable. He was found to have a large nonhealing ulcer of 7 cm × 4 cm × 4 cm on the medial aspect of the lower half of the right thigh with continuous oozing of large-volume blood from the site. On investigating further, he was found to have hemoglobin of 5.2 g/dl and other counts and electrolytes were unremarkable. Doppler ultrasonography of the right lower limb revealed subcutaneous tissue edema and unremarkable for deep-vein thrombosis. He was transfused three units of packed red blood cells (PRBCs) and given a bolus of tranexamic at a dose of 1 g followed by 500 mg intravenously three times a day. The family was prognosticated about the unfavorable outcome and an impending death. The goals of care were discussed at length and documented. After the initial 24 h trial of intravenous (IV) dose of tranexamic acid at 1500 mg/day, there was no reduction in bleeding and we had to re-transfuse three units of PRBCs the following day. With blood transfusion, there was a marked improvement in the sensorium, and the patient became oriented to time, place, and person. However, he was anxious and feared an impending death, and the counseling support was provided to him. He was started on a CIVI of midazolam at 2 mg/h to allay his anxiety. As his bleeding did not respond to the dose prescribed, the dose of tranexamic acid was increased to 1 g (intravenously) 6 hourly with no response after a trial of 24 h, and the patient still needed three units of PRBC transfusion every day. He was then started on CIVI of tranexamic acid at 240 mg/h through an infusion pump, with which the bleeding was completely arrested 12 h after starting the infusion, and the patient did not require any PRBC transfusion in the next subsequent days. His pallor improved, his blood pressure improved to 110/76 mmHg, pulse rate: 80–90/min, and respiratory rate: 16–18/minute. Furthermore, the dressing pad had no blood stain and hemoglobin improved to 9.4 g/dl. The infusion was continued for 72 h. After 72 h, an attempt was made to taper down the dose of tranexamic acid by 50%, but this could not be achieved as the wound started to ooze again and the dose was continued at 240 mg/h. The infusion continued for 1 week, and an attempt was made to down titrate the dose of the drug, which was achieved successfully and converted to oral tablets over 1 week. The IV infusion was converted to tablet tranexamic acid 500 mg three times a day, and the patient was discharged from the hospital. He followed up with us in the outpatient clinic 7 days postdischarge. Moreover, since he had no further episodes of bleeding, we stopped the tranexamic acid. He was followed up through telephone (as a part of our routine service) and was found to be asymptomatic. The patient is still (last follow-up was on February 01, 2020) doing well, performing all his activities of daily living with minimal support.

Case 2

A 32-year-old young gentleman, farmer by occupation, a known case of carcinoma of the left buccal mucosa post completion of disease directed treatment in February 02, 2018, developed a locoregional metastasis on November 10, 2019, to the left lower alveolus, retromandibular trigone, and left upper alveolus. He presented to the emergency department on December 01, 2020, with continuous uncontrollable bleeding from the mass despite the administration of tablet tranexamic acid 1 g four times a day on advice by a local general practitioner in liaison with the doctor in the palliative care team. The patient was extremely anxious and was restless on the bed. He was, however, oriented to time, place, and person. His vitals were stable and were found to have continuous oozing of blood from the wound, and six gauze pieces were soaked in the span of 60 min. He was started on CIVI of tranexamic acid through an infusion pump at 240 mg/h. He was given an initial dose of midazolam 2.5 mg IV bolus to allay his anxiety. Once the patient settled, the team called upon a meeting with the patient and the family members (wife and father of the patient who were there at that time) by the patient's bedside. They were prognosticated about the possibility of an uncontrollable bleed despite all the efforts at arresting the bleed and discussed the goals of care. We also discussed the need for sedation if the medications failed to arrest the bleed. All the discussions were documented in the hospital management system. The patient on understanding the prognosis requested us to tranquilize him as he feared dying of bleeding. We started him on midazolam as a CIVI through the syringe driver at 2 mg/h to tranquilize him. After 24 h trial of tranexamic acid at 240 mg/h, there was a complete arrest of the bleed with only serous discharge from the wound. The patient was comfortable. We tapered down the midazolam dose and stopped over 3 h. The tranexamic acid infusion was continued at 240 mg/h for 72 h. The dose was then tapered over 72 h and converted to tablet tranexamic acid 500 mg three times a day and the patient was discharged from the hospital. The patient followed up with us after 7 days with no further episodes of bleed from the lesion. The tablet tranexamic acid was stopped in the follow-up visit. The patient performed well with minor fluctuations in the pain intensity at the tumor site which was well controlled with opioids. The patient expired on February 13, 2020, at home peacefully.

Discussion

Patients with advanced malignancy present with complex symptom burden often threatening their quality of life. One of the distressing, albeit an uncommon symptom of advanced malignancy, includes hemorrhage or bleeding from the tumor site. Bleeding or hemorrhage could be attributed

to multiple factors such as direct tumor invasion into the blood vessels, chemotherapy/radiotherapy-induced necrosis, thrombocytopenia, coagulopathy, disseminated intravascular coagulation or concomitant administration of anticoagulants, or NSAIDs.[1] Any or all of these factors could coexist in a patient who presents with bleeding episode often posing a great challenge to the treating physician. The current BMJ guidelines emphasize the need for identification of the patient with early signs of bleeding and providing assurance and comfort care to patients and family in case of an event but do not classify the type of bleeding and emphasize on the arterial bleed only.[3] Although a systematic review by Harris and Noble. mentions about the type of hemorrhage, it does not explore beyond arterial bleeds. The limited discussion on bleeds other than arterial cause could be due to a paucity of literature.[2]

In patients with malignancy, hyperfibrinolysis appears to be related to an increased expression of urokinase plasminogen activator (uPA) in the systemic circulation.[4,5] Independent of the fibrin meshwork formation, high levels of uPA activate plasminogen to plasmin which is hypothesized to be the cause for tumor invasion, angiogenesis, metastasis, hemorrhage, and resistance to drugs.[4,5]

This article explored the role of antifibrinolytic agent tranexamic acid in controlling bleeding in a palliative care setting, independent of laboratory investigations or underlying etiopathology. Identifying the etiopathology of bleed is most often a challenge in a palliative care setting in view of life-threatening hemorrhage and grave prognosis. Antifibrinolytics prevent fibrinolysis of blood clot, thus acting as a protectant against blood loss. Tranexamic acid, a synthetic lysine analog,[6] competitively blocks the lysine binding site of plasminogen and thus inhibits the activation of plasminogen to plasmin, a proteolytic enzyme that dissolves the clot. At high concentrations, tranexamic acid noncompetitively blocks plasmin and thus inhibits the dissolution and degradation of fibrin clots by plasmin. Tranexamic acid is also shown to stabilize the clot by enhancing the effect of thrombin-activated fibrinolysis inhibitor.[6]

There is a lack of robust evidence on the effective dose of tranexamic acid. Most studies have discussed that the doses are those from the perioperative period and none in the palliative care setting perhaps due to the challenges of conducting a randomized controlled trial in the palliative care setting.

Tengborn *et al.* cited that after an initial dose of 10–25 mg/kg IV bolus dose of tranexamic acid,[7] 1000 mg three times a day would help to arrest the bleed within 48–72 h. The dose could be escalated to 2000 mg three times a day in case of nonremission of bleeding. We also found that in our patients, the transfusion requirements reduced with the administration of tranexamic acid which corroborated with the findings from other studies.[8]

In a recent meta-analysis published in Lancet 2018, the authors demonstrated that the patients receiving tranexamic acid as compared to placebo were at a lesser risk for developing vascular occlusive events such as myocardial infarction but equally (compared to placebo) at risk for other events such as deep-vein thrombosis, pulmonary embolism, or stroke.[9] However, tranexamic acid a relatively contraindicated in patients with a known history of thromboembolic event in the past. High dose of tranexamic acid (61–259 mg/kg) is known to increase the risk of seizures in the perioperative period.[10] Tranexamic acid is known to bind to $GABA_A$ receptor, thus blocking the GABA-driven inhibition of the central nervous system.[11] This might have a therapeutic implication in the palliative care/cancer setting with the complex neurochemical modulations that may lower the threshold for seizure potential.

Conclusion

Although an uncommon side effect, bleeding in patients with advanced malignancy can be a cause for severe distress in patient and family. Identifying early signs of bleeding and providing assurance and comfort care is primarily essential. It is also important, to an extent, to identify the source of bleeding and possible cause for it as this may help avert the adverse consequences. Antifibrinolytics such as tranexamic acid can be considered in a palliative care setting. It is of course essential to weigh the benefit and risk of the treatment, as studies have shown increased risks such as thromboembolism and seizures with high doses of tranexamic acid. In the palliative care setting, it may be helpful to have the goals of treatment discussed including risks and benefits of the treatment and documented while the treatment is being initiated.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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