LETTER to the EDITOR

Successful Management of Bevacizumab-Associated Surgical Bleeding with an Ankaferd Blood Stopper

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Dear Editor

Bevacizumab is the first antiangiogenic agent clinically proven to extend survival and in combination with 5-fluorouracil (5-FU)–based chemotherapy has been approved by the US Food and Drug Administration (FDA) for the first-line or second-line treatment of metastatic colorectal cancer (CRC). It has been associated with multiple complications after surgery in regard to wound healing, wound infection, and surgical site bleeding (Gordon et al, 2009).

We here would like to stress the possibility of successful management of the intractable bevacizumab-associated bleeding after intravenous port insertion procedure with Ankaferd Blood Stopper (ABS, Ankaferd Health Products Ltd, Turkey). Ankaferd Blood Stopper, a hemostatic agent approved by the Ministry of Health to manage external hemorrhage and dental surgery bleeding in Turkey, is a herbal extract obtained from 5 different plants: *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum* and *Urtica dioica*. For centuries, it has had a historical role in traditional Turkish medicine as a topical hemostatic agent, usually for skin wounds (Goker et al., 2008).

70 years old male patient who were diagnosed metastatic colon carcinoma. He was started to treatment with a combination of capecitabine, oxaliplatin and bevacizumab. With this treatment he get partial remission and the disease were progressed at 20 month of the treatment. We need to vascular access for infusional chemotehrapy (FOLFIRI) administration. His aPTT, INR and platelets were within normal limits. He did not take any non-steroidal anti-inflammatory drugs before procedure. He did not experience abnormal bleeding before and during bevacizumab treatment period. Intravenous port insertion was done at our experienced radiology physicians after 4 weeks of last bevacizumab infusion. After insertion of intravenous port abandon / profound bleeding from the surgical site started and last about 6 hours. We make a resuture and incision site compression. Then we applied the 1 vial of ABS with pads and bleeding stopped within 15 minutes. And it didn't reoccurred. Before the procedure his hemoglobin level was10.2 gr/dL after bleeding his hemoglobin was 8.0 gr/dL. We did not observed any other complication, bleeding did not reoccurred and surgical incision were healed in time properly.

Minor bleeding, predominantly from mucocutaneous membranes (e.g. epistaxis), is a common side effect observed in 20%-40% of patients treated with bevacizumab. Severe bleeding is far less common, with an incidence of ≤ 5% observed in patients with metastatic CRC; in most cases, the incidence of severe bleeding was not significantly greater than that observed with chemotherapy alone (Gordon et al., 2009).

Most episodes of bleeding are minor (usually nosebleeds, gum bleeds or other mucocutaneous bleeding), are easily managed using standard first-aid techniques and do not require modification of bevacizumab treatment. In our case the bleeding could not stopped with standard conventional measures. We strongly believe that this unexpected bleedingis related to bevacizumab usage. Current literature suggests patients should wait at least 6 to 8 weeks (>40 days) after cessation to have surgery (half-life = 20 days). In addition, postoperative reinitiation of bevacizumab must wait > or =28 days to prevent an increased risk of wound healing complications, and the surgical incision should be fully healed.

Ankaferd blood stopper has been used for the management of dermal, external post-surgical and post-dental surgery bleedings. Its exclusive hemostatic effect has been proved with many case reports and animal studies by endorsing the formation of a protein arrangement which creates a 'magnet' effect for vital physiological erythrocyte aggregation, wrapping the classical cascade model of the clotting system by simultaneously acting with the coagulation factors and platelets. Since ABS induced hemostasis mainly through erythrocytes, one may hypothesize that bleeding due to defective hemostasis such as low platelet count, warfarin overdose and chronic NSAID use could be controlled more efficiently with ABS. Moreover, the in vivo hemostatic effect of ABS in rats with defective hemostasis due to enoxaparin and aspirin administration has been studied and ABS was found to be effective in shortening the duration of bleeding and decreasing the amount of bleeding (Cipil et al., 2009; Kurt et al., 2010).

In conclusion, application of the ABS may be a good option for surgical site bleeding related to bevacizumab that could not stopped conventional measures. However, this clinical observation should be supported with preclinical and clinical studies.

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References

Gordon CR, Rojavin Y, Patel M, et al (2009). A review on bevacizumab and surgical wound healing: an important warning to all surgeons. *Ann Plast Surg*, **62**, 707-9.

Goker H, Haznedaroglu IC, Ercetin S, et al (2008). Haemostatic actions of the folkloric medicinal plant extract, Ankaferd blood stopper. *J Int Med Res*, **36**, 163–70.

Kurt M, Akdogan M, Onal IK, et al (2010). Endoscopic topical application of Ankaferd Blood Stopper for neoplastic gastrointestinal bleeding: A retrospective analysis. *Dig Liver Dis*, **42**, 196–9.

Cipil HS, Kosar A, Kaya A, et al (2009). In vivo hemostatic effect of the medicinal plant extract Ankaferd Blood Stopper in rats pretreated with warfarin. *Clin Appl Thromb Hemost*, **15**, 270–6.

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