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SHORT COMMUNICATIONS AND CASE REPORTS

Multiple cutaneous ecchymoses associated with the administration of bevacizumab

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Summary

Nowadays, the introduction of combinational therapies with biological agents against advanced or resistant to chemotherapy tumors or for the treatment of cancer patients with organ failures becomes more and more attractive. The authors describe the case of a 60-year-old female patient with a multi-refractory to conventional cytotoxic therapy laryngeal cancer that was treated with cetuximab and bevacizumab combination therapy. Bevacizumab administration was associated with appearance of multiple cutaneous ecchymoses. This is a first-time reported adverse effect. Due to the recent launch of these agents and the limited experience of their use in clinical practice, their adverse effects and pharmacological toxicities are not well established and call for their detailed registration and reporting.

Keywords: bevacizumab, cetuximab, cutaneous ecchymoses, laryngeal squamous carcinoma, multi-resistant head and neck cancer

Case presentation

We describe the case of a 60-year-old female who was first diagnosed in April 2005 with inoperable locally advanced supraglottic laryngeal squamous cell carcinoma, grade II and TNM stage T3N1M0 (III). The patient was first treated with radiotherapy and synchronous weekly administration of radiosensitizing chemotherapy. In October 2006 she presented with a locoregional tumor relapse and from October 2006 to August 2007 she received multi-lines of chemotherapy, without being able to control the gradual progression of disease. Finally, due to severe haematological toxicities, cytotoxic chemotherapy couldn't be further administered. At that time she was symptomatic with pain and almost impossible deglutition (Eastern Cooperative Oncology Group performance status, PS: 2). After the failure of conventional chemotherapy and because of her rather good general condition, the patient was put on bevacizumab 10 mg/kg every two weeks and cetuximab 200 mg/m^2 weekly, starting from November 2007. With the administration of cetuximab a temporary mild skin rash (grade 1) appeared. Seven days after the first administration of bevacizumab/cetuximab combination the patient presented with spontaneous extensive cutaneous ecchymoses in the extremities and the perineum (Figure 1). The patient's haematological parameters, platelets' functional tests, haemorrhagic and thrombophilic

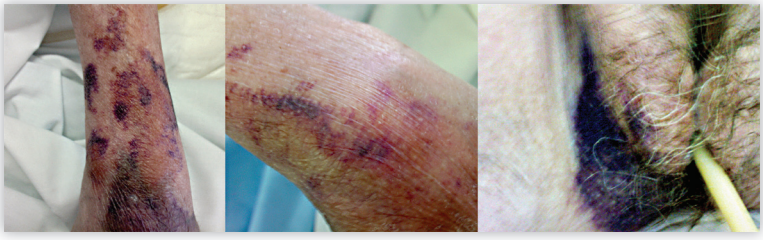

Figure 1. Extensive cutaneous ecchymoses in patient's extremities and perineum were appearing after the first administration of bevacizumab.

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coagulation testing (including coagulation factors' activity assessment) were within normal range. The haemorrhagic skin manifestations persisted even after the reduction of bevacizumab dose at 7.5 mg/kg (without any disorders in patient's blood tests). Because of disease stabilization and prominent improvement of subjective symptoms (pain relief and improvement of deglutition, PS: 1) the treatment with bevacizumab/cetuximab continued for 4 additional months. The ecchymoses persisted unchanged during all that time.

Since the patient didn't reveal any cutaneous haemorrhagic manifestations with the administration of cetuximab (she only had developed a mild acne-like skin rash), these skin ecchymoses had to be associated with the treatment with bevacizumab or the combinational treatment with bevacizumab plus cetuximab. Perhaps bevacizumab as antiangiogenic agent can affect the permeability of capillaries and prior heavy treatment with cytotoxic agents may aid this phenomenon. Nevertheless, to our knowledge, bevacizumab-correlated cutaneous ecchymoses is a first-time reported adverse reaction.

Discussion

Cetuximab has been shown to be a promising therapeutic option in head and neck cancer, and has been approved for use combined with radiotherapy in head and neck squamous cell carcinoma [1]. Cutaneous toxicity is the most evident adverse effect of epidermal growth factor receptor (EGFR) inhibitors because of the specific role of EGFR in skin biophysiology. The dermatological adverse reactions are mainly folliculocentric acne-like rash [2]. Bevacizumab has been used with chemoradiotherapy at a dose of 10 mg/m^2 every 2 weeks, showing antitumor activity and sufficient safety profile, in the treatment of poor-prognosis head and neck cancer patients [3]. Exfoliative dermatitis and a non-specific rash have been reported as very rare toxicities associated with bevacizumab treatment [4].

The effects of vascular endothelial growth factor (VEGF) inhibitors are typically downstream consequences of suppression of cellular signalling pathways important in the regulation and maintenance of the microvasculature. Downregulation of these pathways in normal organs can lead to vascular disturbances and even regression of blood vessels, which could be intensified by concurrent pathological conditions. An increased risk for thromboembolic events (mostly arterial) in the CNS and gastrointestinal tract, pulmonary haemorrhage and gastrointestinal perforation has been recorded with combination of bevacizumab and chemotherapy [5,6].

Treatment with cetuximab and bevacizumab has been reported as effective, safe and feasible. Cetuximab and bevacizumab can be administered concurrently, with a toxicity pattern similar to that expected from the two agents alone [7,8].

Nowadays, targeted biological anticancer agents, monoclonal antibodies and small molecule inhibitors share an ever growing interest in anticancer drug development and treatment because of their reduced toxicity (compared to standard cytotoxic therapy) and improved therapeutic efficacy. Despite the modest results, the use of the monoclonal antibodies cetuximab and antiangiogenic bevacizumab that target the EGFR and VEGF respectively, improves the therapeutic outcome in colorectal cancer and, based on several clinical studies, is gradually expanding to the treatment of several other solid tumors [9,10]. However, due to the recent launch of these agents and the limited experience of their use in clinical practice, their adverse effects and pharmacological toxicities are not well established and call for their detailed registration and reporting.

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