Skin rash secondary to bevacizumab in a patient with advanced colorectal cancer and relation to response

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Bevacizumab (Avastin) in combination with intravenous 5-fluorouracil-based chemotherapy as first-line as well as second-line treatment of metastatic colorectal cancer improves survival. Although skin rash (type unspecified) has been described in some patients following infusion of bevacizumab, it is not a common toxicity of bevacizumab, while acneiform rash occurs in more than 90% of patients who receive cetuximab (Erbitux), the severity of which appears to be predictive of response. We report a patient with colorectal cancer who developed a rash secondary to bevacizumab that correlated with response. A 40-year-old patient with stage IV colorectal cancer received FOLFOX-4 and bevacizumab, which he tolerated very well except for a skin rash related to bevacizumab. The rash cleared every time bevacizumab was eliminated from the chemotherapy regimen. When use of bevacizumab was resumed, similar rash reappeared. Therefore, we believe that this observation of the rash emergence was linked to bevacizumab administration. The most common toxicities associated with bevacizumab include hypertension, hemorrhage, gastrointestinal perforation, arterial thromboembolism, wound healing and proteinuria. Exfoliative dermatitis and a nonspecific rash have been reported with bevacizumab. This case report, we believe, is the first report of a possible correlation between a rash and a positive drug response associated with bevacizumab, and may initiate further investigation of similar observation. ***Anti-Cancer Drugs*** **17:1227–1229**

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Introduction

Bevacizumab (Avastin; Genentech, South San Francisco, California, USA) (BV), in combination with intravenous fluorouracil (FU)-based regimens, is an accepted standard of care for the treatment of metastatic colorectal cancer (CRC) in the first-line setting. For instance, there was an improvement in response rates by 17% with FU/leucovorin (LV), 40% with FU/LV + BV 5/mg/kg and 24% with FU/LV + BV 10 mg/kg in one of the intial randomized phase II studies [1]. The 'TREE-2' trial was the first to combine BV with oxaliplatin-based regimens in the first-line treatment of CRC [2]. Patients were randomized to either BV + FOLFOX, bolus FU with oxaliplatin or capecitabine and oxaliplatin. The results indicated that the response rates among the groups were 49, 34 and 43%, respectively. Overall grade 3/4 toxicities with first-line BV + oxaliplatin-based chemotherapy were less than reported for irinotecan, bolus fluorouracil and leucovorin [2,3]. The BOND-2 trial is a randomized phase II trial of cetuximab and BV vs. cetuximab, BV and irinotecan [4]. The results showed an improvement in the time taken for progression and response rates compared with historical data from the BOND-1 trial. This study proved that combining biological agents is feasible and safe, with no unexpected toxicities.

Trials of BV in CRC have identified proteinuria (all grades 1–28%), hypertension (all grades 3–25%), wound healing complications (1–2%), hemorrhage (2–9.3%), arterial thromboembolism (0–3.8%) and gastrointestinal perforation (1.5%) as BV-associated adverse effects. Skin rash (type unspecified) has been described in some patients following BV infusion [5–7]. On the other hand, acneiform rash occurs in more than 90% patients who receive cetuximab (Erbitux), the severity of which appears to be predictive of response [8]. We report a patient with CRC who developed a rash secondary to BV.

Case report

A 40-year-old male nurse with unremarkable past medical history presented with acute rectal bleeding. Colonoscopy revealed a sigmoid mass approximately 22 cm from the anal verge, while biopsy revealed a well-differentiated adenocarcinoma. A positron emission tomography/computed tomography (CT) scan taken before surgery was negative. The patient underwent a left hemicolectomy during which four liver lesions – all mapping to the right lobe – were discovered. An evaluation for possible liver resection via a liver CT-portogram, however, yielded multiple (more than 10) lesions in both lobes (Fig. 1),

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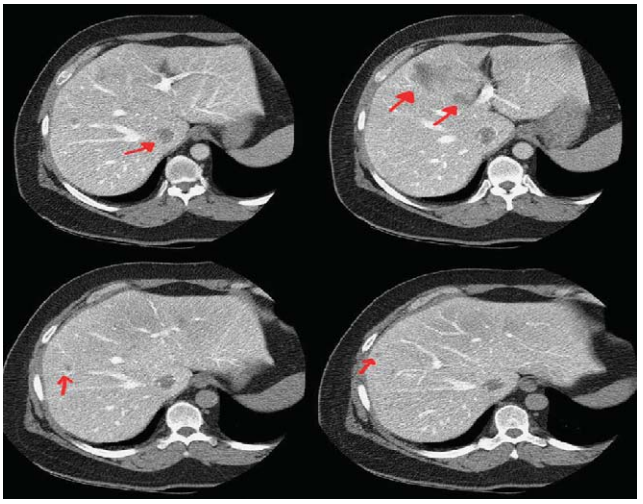
Fig. 1

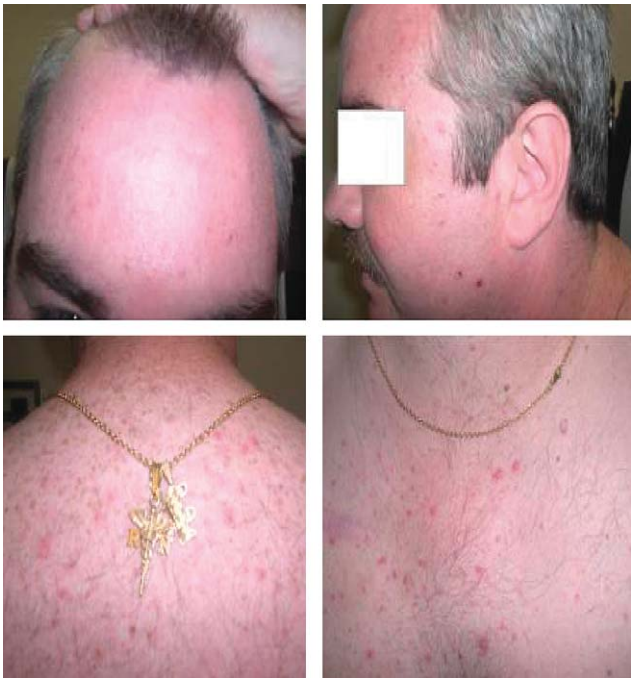


A computed tomography-portogram of the liver showing multiple lesions.

thus precluding this procedure. Chemotherapy was then administered consisting of FOLFOX-4 and BV. Oxaliplatin was administered on day 1 at a dose of 85 mg/m^2 as a 2-h infusion, concurrently with LV 200 mg/m^2/day, followed by bolus 5-FU 400 mg/m^2 and a 22-h infusion of 5-FU 600 mg/m^2 for 2 consecutive days. BV was given as 5 mg/kg intravenously. The treatment was repeated every 2 weeks. The patient exhibited a positive response to chemotherapy except for the development of red papillary nodules on his chest, back, forehead and around the eyes after starting BV (Fig. 2). His liver metastases shrank to two lesions according to a repeat liver CT-portogram. During a subsequent surgical resection, it was discovered that both lesions were necrotic and there were no signs of adenocarcinoma. The procedure was well tolerated with an uneventful recovery period.

FOLFOX-4 was restarted 3 weeks after surgery with BV added from the second postoperative cycle. The patient completed 6 months of therapy and was given a 1-month break at which point his skin rash began to clear up. Maintenance chemotherapy consisting of 5-FU/LV (LV 200 mg/m^2/day, followed by bolus 5-FU 400 mg/m^2 and a 22-h infusion of 5-FU 600 mg/m^2 for 2 consecutive days) and BV was then administered, eliminating oxaliplatin from the protocol [9]. Two weeks after resuming treatment, the patient once again developed red papillary nodules on his chest, back and forehead. Nine months after surgical resection, the patient remains in complete remission as evident by normal liver function tests, carcinoembryonic antigen, liver magnetic resonance imaging and positron emission tomography scans. Maintenance chemotherapy was briefly interrupted because of hernia presentation and repair. After resuming therapy with 5-FU/LV alone (BV was not restarted because of recent surgery), the patient did not demonstrate any dermatological side-effects. When BV was added to the regimen, appearance of red papillary nodules was again documented on his forehead and shoulder with a similar consistency to the previous rash. We therefore believe that the emergence of this rash was linked to BV administration.

Fig. 2



Skin rash after bevacizumab therapy.

Discussion

BV is a monoclonal antibody to vascular endothelial growth factor (VEGF), a key mediator in tumor angiogenesis. VEGF receptors are overexpressed in various malignancies, including CRC [10]. Such interaction leads to cell proliferation and angiogenesis when a tumor attempts to gain an independent oxygen and nutrient supply. The drug is typically well tolerated, and its major side-effects include hypertension, proteinuria, bleeding, gastrointestinal perforation and arterial thrombotic events [1–4,11]. Although exfoliative dermatitis was also described as a side-effect in 19% of patients [12], skin rash (type unspecified) has been rarely described in some patients following infusion of BV [5–7]. In Kabbinavar *et al.*'s study [1], 16 (46%) patients developed rash with only one patient with grade 3 or greater rash at 5 mg/kg dose of BV. On the other hand, only 11 patients (34%) developed rash at 10 mg/kg dose of BV with no patient developing grade 3 or greater rash. No correlation

between rash development and a positive drug response was previously reported.

Recently, BV combined with FU-based chemotherapy has become the standard of care for first-line treatment of metastatic CRC and was recently approved for second-line treatment also. Skin rashes are known to typically develop with epidermal growth factor receptor (EGFR) antagonists, including tyrosine kinase inhibitors and antibodies such as cetuximab (Erbitux) and erlotinib (Tarceva) [8,13]. This toxicity usually occurs in the first 2 weeks of treatment, and affects the face, trunk and extremities. EGFR antagonist-induced skin rashes are characterized by clusters of monomorphic pustular lesions with a histological examination revealing neutrophilic infiltration of the dermis. The skin rashes are dose dependent and can improve or resolve spontaneously. The functional similarity of EGFR and VEGF points to a possibility of a correlation between skin rash development and BV therapy. Rash is not unknown to drugs targeting the VEGF pathway. The toxic effects of BAY 43-9006, another anti-VEGF, also include rash in addition to hypertension, edema, diarrhea, hand and foot syndrome, and hair loss where the rash involved the scalp [14].

In summary, we believe this to be the first report of such an association between rash and response to BV in a patient with CRC. This case report may initiate further investigation of similar cases to support this observation as there is a lack of reports of skin rash with BV therapy We would be interested in finding out if anyone from the oncologists who read journal has experienced a similar coincidence of a remarkable response to the therapy and dermatological side-effects.

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