

ORIGINAL ARTICLE

Bevacizumab-induced nasal septal perforation: Incidence of symptomatic, confirmed event(s) in colorectal cancer patients

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Abstract

Purpose. In breast cancer patients, Mailliez and others described that 5 of 70 patients (7%) developed a bevacizumab-induced nasal septal perforation. However, to date, no studies have reported such rates in colorectal cancer patients, who derive a survival advantage with this drug. **Methods.** This study examined the incidence of bevacizumab-induced, clinically symptomatic, otolaryngology specialist-confirmed nasal septal perforation among 100 patients who had been consecutively-treated for metastatic colorectal cancer. **Results.** The incidence of nasal septal perforation was 1% (95% confidence intervals: -0.95% to 2.95%). This single adverse event was successfully managed conservatively. Within the whole group, 94 had been treated with bevacizumab at 5 mg/kg every two weeks, except for four patients treated at higher doses. The median number of bevacizumab doses (range) was seven (1–96). Concomitant chemotherapy had been prescribed to all patients, consisting of oxaliplatin, 5-fluorouracil, leucovorin, as per one of the FOLFOX regimens (44 patients); irinotecan, 5-fluorouracil, leucovorin, as per the FOLFIRI regimen (13 patients); both these regimens and no other (five patients); or a different regimen (38 patients). **Conclusion.** Nasal septal perforation from bevacizumab occurs infrequently among colorectal cancer patients.

An emerging literature, consisting primarily of case reports, suggests that bevacizumab can induce nasal septal perforation (Table I). The fact that the nasal septal cartilage is poorly vascularized, coupled with the fact that the anti-angiogenic effects of bevacizumab are well-established, add plausibility to the claim that this drug can further compromise the meager vasculature within the nasal septum, thus leading to this newly-recognized adverse event.

Recently and for the first time, Mailliez and others have provided incidence rates for this complication [1]. These investigators evaluated 70 bevacizumab-treated breast cancer patients. Except for three patients receiving lower doses, most received bevacizumab 15 mg/kg every three weeks. Concurrent chemotherapy included docetaxel, paclitaxel, capecitabine, and possibly an anthracycline. An otolaryngologist evaluated all patients and found five nasal septal perforations, thus yielding an incidence rate of 7%. After the diagnosis of perforation, bevacizumab was discontinued in all patients except

one; but no patient suffered major sequelae. These investigators concluded, “A high incidence of nasal septum perforation has been shown in patients with breast cancer receiving bevacizumab together with chemotherapy.”

Such observations raise two clinically relevant questions. First, is the rate of nasal septal perforation also “high” in colorectal cancer patients, who receive lower doses of bevacizumab and somewhat different concomitant chemotherapy regimens? It should be noted that bevacizumab was first approved for metastatic colorectal cancer and has demonstrated life-prolonging effects in this setting. Thus, answering this question in this setting is clinically relevant [2,3]. Second, is the incidence of nasal septal perforation also “high” when based primarily on symptomatology with confirmation of the event by an otolaryngology specialist, as opposed to a specialist’s direct visualization of the nasal septum even in the absence of symptoms? Indeed, Mailliez and others appeared to have evaluated all patients, but reporting on a small, asymptomatic, self-limited

Table I. Summary of case reports of nasal septal perforation with bevacizumab.

Age	Sex	Cancer	N	Bevacizumab dose	Concurrent chemotherapy	Special circumstances/sequelae	Reference
53	male	colon	1	not reported	5-fluorouracil, leucovorin, oxaliplatin (FOLFOX)	None/bevacizumab continued with healing	Fakih and Lombardo 2006 [4]
54	female	breast	1	10 mg/kg every 2 weeks	paclitaxel	None/bevacizumab stopped then healing occurred	Traina, et al. 2006 [6]
53	male	colon	1	5 mg/kg every 2 weeks	5-fluorouracil, leucovorin	Invasive fungus/bevacizumab stopped and antifungal therapy initiated with healing	Ruiz, et al. 2007 [7]
52	female	ovary	1	not reported	none	None/perforation progressed despite stopping bevacizumab, then stabilized; silastic nasal button placed	Burkart, et al. 2008 [8]
39	female	breast	1	not reported	paclitaxel	None/no outcome information	Marin, et al. 2009 [9]
68, 40, 35	1 female, 2 male	colon	3	not reported	1) 1 st patient: 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX); 2) 2 nd patient: 5-fluorouracil, leucovorin; 3) 3 rd patient: 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX)	No special circumstances in any patient/ bevacizumab continued in 1 patient with no sequelae in any patients	Power and Kemeny 2010 [5]

perforation might perhaps seem of lesser clinical value. The current study was undertaken to address both these questions.

Methods

Overview

The primary goal of this retrospective study was to report on the incidence and circumstances of clinically symptomatic nasal septal perforation in a consecutive series of bevacizumab-treated colorectal cancer patients. To this end, this study was approved by the Mayo Clinic Institutional Review Board in Rochester, Minnesota USA.

Acquisition of records and review

This study focused on patients who had metastatic colorectal cancer patients and who began treatment with bevacizumab at the Mayo Clinic in Rochester, Minnesota USA in March of 2004 or later. This starting date was chosen because this month and year mark the Food and Drug Administration’s approval of bevacizumab for the treatment of metastatic colorectal cancer [3].

The study team reviewed each medical record to acquire information on patient age at the time of starting bevacizumab, gender, dose of bevacizumab, and type of concurrent chemotherapy. Patients were classified based on the highest dose of bevacizumab received. If patients received a variety of chemotherapy regimens over time with bevacizumab, the concurrent chemotherapy was classified as “a different regimen.”

Each record was reviewed for the presence of nasal symptoms, such as epistaxis. “Clinically symptomatic” nasal septal perforation was defined as an event that was confirmed by an otolaryngology specialist with symptoms severe enough to require an evaluation by such a specialist. For this reason, each medical record was scrutinized for symptoms and a subsequent specialist consultation. The record(s) of those patients who had developed a clinically symptomatic, otolaryngology specialist-confirmed nasal septal perforation were reviewed in greater depth in order to provide more detail on the circumstances surrounding the perforation, interventions, and outcomes after the adverse event.

Reporting of data

This consecutive series of patients sought a total of 100 bevacizumab-treated colorectal cancer patients. If the incidence of clinically symptomatic nasal septal perforation were to be less than 7%, the rate

cited by Mailliez and others [1], this sample size enabled the investigators to report on the observed incidence of this event with a 95% confidence interval of < 5%. All data are otherwise presented descriptively.

Results

Demographics

This group of 100 consecutively-treated colorectal cancer patients had a median age (range) of 62 years (20–85) and a male/female distribution of 1/1.

Ninety-four patients had been treated with bevacizumab at a dose of 5 mg/kg every two weeks, except for a small subgroup treated with 7.5 mg/kg every three weeks (five patients) and 15 mg/kg every three weeks (one patient). The median number of bevacizumab doses (range) within the group was seven (1–96).

All patients received concomitant chemotherapy. Regimens consisted of oxaliplatin, 5-fluorouracil, leucovorin, as per one of the FOLFOX regimens (44 patients); irinotecan, 5-fluorouracil, leucovorin, as per the FOLFIRI regimen (13 patients); both these regimens and no other (five patients); or a different regimen (38 patients).

Incidence of nasal septal perforation

Although 24 patients in this group manifested mild, self-limited epistaxis, the incidence of clinically symptomatic, otolaryngology specialist-confirmed nasal septal perforation was 1% (95% confidence interval: -0.95% to 2.95%). One other patient had also developed a nasal septal perforation, but this event occurred prior to the initiation of bevacizumab, was thought to be related to prior nasal surgery, and did not recur once the patient started bevacizumab.

Details of the single incident

The bevacizumab-related episode of nasal septal perforation occurred in a 46-year-old woman with no other risk factors. She had episodic epistaxis during her 16 treatments with bevacizumab 5 mg/kg every two weeks, which was given concomitantly with oxaliplatin, 5-fluorouracil, and leucovorin. The otolaryngologist specialist's diagnosis of a 1.5 × 1 centimeter nasal septal perforation occurred after the patient had begun a chemotherapy drug holiday. The perforation itself was managed conservatively with antibiotics and local irrigation with no sequelae. The patient was never retreated with bevacizumab.

Discussion

This study observed that only 1% of colorectal cancer patients treated with bevacizumab suffered a clinically symptomatic, otolaryngology specialist-confirmed nasal septal perforation, a rate much lower than that reported by Mailliez and others [1]. What might explain this discrepancy? First, it should be noted that the patients in our study received lower doses of bevacizumab and somewhat different concurrent chemotherapy regimens. Although, in our study, nasal septal perforation did not occur in any patients who received higher doses of bevacizumab, perhaps the risk of this adverse event increases as a result of higher bevacizumab dosing and different concomitant chemotherapy regimens, such as taxanes. Second, given the retrospective nature of our study, not every patient had undergone an otolaryngological examination – in contrast to the study from Mailliez and others [1] – although we did rely on such subspecialty expertise for confirmation of diagnosis. The current study's reliance on symptomatology may have selected for a smaller incidence rate. Nonetheless, we conclude that colorectal cancer patients, who receive bevacizumab at the doses described in our study and with the chemotherapy regimens described here, appear to have a relatively low incidence of clinically symptomatic, specialist-confirmed nasal septal perforation. This finding might be of value to colorectal patients and their healthcare providers as they consider cancer treatment options that include bevacizumab.

Although the relatively low rate of nasal septal perforation in our study along with a general paucity of reports on this adverse event do not provide adequate information to enable us to comment extensively on management guidelines and outcomes, it should be noted that patients appear to have done well after having sustained this complication. Three previously-reported cases suggest that continuing bevacizumab in the setting of a favorable tumor response and otherwise good tolerance of the agent might be justified [1–3], particularly if an otolaryngologist is available to provide close follow-up. Moreover, an absence of other ostensible explanations for this complication, such as concurrent fungal infection, trauma, or collagen vascular disease, seems often to lead to a self-limited event, which, in the worst case scenario, leaves patients only with noisy nasal airflow and the occasional need for a button procedure.

Finally, we acknowledge that our overall understanding of bevacizumab-induced nasal septal perforation remains nascent. The continued study of this presumably rare adverse event might allow for a better understanding of risk factors of this drug-induced complication, the full spectrum of its clinical

manifestations, a more robust discussion of palliative options, and a more precise assessment of outcomes with a bevacizumab re-challenge.

Declaration of interest: Ms. Ramiscal had been previously employed by Genentech Incorporated, South San Francisco, California USA. This work was funded in part by 5K24CA131099.

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