EXPERT OPINION

An observational study of nasal cavity toxicity in cancer patients treated with bevacizumab

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Background: The nasal cavity is a vulnerable zone which may be damaged by vascular disorders. We systematically assessed the frequency and severity of nasal cavity alterations during bevacizumab treatment, to determine its clinical relevance and factors contributing to its onset.
Patients and methods: We conducted a hospital-based cohort study in 47 consecutive patients with advanced cancers who were on treatment with chemotherapy and bevacizumab at different doses. All patients underwent otolaryngology (ENT) examination at the time of study initiation.
Results: The mean number of cycles at first ENT examination was 16 (standard deviation = 14). A total of 45 patients (96%) showed nose mucosal lesions, of whom 30% had erosions and 62% had grade 1 – 2 epistaxis. One patient had septal perforation. Grades 1 – 4 sinus disorders were noted in 60%. There was a significant trend to a higher risk of grade ≥ 2 nasal events for bevacizumab doses > 7.5 mg/kg, concomitant taxane use and digital nasal self-manipulation.
Conclusions: We found a high incidence of nasal cavity lesions in patients receiving bevacizumab, with evidence for a dose-related effect. Most cases were low grade and manageable without drug interruption, but severe toxicity may rarely occur. Oncologists should be aware of this unusual event.

Keywords: adverse drug event, bevacizumab, epistaxis, nasal septum

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1. Introduction

The use of anti-angiogenesis drugs is now commonplace in the treatment of malignant disease. The most widely used VEGF inhibitor in use today is bevacizumab, a humanized anti–-VEGF mAb which inhibits angiogenesis [1,2] and has been approved for the treatment of several advanced solid tumors [3,4]. The use of bevacizumab has been associated with an increased risk of serious adverse events such as intestinal perforation [5-8], hemorrhage [9], delayed wound healing and serious cardiovascular disorders [10,11]. The most common adverse events are hypertension, proteinuria and asthenia [12-21], but rare cases of nasal septum perforation have been described in case reports [22-29], and unexpected septum perforations with fungal infection were reported [30]. Nasal cavity is a very vulnerable zone as irritation and mucosal lacerations can expose the underlying vascular cartilage. Blood supply to this cartilage depends on the integrity of the mucoperichondrium and this can potentially be damaged by anti-angiogenic drugs.

We have systematically assessed the incidence and severity of nasal adverse events in a consecutive series of patients undergoing bevacizumab treatment to determine which factors may contribute to the onset of this adverse effect.

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Table 1. Main characteristics of patients and bevacizumab therapy.

N	47
Age, years	
Mean ± SD	60 ± 12
Gender	
Male	13 (28%)
Female	34 (72%)
BMI	
Mean ± SD	24.1 ± 4.1
ECOG-PS	
0	40 (85%)
1	7 (15%)
Disease site	
Colon-rectum	21 (45%)
Ovary	16 (34%)
Breast	6 (13%)
Lung	2 (4%)
Kidney	1 (2%)
Cervix	1 (2%)
Concomitant chemotherapy*	
Antimetabolites	35 (75%)
Platinum salts	28 (60%)
Taxanes	13 (28%)
Dose, mg/kg	
5	17 (36%)
7.5	17 (36%)
> 7.5	13 (28%)
Frequency	
Q14	16 (34%)
Q21 – 28	31 (66%)
Number of cycles	
Mean ± SD	16 ± 14
Duration, weeks	
Mean ± SD	44 ± 42
Daily dose per cycle per patient, mg/day	
Mean ± SD	485 ± 146

*Patients may receive more than one agent.
BMI: Body mass index; ECOG-PS: Eastern Cooperative Oncology Group performance status; SD: Standard deviation.

2. Methods

We conducted a mono-institutional hospital-based cohort study to determine the association between frequency and severity of nasal cavity alterations and bevacizumab treatment. All patients aged ≥ 18 years who were candidate to anticancer therapy including bevacizumab from February 2010 to May 2013 underwent ear, nose and throat (ENT) examination during treatment. The study received Institutional Review Board approval.

The initial dose of bevacizumab was administered over 90 min, the second dose over 60 min, and if well tolerated, all subsequent infusions were administered over 30 min. Before each infusion, urine proteins, blood pressure and presence of nasal symptoms were monitored according to guidelines.

The ENT evaluation included assessment of symptoms related to nasal cavity and exclusion of past diseases known to cause potential nasal cavity events, including Wegener's granulomatosis and systemic lupus erythematosus [31]. The nasal cavity adverse events mucosa were categorized and graded according to the different spectrum defined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, which comprise the following adverse events: epistaxis; nasal congestion; postnasal drip and sinus disorder.

The ENT physician also evaluated the presence of any lesion by anterior rhinoscopy and described the characteristics of these lesions: localization and size, level of involvement of the epithelium and state of vascular network and distribution. The diameter of each lesion was measured with a millimetric reference instrument.

Categorical data were summarized as number and percentage of subjects and continuous data as mean, standard deviation (SD) and range. Patients were classified in two groups: patients who experienced no or G1 adverse events and patients who experienced G2 or higher adverse events. Fisher's exact or Pearson's chi-squared tests were used to compare categorical variables, whereas Mann–Whitney U test was used for continuous variables. A logistic regression analysis was performed to evaluate the association between treatment and host characteristics and incidence of G2 or higher adverse events. Two-tailed probabilities were reported and the p value of 0.05 was used to define nominal statistical significance. All analyses were performed with SPSS software (version 13, SPSS Inc., Chicago, IL, USA).

3. Results

From February 2010 to May 2013, we recruited 47 consecutive cancer patients: 13 males (28%) and 34 females (72%). The main patient and treatment characteristics are reported in **Table 1**. They were affected with advanced colorectal (45%), ovarian (34%), breast (13%), lung (4%), renal cell (2%) and cervical cancers (2%) and were treated with bevacizumab plus different chemotherapy drugs, as shown in **Table 1**. Bevacizumab was administered at the dose of 5 (36%), 7.5 (36%), or > 7.5 mg/kg (28%), in 2 (34%) or 3/4 weekly courses (66%). The mean number of bevacizumab cycles was 16 (SD = 14).

The distribution of adverse events according to the NCI CTCAE is summarized in **Table 2**. All patients but two developed some form of mucosal lesions which were associated with grade 1 or grade 2 epistaxis in 29 cases (62%). The lesions were bilateral in 81%, multicentric in 83%, associated with dyschromia in 57% and with erosion in 30% of the cases. The overall ENT findings are summarized in **Table 3**. There was one case of septal perforation (2%). A total of 36% of the patients reported digital nasal self-manipulation. The median diameter of lesions was 10 mm (range: 1 – 20). Bevacizumab was not discontinued in any case due to septal disorders nor was there a significant correlation between nasal cavity toxicity and tumor response (**Figure 1**).

Table 2. Nasal cavity adverse events.

	Epistaxis*	Nasal cavity adverse events*
G1	23 (49%)	22 (47%)
G2	6 (13%)	2 (4%)
G3	-	3 (6%)
G4	-	1 (2%)

*According to NCI CTCAE v4. NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 3. Descriptive characteristics of ENT findings.

	N (%)
Patients with mucosal disorders	45 (96)
Monolateral/bilateral	7 (15)/38 (81)
Single/multicentric	6 (13)/39 (83)
Lesions with varices	22 (47)
Epithelial involvement:	
Normal	3 (6)
Dyschromia	27 (57)
Erosion	14 (30)
Perforation	1 (2)
Digital nasal self-manipulation	17 (36)
Preexisting sinus disease	14 (30)
Preexisting hypertension	7 (15)
Hypertension during Bevacizumab	23 (49)

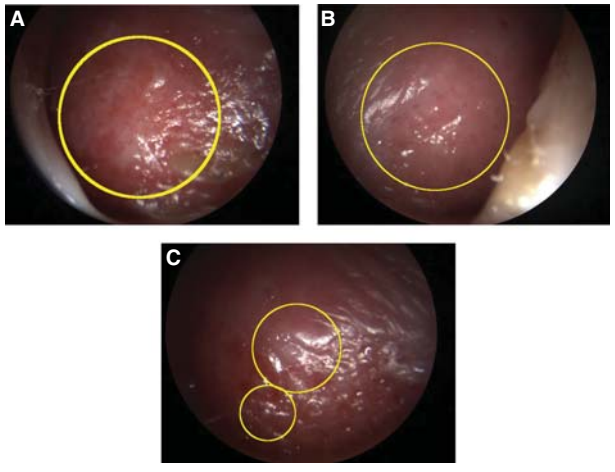

Figure 1. Rhinoscopic video frames slightly deformed due to technical artifacts show a context of widespread bruising in different stages of development: **(A)** dyschromia, **(B)** with erosion crater-like appearance, **(C)** confluent microvarices.

Medical intervention was required in six patients, consisting of electrocautery in three patients and nasal unblocking in five patients (2 patients needed both). In addition, a preventive topical treatment with placental extracts was indicated in 28 patients (60%).

The logistic regression analysis, shown in Table 4, shows which factors significantly affected the onset of a grade 2 or higher sinus disorders or epistaxis. There was a trend to a higher risk of developing grade 2 or higher sinus disorders or epistaxis for bevacizumab doses > 7.5 mg/kg (odds ratio [OR] = 33.3, 95% CI = 2.03 – 546.16, p = 0.014), for concomitant taxane chemotherapy (OR = 112.4, 95% CI = 4.92 – 2597.4, p = 0.003) and for digital nasal self-manipulation (OR = 12.7, 95% CI = 1.37 – 118.36, p = 0.025). No significant effect of age, gender, body mass index, concomitant platinum salts or antimetabolites, prior sinus disorders and hypertension during bevacizumab was noted.

4. Discussion

We report our experience of a high prevalence of nasal cavity lesions in patients with advanced disease receiving bevacizumab plus chemotherapy without correlation with common bevacizumab adverse events or tumor response. Most cases were low grade, but rare cases of severe toxicity resulting in function alterations occurred. We found a trend to a higher risk of grade ≥ 2 adverse events with a single dose > 7.5 mg/kg and in patients on concomitant taxanes.

The management of this unusual adverse effect has yet to be determined. In our series, bevacizumab was not discontinued in any case and the majority of patients received conservative treatment measures, including topical therapy with placental extracts and intranasal saline spray. A more definitive medical intervention was needed only in six patients including electrocautery in three patients and nasal unblocking in five patients.

The exact mechanisms underlying disorders of the nasal cavity under bevacizumab are yet to be understood. A few reports have shown cases of nasal perforation related to bevacizumab treatment, but no data regarding additional nasal cavity disorders have been reported [32]. Also, it is not known whether a different class of anti-angiogenic drugs, such as the small tyrosine-kinase inhibitor molecules, is associated with similar effects. It is plausible that chemotherapy induced mucositis and additional chronic trauma such as digital nasal self-manipulation or frequent nose blowing can weaken the nasal mucosa and thus contribute to the onset of a serious event such as nasal septum perforation. Also the anti-angiogenic action of bevacizumab can inhibit the normal mechanisms of tissue repair and thus delay wound healing. Whatever the mechanisms involved, our findings indicate a high prevalence of a global nasal involvement, which was bilateral in 81% and multicentric in 83%, and with a median diameter of lesions which was > 10 mm. Moreover, nasal cavity adverse events were noted in nearly 60%.

Our study has several limitations including lack of a baseline evaluation and repeated assessment to determine the timing of nasal toxicity onset. However, we show a high prevalence of nasal disorders, some of which can lead to serious septal perforations, which should raise awareness of

Table 4. Logistic regression model of factors affecting nasal cavity events during bevacizumab treatment.

	N	OR	95% CI	p*
Age, years‡	47	1.1	0.99 – 1.19	0.064
Gender				0.463
Male	13	1.0		
Female	34	0.4	0.03 – 4.76	
BMI				0.239
< 25	28	1.0		
≥ 25	19	0.3	0.02 – 2.53	
Bevacizumab dose (mg/kg)				**0.014**
≤ 7.5	34	1.0		
> 7.5	13	33.3	2.03 – 546.16	
Duration of bevacizumab treatment§				0.060
< 28 months	22	1.0		
≥ 28 months	25	0.1	0.01 – 1.11	
Concomitant taxanes				**0.003**
No	34	1.0		
Yes	13	112.4	4.92 – 2597.4	
Digital nasal self-manipulation				**0.025**
No	30	1.0		
Yes	17	12.7	1.37 – 118.36	

The bold charachter indicates the statistical signifance.
BMI: Body mass index; OR: Odds ratio; SE: Standard error.
*Two-sided likelihood ratio test.
‡Age was considered as continuous data.
§Median duration of bevacizumab treatment.

this potentially serious adverse event. It is also necessary to instruct the patient about a proper nasal hygiene management, including avoidance of digital nasal self-manipulation. Finally, a multidisciplinary surveillance of patients involving an ENT specialist is recommended especially for patients candidated to taxanes associated with bevacizumab dose > 7.5 mg/kg. Clinicians should be aware of this unusual adverse event, although its real clinical implication remains unclear.

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Declaration of interest

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• **No standard evidence about the management of these side effects.**

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