

Bowel Perforation Following Continuation of Bevacizumab Post Nasal Septal Perforation—A Case Report

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Abstract

We report the case of a 63-year-old male with an inoperable T4N1 adenocarcinoma of colon, *K-RAS* mutant, who received first line chemotherapy with capecitabine and oxaliplatin. A CT scan following 4 cycles demonstrated progressive disease, and second line therapy with capecitabine, irinotecan and bevacizumab was commenced. CT scans at 3 and 6 months during this treatment regime demonstrated radiologically stable disease, and therefore the treatment was continued. The patient developed nasal septal perforation, a rare but recognised complication of bevacizumab therapy, which was managed conservatively. Here we highlight that no consensus exists on whether bevacizumab should be continued in this situation. After a detailed discussion about the risks and benefits, this patient continued on with the same therapeutic regime. However, eight weeks later, this patient then developed a localised tumour perforation, necessitating an emergency admission to his local hospital. We recommend caution in continuing bevacizumab in patients with colorectal cancer following a nasal septal perforation and advise a detailed discussion of risk with the patient, especially when the primary tumour remains *in-situ*.

Keywords

Colorectal Cancer, Bevacizumab, Avastin, Nasal, Septal, Perforation

1. Case History

We report the case of Mr L., a 63-year-old man, who presented with an abdominal mass and hydronephrosis, and was found to have a T4N1 mucinous, poorly differentiated adenocarcinoma of the colon, which was *K-RAS* mutant. He had an attempted resection in July 2012 but the tumour was inoperable so nephrostomies were fa-

shioned. This patient commenced on 1st line chemotherapy with Capecitabine (1000 mg/m²·days 1 - 14) and Oxaliplatin (130 mg/m²·day 1), each on a 21 day cycle. A CT scan following 4 cycles of chemotherapy demonstrated progression of disease, and he was changed to second line therapy with Capecitabine (1000 mg/m²·days 1 - 14), Irinotecan (250 mg/m²·day 1) and Bevacizumab (7.5 mg/m²·day 1), each on a 21 day cycle. CT scans at 3 and 6 months during this treatment demonstrated radiological stable disease. This patient then presented with a self-detected perforation of the nasal septum. He was reviewed by ENT who did not recommend any intervention but planned for careful observation and monitoring. The risks (deterioration of nasal perforation and possibility of gastro-intestinal perforation), and benefits (evidence of tumour control), were discussed with the patient, and it was decided to continue with the Bevacizumab. Eight weeks later, RL was admitted to his local hospital with severe abdominal pain, and found to have localised tumour perforation. He was managed conservatively, and to date is making a slow recovery. Bevacizumab has now been discontinued indefinitely.

2. Discussion

Bevacizumab, or Avastin[®], is a recombinant humanised monoclonal antibody that targets human Vascular Endothelial Growth Factor (VEGF). It exerts an anti-cancer activity by preventing tumour angiogenesis, and inhibiting immature blood vessel formation, thus reducing the ability of cancer to develop and maintain a blood supply [1]. It is currently licensed for use in metastatic colorectal cancer in combination with fluoropyrimidines, however, its use is not currently supported by NICE (NICE Technology Appraisal TA212, December 2010) [2].

There is a 1% - 9% reported incidence of nasal septal perforation with the use of Avastin[®], which may be higher in breast cancer patients, compared with colorectal cancer patients, possibly due to concurrent use of taxanes [3]-[5]. Nasal septal perforation is largely thought of as a non-life threatening, self-limiting event. Patients may experience noisy nasal airflow and/or epistaxis. It may be an under-reported adverse event, as not all patients receiving bevacizumab therapy, who experience epistaxis, have assessment by ENT [4].

There is very little guidance in the literature with regard to the management of bevacizumab induced nasal septal perforation, specifically whether or not treatment with bevacizumab should be continued. Malliez (2010) concluded that for this patient group, assessment and monitoring by an ENT specialist is warranted, but whether to continue bevacizumab is unclear. They report a cohort of patients treated with bevacizumab who had favourable tumour responses, despite the development of nasalseptal perforation, and without objective worsening of the defect. There is no data on whether nasal septal perforation heralds an increased risk of other perforations, e.g. gastro-intestinal perforations [5].

In a meta-analysis, the incidence of gastro-intestinal (GI) perforation, in patients being treated with bevacizumab, was 0.9%. This is a significantly increased risk compared to controls (RR 2.14, 95% CI 1.19-3.85, p = 0.011). The risk is higher for patients with colorectal cancer, and could be related to dose, comparing 5 mg/kg/week (RR 6.95 (95% CI 0.36-133.97)) with 2.5 mg/kg/week (RR 2.86 (95% CI 1.11-7.35)) [6]. A subsequent literature review by Hompes (2011) [7] recounts that from the First BEAT study, patients with unresected primary tumours treated with bevacizumab and GI perforation was seen in 8 of 223 (4%): only 3 of which occurring at the primary tumour site [8]. In the BRiTE study, GI perforation rate for this group of patients was 3%, versus almost 2% in patients that the primary tumour had been resected [9]. Multivariate analysis rated this as an independent risk factor for GI perforation, but event numbers were low. Whether these perforations occurred at the primary tumour site, was not specified. Poultsides, *et al.*, (2009) reveal that GI perforation usually occurs within the first 3 months of commencing bevacizumab therapy, though later onset cases have been reported, and they can occur anywhere along the GI tract [10].

In hindsight, the development of a nasal septal perforation in a patient with a primary tumour *in-situ*, might have led to a decision to discontinue bevacizumab at an earlier stage, but the risks and benefits of continuation of treatment were discussed with the patient and in the absence of a clear contraindication, the treatment was continued. We recommend caution in continuing bevacizumab therapy in patients with colorectal cancer following the development of nasal septal perforation, and advise a detailed discussion of risk with the patient.

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