



## Incidence and management of bevacizumab-associated gastrointestinal perforations in patients with recurrent ovarian carcinoma<sup>☆</sup>

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### ABSTRACT

**Objective.** The objective of this study was to examine the incidence and management of bevacizumab-associated gastrointestinal (GI) perforations in patients with recurrent ovarian carcinoma.

**Methods.** We identified all patients who received bevacizumab off protocol from August 2004–August 2008. We examined their medical records for reports of confirmed GI perforation, associated clinicopathological factors, treatment, and outcomes.

**Results.** Six (4%) of 160 patients with ovarian carcinoma who had been treated with bevacizumab developed GI perforations, with a median of 4 (range, 2–8) previous cytotoxic regimens. The median serum CA-125 at the start of treatment was 228 U/mL (range, 50–3106 U/mL). The median number of bevacizumab cycles prior to perforation was 10.5 (range, 2–20). The median time from the last bevacizumab dose to diagnosis of GI perforation was 13 days (range, 1–28 days). Four (67%) patients underwent an exploratory surgery. At laparotomy, one had a gastric perforation and one had an appendiceal perforation; the site of perforation could not be identified in the other 2. Two patients (33%) were managed conservatively—one with a PEG tube and the other with supportive care. The median time of death from the date of diagnosis of GI perforation was 27 days (range, 4–326 days). Only two patients—one with a gastric and the other with an appendiceal perforation—survived >65 days. The 30-day mortality rate following a bevacizumab-associated GI perforation was 50%.

**Conclusion.** Bevacizumab-associated GI perforations in patients with recurrent ovarian carcinoma occurred in 4% of our patients. The prognosis of patients diagnosed with bevacizumab-associated GI perforations in this study was poor, and treatment should be individualized.

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### Introduction

In 2009, approximately 21,550 women will be diagnosed with ovarian carcinoma and more than 15,000 women will die from this disease [1]. Most of these women will be treated with an aggressive cytoreductive surgery followed by platinum and taxane-based chemotherapy. Despite treatment, most of these patients will recur and ultimately yield to their disease [2,3]. In an effort to improve clinical outcomes, investigators have looked beyond conventional cytotoxic chemotherapy to biological agents. Angiogenesis appears to play a central role in the pathogenesis and clinical behavior of epithelial ovarian carcinoma. Vascular endothelial growth factor A (VEGF-A) is an important mediator of angiogenesis and is expressed in the majority of tumor specimens from patients with epithelial

ovarian cancer [4–8]. These observations suggest that VEGF-A may be an important therapeutic target in patients with ovarian carcinoma.

Bevacizumab, a humanized IgG1 targeting VEGF-A, has been extensively studied in phase III clinical trials and is now approved in combination with chemotherapy by the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the treatment of metastatic colorectal cancer, non-small cell lung cancer, breast cancer, renal cell carcinoma, and recurrent glioblastoma [9–14]. The role of bevacizumab in ovarian carcinoma was initially explored in two single-agent phase II trials in recurrent disease, one of which showed objective responses and prolongation of progression-free survival (PFS) when compared to historical controls [15]. The other trial, the ORBIT trial, was closed prematurely due to an unexpectedly high number of gastrointestinal (GI) perforations (5/44 [11%]), which were fatal in 3 patients (7%) [16]. The real assessment of the safety and efficacy of bevacizumab added to standard chemotherapy in first-line treatment following optimal surgical debulking can only come from large randomized trials that are currently ongoing [17,18].

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