European Journal of Cancer (2012) **48**, 1126–1132

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Gastrointestinal perforation associated with bevacizumab use in metastatic colorectal cancer: Results from a large treatment observational cohort study

Fairooz F. Kabbinavar [a,*,f], Patrick J. Flynn [b,f], Mark Kozloff [c,f], Mark A. Ashby [d,f], Amy Sing [d,f], Charles E. Barr [d,f], Axel Grothey [e,f]

[a] *Department of Medicine, Division of Hematology & Oncology, University of California at Los Angeles, 924 Westwood Blvd, Suite #1050, Los Angeles, CA 90095-7207, USA*
[b] *Minnesota Oncology Hematology, PA, 910 East 26th Street, Suite 200, Minneapolis, MN 55404, USA*
[c] *Ingalls Hospital and the University of Chicago, 71 West 156th Street, Suite 401, Harvey, IL 60426, USA*
[d] *Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA*
[e] *Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA*

Available online 15 March 2012

KEYWORDS
Registry
Systemic therapy
Antiangiogenesis
Vascular endothelial growth factor inhibition
Biologics
GI perforation

Abstract ***Background:*** Bevacizumab prolongs overall and progression-free survival when added to fluorouracil-based chemotherapy in patients with metastatic colorectal cancer in randomised controlled trials (RCTs). However, gastrointestinal perforation (GIP) occurs in 1–2% of treated patients. We sought to describe the incidence, temporal pattern, outcomes and potential risk factors for GIP in a large, community-based observational cohort study of patients treated with bevacizumab.

Patients and methods: Baseline patient and tumour characteristics, including potential GIP risk factors, were collected at study entry. Treatment, targeted adverse events, progression events and survival data were recorded every 3 months. Detailed clinical information was collected for all patients experiencing a GIP event. Effects of baseline risk factors on GIP risk were investigated using Cox proportional hazards regression.

Results: Of 1953 evaluable patients followed for a median of 20.1 months, 37 (1.9%) experienced GIP. Most GIP events were surgically managed with successful outcomes; four events were fatal. The majority of GIP events (26/37) occurred $\leqslant$6 months after starting bevacizumab (median, 3.35 months). Univariate and multivariate analyses showed that age $\geqslant$65 years was significantly associated with lower GIP risk. In multivariate analyses, intact primary tumour

* *Corresponding author.* Tel.: +1 310 206 3921; fax: +1 310 267 0151.
E-mail address: fkabbina@mednet.ucla.edu (F.F. Kabbinavar).
[f] On behalf of the BRiTE Investigators and Patients.

doi:10.1016/j.ejca.2012.02.052

and prior adjuvant radiotherapy were significantly associated with increased risk of GIP within 6 months after starting bevacizumab. A regression analysis that assessed the risk of GIP over time showed no cumulative risk associated with bevacizumab exposure.

Conclusion: The observed rate of GIP in this large, community-based experience was consistent with rates reported in RCTs. Most events were successfully managed with surgical intervention.

1. Introduction

Bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA), a recombinant humanised monoclonal antibody targeting vascular endothelial growth factor, is an antiangiogenic agent approved for the treatment of multiple solid tumours. In the first- and second-line treatment of metastatic colorectal cancer (mCRC), bevacizumab prolonged overall survival (OS) and progression-free survival when combined with fluorouracil (FU)-based chemotherapy regimens.[1–3] In two phase 3 trials of bevacizumab in mCRC, gastrointestinal perforation (GIP) was an uncommon but serious adverse event occurring at rates of 1.5% and 1.1%.[1,3]

Because GIP events in these randomised controlled trials (RCTs) were infrequent and patient follow-up was not longitudinal, the risk of experiencing a GIP over time with bevacizumab exposure and the contribution of potential risk factors are not well characterised. Moreover, patients selected for clinical trials likely differ from the general population of patients with mCRC.

BRiTE (Bevacizumab Regimens' Investigation of Treatment Effects), a prospective, observational cohort study (OCS) initiated when the US Food and Drug Administration approved bevacizumab for the first-line treatment of mCRC, was designed to explore clinical outcomes with bevacizumab-based therapy in a community or 'real-world' cohort of patients, including the incidence, clinical course and potential risk factors associated with uncommon but serious adverse events, such as GIP. Baseline patient characteristics and clinical outcomes in BRiTE have been published previously.[4,5] Here we report a protocol-specified analysis that examined risk factors and long-term outcomes associated with GIP in BRiTE, including analyses of timing and potential associations with known risk factors.

2. Patients and methods

2.1. Study design and patients

Details of the study design were reported previously.[4,5] In brief, this prospective OCS followed patients with metastatic or locally advanced and unresectable colorectal cancer receiving bevacizumab with initial chemotherapy. No other eligibility requirements were specified. Chemotherapy regimens, dose, duration of bevacizumab treatment and any tumour assessments were at the physician's discretion.

2.2. Data collection

Patient data were recorded at baseline and then quarterly until study completion, patient death, withdrawal of consent, loss to follow-up or study data cutoff (15th October 2008), whichever occurred first. Prespecified potential baseline risk factors for GIP, including intact primary tumour, sigmoidoscopy or colonoscopy within 1 month preceding the start of bevacizumab administration, recent major surgery, prior adjuvant radiotherapy, chronic use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and a history of peptic ulcer disease or diverticulosis were recorded. At follow-up, sites were required to answer the following question with a 'yes' or 'no': Has the patient experienced a GIP event? If the response was 'yes', information on the event onset and resolution dates, suspected cause, change in bevacizumab treatment and additional GIP risk factors were collected. Potential GIP events, based on Common Terminology Criteria for Adverse Events (v. 3.0),[6] were reviewed clinically to ensure identification of all events and to distinguish multiple events from the continuation of a single event.

2.3. Statistical analysis

All patients who received at least one dose of bevacizumab and for whom safety data were collected were included in the analysis. Baseline patient and disease characteristics were summarised using descriptive statistics. The number and corresponding rate of GIP events were determined for the overall BRiTE sample and for patients with predisposing risk factors at baseline.

The effects of baseline risk factors on the length of time to first GIP event were investigated using Cox proportional hazards regression. Patients without a GIP event were censored at the time of death, study discontinuation, study data cutoff or 90 days after receiving the last bevacizumab dose, whichever occurred first. Risk factors examined included Eastern Cooperative Oncology Group (ECOG) performance status, age, chronic aspirin (>325 mg) or NSAID therapy, peptic ulcer disease requiring medication, known diverticulosis, intact primary tumour, sigmoidoscopy or colonoscopy