EUROPEAN JOURNAL OF CANCER 48 (2012) 475–481

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Safety of bevacizumab in metastatic breast cancer patients undergoing surgery

Javier Cortés [a,*], *Mireia Caralt* [b], *Suzette Delaloge* [c], *Hernan Cortes-Funes* [d], *Jean-Yves Pierga* [e], *Kathleen I. Pritchard* [f], *David T. Bollag* [g], *David W. Miles* [h]

[a] *Department of Oncology, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain*
[b] *Department of Hepatobiliopancreatic Surgery and Transplants, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain*
[c] *Breast Oncology Department, Institut Gustave Roussy, Villejuif Cedex, France*
[d] *Medical Oncology Division, '12 de Octubre' University Hospital, Madrid, Spain*
[e] *Department of Medical Oncology, Institut Curie, Université Paris Descartes, Paris, France*
[f] *Sunnybrook Odette Cancer Centre and the University of Toronto, Toronto, Canada*
[g] *Department of Clinical Research, Division of Oncology & Hematology, F. Hoffmann-La Roche Ltd., Basel, Switzerland*
[h] *Breast Unit, Mount Vernon Cancer Centre, Middlesex, United Kingdom*

ARTICLE INFO

Article history:
Available online 22 December 2011

Keywords:
Bevacizumab
Breast neoplasms
Surgery
Safety
Haemorrhage
Wound-healing complications

ABSTRACT

Background: Evaluate the safety of surgery in relation to bevacizumab in the first-line treatment of metastatic breast cancer (mBC) in two international trials.

Patients and methods: The incidence, type and timing of post-surgical bleeding events and wound-healing complications were assessed in surgical patients in the AVastin And DOcetaxel (AVADO) (NCT00333775) and Avastin THErapy for advaNced breAst cancer (ATHENA) (NCT00448591) trials. Both study protocols followed recommendations to withhold bevacizumab for at least 6 weeks before elective surgery and to wait 28 days (or until the wound was fully healed) after major surgery before recommencing bevacizumab therapy.

Results: In AVADO, 221 surgical procedures (55 major, 166 minor) were performed in 155 patients. In ATHENA, 1190 surgical procedures (435 major, 755 minor) were performed in 672 patients. One bevacizumab-treated AVADO patient (0.9%) who underwent surgery experienced a grade 3 bleeding event. In ATHENA, six patients (0.9%) who underwent surgery experienced grade 3 bleeding events and one patient (0.1%) experienced a grade 4 bleeding event. No grade 5 bleeding events in patients undergoing surgery were reported in either study. One grade 3 wound-healing complication was reported in each of the AVADO arms: placebo ($n = 46$, 2.2%), bevacizumab 7.5 mg/kg ($n = 57$, 1.8%) and bevacizumab 15 mg/kg ($n = 52$, 1.9%). Incidence of grade 3–4 wound-healing complications in ATHENA was 2.2% and 1.3% in patients undergoing minor or major surgery, respectively.

Conclusions: Surgery can be performed on patients with mBC undergoing bevacizumab therapy with a low risk of severe bleeding or wound-healing complications post surgery, if current labelling recommendations are adhered to.

* *Corresponding author:* Tel.: +34 948 296696; fax: +34 948 255500.
E-mail address: jacortes@vhebron.net (J. Cortés).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.11.021

1. Introduction

Bevacizumab (Avastin®; F. Hoffmann-La Roche Ltd.), a recombinant humanised monoclonal antibody that blocks the activity of vascular endothelial growth factor (VEGF),[1] has demonstrated significant clinical benefit in several solid tumours.[2–8] In combination with other agents as a first-line therapy, bevacizumab has prolonged progression-free survival (PFS) and increased response rates in patients with locally recurrent (LR) or metastatic breast cancer (mBC).[3–6,9] In the Eastern Cooperative Oncology Group 2100 (E2100) trial, bevacizumab plus weekly paclitaxel increased the median PFS from 5.8 to 11.4 months (hazard ratio [HR] 0.42, $p < 0.0001$) in patients who had received no previous chemotherapy for LR or mBC[3,6]; which was confirmed by an independent review (5.8 versus 11.3 months, HR 0.48, $p < 0.0001$).[6] In the placebo-controlled AVastin And DOcetaxel (AVADO) trial (BO17708), bevacizumab 15 mg/kg plus docetaxel significantly increased PFS versus placebo plus docetaxel (10.0 versus 8.1 months, respectively, stratified analysis: HR 0.67, $p = 0.0002$) and overall response rates (46% [placebo] versus 64%; $p = 0.0003$).[4,5] The phase III, Regimens In Bevacizumab for Breast Oncology (RIBBON-1) study of bevacizumab combined with taxanes, anthracyclines or capecitabine, also met its primary end-point of improved PFS with combination therapy versus chemotherapy plus placebo.[9]

Soft-tissue and vascular toxicities have been observed in patients undergoing major surgery while receiving bevacizumab.[10,11] VEGF is a key mediator of angiogenesis and tumour progression,[12,13] and likely plays multiple roles in normal wound-healing, inducing angiogenesis and stimulating epithelialisation and collagen deposition.[14] VEGF inhibition may therefore impair or delay wound-healing, or result in bleeding; a consideration when performing routine and emergency surgery in patients with mBC. Given bevacizumab's long elimination half-life (18–20 days)[15] effects may persist despite treatment discontinuation during the pre-operative period. Current labelling recommends that bevacizumab is withheld for elective surgery, and that treatment is delayed for at least 28 days after major surgery or until the wound has fully healed.

Results from large, international trials including the phase III AVADO and phase IIB Avastin THErapy for advaNced breAst cancer (ATHENA) studies have confirmed the general safety of bevacizumab as a first-line treatment option for mBC.[3–5,9,16] As a proportion of patients in these trials underwent major or minor surgery as part of their ongoing cancer care, we report safety data for patients with mBC receiving bevacizumab in the surgical setting in AVADO and ATHENA.

2. Methods

Two large, international, multicentre studies, AVADO and ATHENA, were included in this analysis. The study methods, including patient eligibility criteria, study design, treatment and assessments, have been reported previously.[4,16]

AVADO was a randomised, double-blind, placebo-controlled, phase III trial that investigated bevacizumab in combination with first-line docetaxel chemotherapy in patients with LR or mBC.[4] From March 2006 to April 2007, 736 patients in 24 countries received docetaxel 100 mg/m^2 every 3 weeks (q3w; maximum nine cycles) plus either placebo or bevacizumab (7.5 or 15 mg/kg q3w). The primary end-point was PFS, and secondary end-points included safety.

ATHENA was a single-arm trial that evaluated the safety of bevacizumab combined with first-line taxane-based (or other non-anthracycline) chemotherapy for LR or mBC.[15] Between September 2006 and June 2008, 2251 patients were recruited from 37 countries. Patients received bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg q3w plus a taxane (either alone or with other chemotherapy) or other non-anthracycline chemotherapy. The primary study end-point was safety, with particular emphasis on the incidence of serious adverse events (SAEs) and adverse events (AEs) of special interest with bevacizumab.

Minor surgery included any surgical procedure not involving general anaesthesia (local or regional anaesthesia permitted) or respiratory assistance. Major surgery included any surgical procedure involving anaesthesia or respiratory assistance; all operations involving opening body cavities or in which severe haemorrhage was possible; all potentially life-threatening conditions; and any procedure with the potential to induce permanent anatomic (physical) or physiological impairment and/or associated with orthopaedics or extensive tissue dissection.

Both studies excluded patients who had undergone major surgery, including open biopsy, within 28 days, or minor surgery within the previous 24 h at the time of randomisation. During the study, bevacizumab (or placebo in the blinded AVADO study) was withheld for at least 6 weeks (two half lives) before elective surgery. Both study protocols recommended waiting 28 days (or until wound fully healed) from major surgery to recommencement of therapy; no guidance was given for minor surgery. If necessary, it was recommended that emergency surgery be performed without delay after a careful risk–benefit assessment.

The incidence, type and timing of post-surgical bleeding events and wound-healing complications (WHC) were assessed in all patients who underwent surgery in ATHENA and AVADO. AEs were categorised by MedDRA (version 10.1) and AE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.[17] In general, the NCI-CTCAE grades are: Grade 1 Mild AE, Grade 2 Moderate AE, Grade 3 Severe AE, Grade 4 Life-threatening or disabling AE, Grade 5 Death related to AE. Specific details associated with grading of WHC and bleeding events are in the NCI-CTCAE guidelines.[17]

3. Results

3.1. *Types and number of procedures performed*

A total of 221 major or minor surgical procedures were performed on 155 patients in AVADO, including those in the control group (87 procedures in the bevacizumab 7.5 mg/kg arm, 74 in the bevacizumab 15 mg/kg arm) (Table 1). In ATHENA, 1190 surgical procedures (435 major, 755 minor) were performed in 672 patients. Table 2 summarises the most common procedures in this study.