Title

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Journal

Journal of the National Cancer Institute, 109(11)

ISSN

0027-8874

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Publication Date

2017-11-01

DOI

10.1093/jnci/djx067

Peer reviewed

JNCI J Natl Cancer Inst (2017) 109(11): djx067

doi: 10.1093/jnci/djx067
First published online May 22, 2017
Editorial

EDITORIAL

Microvascular Density as a Predictive Biomarker for Bevacizumab Survival Benefit in Ovarian Cancer: Back to First Principles?

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Vascular endothelial growth factor–A (VEGF-A) is a key regulator of physiological and pathological angiogenesis (1). Following promising preclinical data showing growth inhibition in multiple tumor xenograft models, a murine anti-VEGF-A monoclonal antibody was humanized to enable clinical trials in cancer patients (2). This humanized antibody, known as bevacizumab, was first approved by the US Food and Drug Administration (FDA) for previously untreated metastatic colorectal cancer in 2004, after a phase III trial that showed that bevacizumab plus chemotherapy increased both progression-free survival (PFS) and overall survival (OS) relative to chemotherapy alone (3). These benefits were seen despite the lack of a biomarker to select patients most likely responsive to the treatment (3). To put this in perspective, a very effective therapeutic like trastuzumab would have required a much larger trial to demonstrate benefits in the absence of selection of breast cancer patients for human epidermal growth factor receptor 2 (HER2) overexpression (4). Bevacizumab has been tested in numerous tumor types and today is FDA approved in multiple indications (5), including metastatic cervical cancer (6), platinum-resistant ovarian cancer (7), and, most recently, platinum-sensitive, recurrent ovarian cancer (http://www.roche.com/media/store/releases/med-cor-2016-12-07.htm). However, not all studies have demonstrated an OS benefit. While this may be attributed, at least in part, to patient crossover from the control group to bevacizumab or other treatment groups, it is clear that the response to bevacizumab and other anti-VEGF agents has been heterogeneous (5).

Although a number of predictive biomarkers for bevacizumab and other VEGF pathway inhibitors have been suggested on the basis of small patient series, including hypertension, tumor imaging, soluble VEGF receptors, circulating proinflammatory cytokines, or gene signatures, none has been prospectively validated yet [reviewed in (5,8)]. This difficulty might also reflect the complexity of the angiogenesis process, which is influenced by multiple players within the microenvironment, as compared with tumor-intrinsic changes such as oncogene mutations or amplifications (5).

An additional level of complexity—and potentially a confounder—is represented by the use of cytotoxic agents in conjunction with anti-VEGF therapy. In fact, several cytotoxic agents (including paclitaxel) have been shown to have antivascular effects (9), and rebound angiogenesis, mediated by mobilization of myeloid cells, has been reported to be a mechanism of tumor resistance to certain cytotoxics (10).

It has been speculated that most of the benefits of anti-VEGF therapy derive from facilitating tumor delivery of cytotoxic agents through "normalization" of the vasculature (11). However, preclinical studies have clearly shown single-agent activity of VEGF inhibitors in a variety of tumor models (12), including ovarian cancer models. An early study reported that monotherapy with an anti-VEGF antibody resulted in suppression of angiogenesis and growth of human ovarian cancer cells implanted in immunodeficient mice (13). This study also emphasized the importance of long-term VEGF inhibition because interruption of the antibody treatment resulted in resumption of tumor growth as well as ascites formation (13). A more recent study by Mabuchi et al. went further, showing that while combination of bevacizumab with chemotherapy improved survival of mice implanted with ovarian cancer cells relative to chemotherapy alone, the greatest benefit was observed in the group that received long-term "maintenance" with single-agent bevacizumb after the administration of bevacizumab plus chemotherapy (14).

The Gynecological Oncology Group (GOG)-218 study, by virtue of its innovative design, is an important study in anti-angiogenesis. Over 1200 patients with newly diagnosed stage III

Received: March 7, 2017; **Accepted:** March 17, 2017

and IV ovarian cancer were randomly assigned to three groups (15). All three groups included paclitaxel and carboplatin for cycles 1 through 6. The control treatment was chemotherapy with placebo added in cycles 2 through 22. Bevacizumab initiation treatment was chemotherapy with bevacizumab (15 mg/kg every three weeks) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Bevacizumab throughout treatment was chemotherapy with bevacizumab added in cycles 2 through 22. Interestingly, bevacizumab throughout was the only treatment group that had a statistically and biologically significant improvement in PFS, the primary end point of the trial. The increase was four or six months, depending on how PFS was evaluated (15). A parallel randomized phase III study, ICON7, also tested a "maintenance" arm, but the dose of bevacizumab was lower (7.5 mg/kg every three weeks) and the improvement in PFS was of lesser magnitude compared with GOG-218, suggesting a dose dependence (16). However, in spite of the improvement in PFS, no statistically significant OS improvement was seen in GOG-218, although crossover from the chemotherapy-alone arm to bevacizumab-containing therapy (or other treatment lines) might have potentially masked an effect on OS.

Bais et al. (17) sought to evaluate potential tumor biomarkers from patients in the GOG-218 study. Nine hundred and eighty patients (78.5% of the patients that were enrolled in the trial) were evaluable. Candidate biomarkers were assessed by immunohistochemistry (IHC) after completion of the clinical trial using sections taken from the pretreatment tumor samples. The authors found that while no prognostic or predictive associations were observed for cMet, Neuropilin-1, and VEGFR-2, tumor-VEGF was associated with OS, although not with PFS. Intriguingly, the marker that showed the strongest association with clinical benefit was microvascular density (MVD). The effects of bevacizumab treatment on both PFS and OS were greater in patients with higher MVD in tumor sections. Although the analysis by Bais et al. is retrospective, it was prespecified (17).

The study by Bais et al. is important and, if confirmed, is likely to have a major impact in the design of future trials. It represents possibly the largest biomarker study in anti-angiogenesis to show a statistically significant association with benefit, including OS. However, previous studies did not identify MVD as a predictive marker of bevacizumb benefit. For example, Jubb et al. (18) retrospectively evaluated several potential predictive biomarkers, including MVD, from a randomized colorectal cancer study (3) but did not find any correlation with treatment outcomes. However, the samples analyzed accounted for only a fraction of the patients enrolled in the trial (18). Also, in the samples from the GOG-218 trial, MVD was assessed by CD31 IHC (17), while in the study by Jubb et al. it was assessed by CD34 IHC (18), although it is unknown whether this difference may have affected the outcome. It is also possible that the design of GOG-218 may have enabled assessment of markers of bevacizumab outcomes with greater fidelity than other studies because the group that showed benefit received single-agent bevacizumab for the majority of the trial, thus reducing the aforementioned potential confounding effects of chemotherapy. Alternatively, one cannot rule out the possibility that biomarkers predictive of bevacizumab outcomes may be tumor type specific, as suggested for glioblastoma multiforme (19).

The actions of VEGF are complex, and recent studies have emphasized, for example, effects on the immune system that could have not been adequately evaluated in studies conducted in immunodeficient mice (20). Nevertheless, it is refreshing that endothelial cells, the main target of VEGF, are back at the center stage. Previous studies showed a correlation between MVD and malignant behavior in human tumors (21), and preclinical studies directly showed a correlation between inhibition of tumor growth by an anti-VEGF antibody treatment and suppression of angiogenesis (22). Intuitively, patients with tumors having the highest MVD and/or VEGF content are expected to derive the greatest benefit from anti-VEGF therapy.

Note

The author has no conflicts of interest to disclose.

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