Bevacizumab for Advanced Breast Cancer: Hope, Hype, and Hundreds of Headlines

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Key Words. Media • Health services • Bevacizumab • Breast cancer • Drug funding

Learning Objectives

Summarize findings regarding the media's portrayal of bevacizumab with each phase of therapeutic development.

Identify media sources of information about bevacizumab in each phase of therapeutic development.

ABSTRACT

Introduction. On February 22, 2008, the Food and Drug Administration granted accelerated approval for the use of bevacizumab (Avastin) in metastatic breast cancer. Based on subsequent clinical trials, this approval was revoked on November 18, 2011. In this study, we categorize and analyze the newspaper reports related to bevacizumab's use in advanced breast cancer.

Methods. Using the Factiva media database, we reviewed all newspaper reports published in North America from January 4, 2002, to January 4, 2013, containing the words "breast cancer" and "Avastin," or "bevacizumab." Articles were classified as pre-approval (January 4, 2002–February 21, 2008), approval (February 22, 2008–November 17, 2011), or post-approval loss (November 18, 2011–January 4, 2013). Information regarding benefits, side effects, costs, interview-

ees, and article tone and theme were abstracted from each article by two independent reviewers. Differences among the three study phases were compared using the chi square analysis.

Results. A total of 359 articles met study inclusion criteria. The number of reports having a positive headline tone and/or positive article tone declined with each study period. The proportion of articles discussing side effects and financial costs increased, whereas those discussing efficacy decreased with each study period. Drug representatives were most likely to be quoted in newspaper articles prior to bevacizumab's approval.

Conclusion. Media reports are a common source of medical information for patients, practitioners, and policy makers. We observed substantial fluidity of media reports over time. *The Oncologist* 2013;18:1174–1179

Implications for Practice: Drug development is a complex process involving patients, researchers, drug representatives, advocacy groups, and physicians. The media provides a forum whereby these groups can discuss health care issues. Patients ask physicians about medical information they read in newspaper articles. Our study revealed that the content and tone of newspaper articles about bevacizumab varied with time. Drug representatives were most often quoted prior to bevacizumab's approval. Patients and physicians should be mindful of media reports and their quoted sources. Physicians should note the fluidity of media reports and remind their patients that they are neither written nor reviewed by medical professionals.

INTRODUCTION

On February 22, 2008, the U.S. Food and Drug Administration (FDA) approved the use of bevacizumab in combination with paclitaxel for the treatment of HER-2/neu-negative metastatic breast cancer. The approval, issued by the FDA's Center for Drug Evaluation and Research, was granted through the accelerated drug approval process. This process allows drugs

that treat life-threatening conditions to receive expedited approval based on a surrogate endpoint. In the case of bevacizumab, the surrogate endpoint was progression-free survival. Paclitaxel plus bevacizumab significantly prolonged progression-free survival, yet provided no overall survival benefit compared with paclitaxel alone in the landmark trial E2100 [1].

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Table 1. Article themes

Theme	Determination	Example
Benefits/efficacy	The majority of the article discussed the benefits of bevacizumab	"Trials of bevacizumab demonstrated a 5 1/2-month delay in the growth of metastatic breast cancer tumors."
Side effects	The majority of the article discussed the side effects of bevacizumab	"Bevacizumab should no longer be used since it causes dangerous side effects including..."
Lack of efficacy	The majority of the article discussed bevacizumab's lack of efficacy	"Bevacizumab provided little or no benefit..."
FDA approval	The majority of the article discussed the approval of bevacizumab	"...Food and Drug Administration (FDA) approval of bevacizumab to treat breast cancer."
Loss of approval	The majority of the article discussed bevacizumab's loss of approval	"...an FDA panel voted to revoke approval of a popular treatment." (bevacizumab)
Cost	The majority of the article discussed the cost of bevacizumab	"...bevacizumab in the U.S. costs up to \$56,000, and such findings are certain to raise questions about whether the benefit is worth the price."

Abbreviation: FDA, U.S. Food and Drug Administration.

The accelerated approval granted for bevacizumab was contingent on two follow-up studies to verify the clinical benefit: Randomised, Double-Blind, Placebo-Controlled, Study of Bevacizumab Plus Docetaxel Compared with Placebo Plus Docetaxel for the First-Line Treatment of Locally Recurrent or Metastatic Breast Cancer (AVADO) and Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Chemotherapy With or Without Bevacizumab for First-Line Treatment of Human Epidermal Growth Factor Receptor 2-Negative, Locally Recurrent or Metastatic Breast Cancer (RIBBON-1). As neither study demonstrated a clinical benefit significant enough to warrant the combination therapy of bevacizumab and chemotherapy [2, 3], the FDA revoked approval of bevacizumab in November 2011.

The initial approval and subsequent loss of approval of bevacizumab garnered a considerable amount of attention in the print media, namely newspapers. Newspapers, unlike the scientific literature, lack peer review or formalized methodology for reporting scientific results. Not surprisingly, scientific information portrayed by newspapers can vary significantly in terms of accuracy, quality, and completeness [4–6]. Newspapers also tend to focus on certain diseases and illnesses more than on others. Breast cancer, for example, often receives a great amount of media attention compared with other cancers [7, 8].

The effect the media has is complex and can influence patients [9, 10], physicians [4, 11–14], and possibly policy makers [15–17]. The objective of our study was to categorize and analyze the newspaper reports surrounding bevacizumab's use in metastatic breast cancer and to assess whether the nature of this reporting varied with time.

METHODS

Sampling

To develop a representative sample of newspaper articles, we used the Factiva news media database. Factiva is updated daily and archives newspaper articles from approximately 1,100 newspapers across North America. We reviewed all newspaper reports in the United States and Canada from January 4, 2002, to January 4, 2013. January 4, 2002, marked the start of the E2100 trial. We included the search terms "breast

cancer" and "Avastin" or "bevacizumab" and limited our search to North American newspapers. The exclusion criteria included letters to the editor, articles where the full article was not available, articles pertaining to solely financial reports, articles discussing bevacizumab where breast cancer was not the main focus (i.e., lung cancer), articles not pertaining to bevacizumab, and articles pertaining to the use of bevacizumab in the neoadjuvant setting. Articles were categorized into one of three time periods: pre-approval (January 4, 2002–February 21, 2008), approval (February 22, 2008–November 17, 2011), and post-approval loss (November 18, 2011–January 4, 2013).

Coding Variables

Each article was read and coded by two independent reviewers (C.F., M.R.) trained in the technique of content analysis and coding as described previously [18]. Each reviewer worked from a codebook outlining the details for data extraction. The codebook was developed using guidelines discussed in previous articles [18–20]. The codebook was pretested by three separate reviewers (M.F., M.R., C.F.) using a data set of 30 articles on bevacizumab for ovarian cancer [18].

Sampled articles were coded for the following variables: article identification number, publication date, publication name, and article type. In addition to identification codes, several descriptive codes were assigned to each article, including article theme (Table 1), headline tone, and article tone. Article themes were preselected and agreed on by two independent reviewers (M.F., M.B.) after a random sample of 15 articles from each time period was reviewed in detail. Only one theme could be selected for each article. The theme of each article was chosen based on the majority of the article's content. The mention of side effects, benefits, lack of benefits, and cost was also recorded for each article in a binary fashion (i.e., noted or not noted). Parties quoted in each article were also recorded and divided into the following groups: medical doctor, patient, drug company representative, and cancer advocate.

Article tone was coded as positive, negative, or neutral toward the use of bevacizumab for metastatic breast cancer, according to previously validated methodology [19]. This methodology first analyzes the content of the headline and

Table 2. General characteristics and article themes for each time period

Article characteristic	Pre-approval (n = 78)	Approval (n = 222)	Loss of approval (n = 59)
American newspaper	97%	94%	66%
Type			
News story	94%	91%	93%
Editorial	7%	9%	7%
Doctor's column	0	0	0
Other	0	0	0
Theme			
Bevacizumab benefits/efficacy	45%	8%	9%
Bevacizumab side effects	0	4%	2%
Lack of efficacy	0	5%	2%
U.S. Food and Drug Administration approval	41%	14%	3%
Loss of approval	3%	58%	83%
Cost	12%	12%	2%

Because of rounding, some values may not total 100%.

then the article content. Coding headline tone was relatively simple because headlines consist of short and easily interpretable phrases. Headline tone was recorded as positive, negative, neutral, or not applicable. Classifying the tone of the article was more difficult because of the quantity and complexity of information contained in the body of the article. Applying the methodology of Brodie et al., the tone of individual sentences was assessed by quantifying the number of positive and negative interpretations (or assertions) noted by the author of the article, the number of quotations from individuals interviewed, and the number of facts highlighted within the article [19]. The overall tone was determined by totaling the number of positive and negative instances, with headlines given double weight. If the ratio was 1:2 (positive:negative) or greater, the overall tone was coded as negative; if the ratio was 2:1 (positive:negative) or greater, it was coded as positive. When the ratio was less than 2:1, the article tone was considered neutral [19].

Data Analysis and Coder Reliability

The primary author was responsible for applying the study exclusion criteria, with the other authors available wherever ambiguity or uncertainty arose. Authors C.F. and M.R. coded all of the articles independently. Inter-coder reliability was determined using Cohen kappa calculated using the entire data set. A kappa value greater than 0.8 was considered acceptable [19]. Where disagreement arose, a third reviewer (M.F.) provided the final decision on the variable in question. Comparisons among study periods were made using the chi square analysis.

RESULTS

General Characteristics

Our search strategy yielded 884 articles, of which 359 (41%) met study criteria. Excluded articles included articles not on breast cancer (42%), financial reports (31%), articles not pertaining to bevacizumab (8%), articles where the full text was not available (7%), letters to the editor (7%), and neoadjuvant articles (5%). The percentage of articles excluded is consistent with previous content analysis studies using newspaper data-

bases [17, 20, 21]. Of the articles, 22% were from the pre-approval time period, 62% were from the approval period, and 16% were from the loss of approval time period. The vast majority of all articles were news stories from American newspapers (Table 2).

Article Themes

The two most common pre-approval themes were bevacizumab benefits/efficacy and FDA approval (Table 2). This differed from the approval time period, in which articles most commonly focused on either loss of approval or FDA approval. Articles published during the loss of approval time period mainly discussed, not surprisingly, loss of approval. Inter-coder reliability for theme was acceptable.

Article and Headline Tone

Article tone was assessed according to whether the article supported the use of bevacizumab for metastatic breast cancer (Table 3). Positive headline tone (36%, 18%, 9%; $p = .0002$) and/or positive article tone (42%, 19%, 15%; $p < .0001$) varied significantly over the study periods (Table 3). Inter-coder reliability for both article and headline tone were acceptable (Table 4).

Other Characteristics

The proportion of articles discussing the side effects of bevacizumab increased over the three study periods (25%, 49%, 58%; $p = .0002$) (Table 3). The proportion of articles discussing the efficacy of bevacizumab decreased (82%, 59%, 20%; $p < .0001$), and explicit statements regarding the lack of efficacy of this therapy increased substantially over the study period (23%, 57%, 56%; $p < .0001$). The proportion of articles discussing the financial cost of bevacizumab increased over time (19%, 46%, 40%; $p = .0001$). After initial FDA approval, fewer representatives from the pharmaceutical industry were quoted (33%, 23%, 11%; $p = .014$). Inter-coder reliability was considered acceptable for all of the article characteristics with the exception of lack of efficacy (Table 4).

Table 3. Article characteristics including benefits, side effects, costs, and parties quoted for each time period

Article characteristic	Pre-approval (n = 78)	Approval (n = 222)	Loss of approval (n = 59)	p
Headline tone				
Positive	36%	18%	9%	.0002
Negative	32%	34%	53%	
Neutral	17%	28%	15%	
Not applicable	15%	19%	23%	
Article tone				
Positive ^a	42%	19%	15%	<.0001
Negative	26%	41%	72%	
Neutral	32%	40%	25%	
Article characteristics				
Side effects noted	24%	50%	58%	.0002
Efficacy noted	82%	59%	20%	<0.0001
Lack of efficacy noted	23%	57%	56%	<.0001
Doctor quoted	22%	28%	36%	.20
Patient quoted	12%	19%	11%	.19
Advocate quoted	8%	19%	8%	.02
Drug representative quoted	33%	24%	11%	.014
Cost noted	19%	46%	40%	.0001
High cost noted	17%	39%	34%	.001

Statistical analysis completed using chi-square analysis.

^aPositive tone was compared with other tone (i.e., all other possible options).

Table 4. Inter-rater reliability scores

Variable	Cohen kappa	Standard error (95% confidence interval)
Article type	0.85	0.02 (0.82–0.88)
Article theme	0.79	0.03 (0.75–0.85)
Headline tone	0.84	0.02 (0.79–0.87)
Article tone	0.80	0.02 (0.78–0.82)
Side effects	0.88	0.03 (0.83–0.93)
Efficacy	0.91	0.02 (0.87–0.95)
Lack of efficacy noted	0.75	0.03 (0.68–0.81)
Doctor quoted	0.95	0.02 (0.92–0.98)
Patient quoted	0.89	0.03 (0.82–0.94)
Advocate quoted	0.94	0.02 (0.89–0.99)
Drug representative quoted	0.92	0.02 (0.87–0.97)
Cost noted	0.98	0.01 (0.95–0.99)
High cost noted	0.90	0.023 (0.87–0.95)

n = 359 articles.

DISCUSSION

Our study systematically analyzed 11 years of newspaper reports from across North America related to the use of bevacizumab for metastatic HER-2/neu-negative breast cancer. We found that article and headline tone was less likely to be positive and that articles tended to increasingly focus on the side effects and financial cost of bevacizumab with each subsequent time period. Interestingly, drug company representatives were most likely to be quoted prior to bevacizumab's approval, yet the relative frequency of other key stakeholders

(i.e., patients, doctors) did not vary significantly among time periods.

Our study demonstrated that during the pre-approval study period, the mass media reports tended to slant toward having a positive view of the drug's efficacy and benefits. Previous research has pointed to mass media having a positive bias toward reporting a drug or health technology's benefits during early stages of its development [4, 22]. There may be a number of reasons for this trend. Journalists may be influenced by marketing strategies from pharmaceutical companies to increase product awareness. Additionally, the media may capitalize on emotive aspects of an issue as a means to increase readership—emphasizing the potential of a new treatment for cancer would help sustain newsworthiness.

Overly positive reporting of health technologies early in their development is considered an indication of the unreliability and bias of health technology reporting in mass media [17, 23]. However, our research on bevacizumab shows that although media sources highlighted the drug's efficacy and benefits in the period before FDA approval, there was restraint in the overall reporting. For example, during the pre-approval period, approximately half of the articles expressed a non-positive tone (i.e., neutral or negative) in both the headline and the article body. The nuance in the media's reporting of bevacizumab may have been influenced by scientific data, including that of the E2100 trial, which was a key factor in the FDA's decision to award fast-track approval status to the drug in February 2008.

During the period of bevacizumab's FDA approval (February 22, 2008 to November 17, 2011) to when its approval status was revoked by the drug regulatory authority (November

18, 2011 to January 4, 2013), the media increased reporting of the drug's lack of efficacy, its side effects, and high cost. It appears that over the course of this period, journalists emphasized the lack of potential benefits of bevacizumab for those with breast cancer. The media explained and quantified the drug's potential harms as well as its high costs. Thus, starting in 2008, the narrative regarding bevacizumab changed significantly. This shift in the narrative coincided with the publication of the required follow-up clinical trials to E2100, AVADO and RIBBON-1 [3, 24]. Neither AVADO nor RIBBON-1 showed significant differences in overall survival, and both highlighted the serious adverse events associated with bevacizumab. Based on data from the AVADO and RIBBON-1 trials, the FDA revoked bevacizumab's approval. It appears that newspaper media sources had begun to note the scientific data from the AVADO and RIBBON-1 clinical trials, interpret it, and inform their readers in a timely fashion. Although previous research has discussed the unreliability and inaccuracies of news media in health technology reporting, this study showed the contrary. In the case of bevacizumab, mass media sources generally presented information to the public consistent with the scientific literature.

Drug development is a complex phenomenon and is shaped by interactions of diverse institutional actors—including pharmaceutical firms, the scientific community, the medical profession, patient advocacy groups, regulatory authorities, and insurance companies [25]. By including the perspectives of the various relevant actors, the media can provide a more complete picture of a particular medication in current clinical practice. As discussed above, our study findings suggest that news media accessed scientific data from clinical trials involving bevacizumab to inform its narrative regarding the drug's efficacy or lack thereof. Our data also show that the media turned to physicians, patients, cancer care advocates, and pharmaceutical company representatives to inform their reporting regarding bevacizumab. Although the views of these various groups are cited in mass media reports, their voices were not present with equal frequency during each time period. Notably, drug representatives were most likely to be quoted during the pre-approval time period, whereas neither doctors nor patients were more or less likely to be quoted in a specific study time period. Later in the study period, the medical community had the strongest presence in the media articles. This suggests that media may tend to emphasize social actors whose perspective best fits its particular chosen narrative, while potentially ignoring critical voices.

Several limitations of this study merit emphasis. First, our study focused on a single anticancer medication for a single cancer type, which limits the generalizability of our results. It would be interesting to see how media coverage varies among

different drugs and different cancer types. In addition, inherent to both content analyses and retrospective studies, our study was unable to discern cause from effect. For example, we observed that articles were more likely to discuss the cost of bevacizumab with each subsequent time period, but we cannot say with certainty that the cost of bevacizumab was a causal factor in its loss of approval. Finally, the media encompasses not only newspapers, but also blogs, tweets, podcasts, and many other forms of online communication, all of which disseminate information. Our study focused on newspaper reports because of the availability of the robust Factiva database; however, not including other forms of media likely underestimated the absolute effect the media has on drug development.

CONCLUSION

In summary, this study provides a descriptive account of more than 300 newspaper articles during three phases of bevacizumab's development. A key role of the print media is to provide the public with accurate, unbiased reporting on health matters in a timely manner. External factors, including the influence of the media, may contribute to drug policy decisions and patient care. The FDA's initial approval and subsequent revocation of approval of bevacizumab allowed us to assess the media's portrayal of bevacizumab with each phase of therapeutic development. Our data confirm the fluidity of media reports, with increasing emphasis on toxicity, lack of benefit, and financial cost of the drug over time.

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AUTHOR CONTRIBUTIONS

Conception/Design: Michael Fralick, Christopher M. Booth, Mark J. Clemons
Provision of study material or patients: Michael Fralick, Monali Ray, Christopher M. Booth, Mark J. Clemons
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DISCLOSURES

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