VOLUME 30 · NUMBER 28 · OCTOBER 1 2012

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Progress Against Solid Tumors in Danger: The Metastatic Breast Cancer Example

Javier Cortés, *Vall d'Hebron University Hospital; Medica Scientia Innovation Research, Academic Research Organization, Barcelona, Spain*
Emiliano Calvo, *South Texas Accelerated Research Therapeutics—Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain*
Antonio González-Martín, *Centro Oncológico MD Anderson International España, Madrid, Spain*
Shaheenah Dawood, *Dubai Hospital, Dubai Health Authority, Dubai, United Arab Emirates*
Antonio Llombart-Cussac, *Arnau de Vilanova Hospital, Valencia; Medica Scientia Innovation Research, Academic Research Organization, Madrid, Spain*
Leticia De Mattos-Arruda and Patricia Gómez, *Vall d'Hebron University Hospital, Barcelona, Spain*
Orlando Silva, *Sylvester Comprehensive Cancer Center, Miami, FL*
Edith A. Perez, *Mayo Clinic Cancer Center, Jacksonville, FL*
Hope S. Rugo, *University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*
Ana Lluch, *Hospital Clinico, Valencia, Spain*
Gabriel N. Hortobagyi, *The University of Texas MD Anderson Cancer Center, Houston, TX*

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In 2012, the estimated number of cancer diagnoses in the United States will exceed 1.6 million, with more than a half-million deaths.[1] In broad terms, the goals of treatment for patients with metastatic solid tumors are improving quality of life and overall survival (OS). From a regulatory standpoint, an improvement in OS is the gold standard for approval, but in some diseases and treatment settings, progression-free survival (PFS) is a valid surrogate end point. In fact, PFS has several important advantages: first, it is a timely end point that is reached before OS; second, it is well-known that disease control provides meaningful patient benefit[2]; and third, it is not affected by subsequent therapies. For example, for metastatic breast cancer (MBC), an increasing number of agents are available for use; thus, patients may receive multiple lines of therapy, and it is always possible that better and/or subsequent therapies will be administered to patients preferentially in one study arm, which creates imbalances that can affect OS but not PFS.

However, some aspects should be considered when PFS is the primary end point of clinical trials. First, it is important to highlight the importance of independent PFS assessments. Second, PFS does not capture any adverse impact of the initial treatment on the responsiveness and duration of response to subsequent therapies that could impact on OS. Third, although an association of PFS and OS has been seen for some malignancies, it has not been clearly demonstrated in others, like MBC.

Recently, the US Food and Drug Administration (FDA) announced its decision to revoke the approval of bevacizumab for MBC treatment resulting from concerns about safety, considering that bevacizumab does not appear to improve OS, after reviewing data from different randomized studies.[3-6]

Bevacizumab Activity in MBC and the FDA

One of the major criticisms of bevacizumab as a first-line treatment for MBC has been its lack of an OS benefit. However, in our opinion, a lack of evidence of OS benefit does not indicate that there is evidence of no OS benefit. Although evidence of no benefit suggests that the issue has been settled and the value of doing additional trials is limited, a lack of evidence of benefit does not suggest that we assume benefit until proven otherwise but rather that we continue to study the therapy with well-designed trials that allow a determination of whether benefit exists.

Three randomized phase III trials have assessed the benefit of bevacizumab in first-line therapy as assessed by PFS, the primary objective.[3,4,6] In all three trials, bevacizumab-based therapy significantly increased PFS, with hazards ratios (HRs) ranging from 0.48 to 0.69. None of these studies reported an increase in OS, but these studies were not designed to specifically answer that question and actually included some options that limited their ability to demonstrate such potential improvement. Moreover, when the FDA gave accelerated approval to bevacizumab in MBC, Genentech was required to submit data from two trials to provide verification of the treatment effect on PFS. The phase III Avastin and Docetaxel (AVADO) and Regimens in Bevacizumab for Breast Oncology (RIBBON1) trials reported HRs of 0.75. The FDA reviewed the trial designs and approved them or at least did not object to them. At no time did the FDA require a demonstrated OS benefit to convert from accelerated to full approval. This insidious change in rules appears to lack fairness.

A meta-analysis of these three studies concluded that bevacizumab improved PFS, with a HR of 0.64, and interestingly, this was observed in all patient subgroups.[7] As observed in the individual studies, no increase in OS was observed in the meta-analysis. However, it is unclear why a meta-analysis was used to evaluate differences in OS. In our opinion, this is another statistical pitfall. The objectives of meta-analyses include establishing statistical significance among studies with conflicting results, developing a more correct estimate of effect

magnitude, and examining subgroups with individual values that are not statistically significant. However, meta-analyses should not be used to draw conclusions for end points from primary clinical trials that were not designed to measure those end points. All of the confounding variables that affected OS in the three randomized clinical trials of bevacizumab as a first-line MBC therapy also affect the conclusions of the meta-analysis. In these trials, patients who progressed to bevacizumab/control might have received different treatment options. Moreover, it should be highlighted that a high number of patients received bevacizumab-based therapies in subsequent treatments. This is an example of a clear confounding variable for considering OS a good end point for these clinical trials because bevacizumab is known to improve PFS when administered in second-line therapy.[8] Moreover, recent findings indicate that some chemotherapeutic agents used in subsequent therapy might improve survival,[9] which could also affect OS when it was not the primary end point in first-line clinical trials. Nevertheless, a multivariate proportional hazard regression analysis considering cross-over as a time-dependent covariate in the bevacizumab trials would have been of great interest.

Finally, we believe that OS should not be considered appropriate as a sole primary end point in first-line MBC clinical trials. Broglio and Berry[10] addressed the importance of survival postprogression (SPP) in understanding treatment effects. Importantly, for clinical trials with a PFS benefit, the lack of statistical difference in OS does not suggest a lack of improvement in OS, particularly for diseases with long median SPPs, such as breast cancer, even if it is assumed that the experimental and control arms have equivalent SPPs. It is easy to understand that if a drug prolongs PFS, it also prolongs OS, although this has not been demonstrated by clinical trials. This is true, except cases in which deleterious effects occur when a drug therapy is stopped. It has been proposed that accelerated disease progression after the cessation of antiangiogenic agents might occur and explain why differences in PFS do not translate into differences in OS. Although this is undoubtedly debatable, this has not been observed with bevacizumab. A meta-analysis of five phase III studies in different tumor types did not find an increase in tumor progression when bevacizumab therapy was stopped prematurely for reasons others than progressive disease.[11]

Having said that, it has been argued that, even if PFS is accepted as a measure of meaningful clinical benefit, trials should be powered for OS as well, to ensure that the risks do not exceed the benefits because of the ability of OS to capture disease-related events as well as fatal adverse events.[12]

It is clear that the survival of patients with MBC has improved in recent decades.[13] Excluding eribulin, no agent has increased survival in anthracycline- and taxane-pretreated patients with MBC. However, in the mid-2000s, chemotherapy-based clinical trials of first-line therapy in patients with MBC reported a median OS of 12 to 20 months,[14,15] and OS commonly exceeded 2 years in clinical trials published last year.[4,6] How is it possible to observe a median OS exceeding 2 years if no single agent has improved OS? Many of the strategies that prolong PFS may also prolong survival, although as previously mentioned, this has not been demonstrated in clinical trials. Only with specific clinical trials of late-line therapies in which SPP is short can improvements in PFS translate into improvements in OS.[9]

Different Drugs: Similar Results but Different Conclusions

The FDA has initiated reversal of its approval of bevacizumab, partly because of a lack of demonstrated OS improvement. Will the FDA reverse the approval of other drugs that did not increase OS? OS is the optimal end point for some tumor types, but it is not optimal for MBC and other tumor types. In pancreatic cancer, for example, modest increases in PFS have translated into improvements in OS.[16] Nevertheless, survival outcomes are beginning to change when SPP is prolonged. The FDA recently approved everolimus, an oral inhibitor of mammalian target of rapamycin, for patients with advanced pancreatic neuroendocrine tumors. The pivotal trial randomized patients with advanced, low-grade intermediate-grade pancreatic neuroendocrine tumors to receive either everolimus or placebo.[17] The median PFS was 11.0 months with everolimus and 4.6 months with placebo, with a rarely observed HR of 0.35 (95% CI, 0.27 to 0.45; $P < .001$). However, the HR for OS was 1.05 (95% CI, 0.71 to 0.59; $P = .59$). The prolonged survival and the fact that everolimus was offered after progression in patients who were randomly assigned to receive placebo might explain why differences in OS were not observed.

Human epidermal growth factor receptor 2 (HER2) –positive breast cancer prognosis has dramatically changed since trastuzumab was approved. Recently, lapatinib, a tyrosine kinase inhibitor that targets HER2, has been approved for the treatment of previously trastuzumab-pretreated MBC. Patients who were randomly assigned to receive lapatinib and capecitabine had a statistically and clinically meaningful increase in PFS with respect to patients who received capecitabine alone.[18] However, no increase in OS was demonstrated. In a similar trial, patients with trastuzumab-resistant, HER2-positive MBC benefited if trastuzumab was maintained in second-line therapy, but no increase in OS was observed.[19] Does it mean that we should withdraw anti-HER2 therapies if patients fail to respond to trastuzumab? Moreover, patients with HER2- and hormone receptor–positive tumors treated with aromatase inhibitors should also be treated with anti-HER2 therapies. As observed in other studies, despite the important improvement in PFS when lapatinib or trastuzumab was added to hormonal therapy, an OS benefit was not demonstrated. Interestingly, median OS exceeded 2 years in both trials, and most patients received anti-HER2 therapies in second-line therapy.[20,21]

Treatment with aromatase inhibitors in postmenopausal women with hormone receptor–positive cancer is the standard first-line treatment across the world. PFS was significantly increased in most phase III trials when compared with tamoxifen therapy, but no increase in OS was observed.[22] However, the role of aromatase inhibitors in this setting is unquestionable.

Bevacizumab Toxicity in MBC and the FDA

Toxicity profile issues have also been considered by the FDA regarding the reversal of the approval of bevacizumab. Dozens of chemotherapeutics have been approved for the treatment of cancer, and most of them have well-established adverse events (ie, anthracyclines, taxanes, and ixabepilone). Although more grade 3 to 4 adverse events have been reported in patients who received bevacizumab-based therapy in clinical trials, most patients were asymptomatic, and adverse events, such as grade 3 hypertension or proteinuria, were easily controlled in most patients and unlikely to affect patient quality of life. Interestingly, in the Eastern Cooperative Oncology Group (ECOG) 2100 trial, the addition of bevacizumab was not associated with

additional adverse effect burden from the patient perspective and was associated with a greater reduction in breast cancer–specific concerns.[23]

Although potentially life-threatening adverse events have been related to bevacizumab therapy in several meta-analyses, the variability between different tumor types should be considered.[24-30] As mentioned previously, these controversial findings should be viewed with caution in the absence of an in-depth analysis of possible confounding factors. Three important toxicities have been consistently associated with bevacizumab: thrombosis events, GI perforation, and congestive heart failure. Although the relationship between thrombosis and GI perforations has been established in several meta-analyses, it has not been observed in patients with breast cancer who were treated with bevacizumab.[27,28,30,31] Increased risk has also been reported regarding congestive heart failure.[24] However, no information regarding risk factors for left ventricular dysfunction was provided in those studies. In addition, patients with prolonged time to progression, such as those treated with bevacizumab, are exposed to longer periods under controlled conditions, increasing the likelihood of events being detected. However, even with these statistical limitations, the overall incidence of congestive heart failure in bevacizumab-treated patients was 1.6%, which seems lower than the incidence of 2% observed with the worldwide use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy in patients with HER2-positive tumors.[32] In a recent meta-analysis of 16 randomized trials, patients treated with bevacizumab-based therapies had an increased risk of fatal adverse events, but in line with other findings, this was not demonstrated in patients in breast cancer, who had the lowest risk of fatal adverse events.[29]

Summary

The high prices of drugs and the worldwide economic and financial crisis are concerning. Of course, additional research might elucidate the subgroup of patients who will experience greater benefit, but as scientists and physicians, we should clearly separate value and price. A survey to assess the perception of health care workers involved in the management of women with MBC on the FDA's decision to ascertain how it will affect practice and to determine how bevacizumab is commonly used in the community for MBC was conducted. These survey results highlight the discord between the opinion of community oncologists and the FDA's recent decision to withdraw the indication of bevacizumab for MBC.[33]

A positive trial is based on a statistically significant *P* value, which should not be confused with clinical meaning. In addition, the concept of clinical meaning is closely related with costs. If OS is the primary end point of first-line trials, only the prognosis of a few tumors will be improved, and only over the course of a few years. This controversy is not only relevant to bevacizumab in MBC. The lack of consistency and transparency in the drug approval process is dangerous and likely to discourage pharmaceutical companies from developing new drugs. Progress in our fight to cure cancer will be jeopardized if we confuse value and price.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Javier Cortés, Novartis (C), Roche (C), Celgene (C); Emiliano Calvo, Novartis (C), Astellas (C), Genentech (U), GlaxoSmithKline (U); Antonio Llombart-Cussac, Roche (C); Ana Lluch, Celgene (C), Roche (C), Novartis (C); Gabriel N. Hortobagyi, Genentech (C), sanofi-aventis (C), Novartis (C) **Stock Ownership:** None **Honoraria:** Javier Cortés, Novartis, Roche, Celgene, Eisai; Emiliano Calvo, Novartis; Shaheenah Dawood, Roche; Antonio Llombart-Cussac, Roche; Ana Lluch, Novartis, Roche, Celgene; Gabriel N. Hortobagyi, Genentech **Research Funding:** Emiliano Calvo, Amgen, Astellas, Biosciences, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Millenium, Nektar, Nerviano, Novartis, Oncomed, Roche/Genentech, Pfizer, PharmaMar, sanofi-aventis, Serono, Spectrum Pharmaceuticals; Edith A. Perez, Genentech; Hope S. Rugo, Genentech, Pfizer; Gabriel N. Hortobagyi, Novartis **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Administrative support: Javier Cortés, Emiliano Calvo
Provision of study materials or patients: Javier Cortés, Emiliano Calvo, Shaheenah Dawood, Ana Lluch, Gabriel N. Hortobagyi
Manuscript writing: All authors
Final approval of manuscript: All authors

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DOI: 10.1200/JCO.2012.41.9580; published online ahead of print at www.jco.org on August 27, 2012

