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Commentary

Weighed, Measured, and Still Searching: Bevacizumab in the Treatment of Unselected Patients with Advanced Breast Cancer

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In this issue of ***The Oncologist***, Alvarez et al. [1] present a timely and comprehensive review of the data concerning bevacizumab in the treatment of patients with advanced breast cancer. The authors discuss the role of angiogenesis, including related therapeutic approaches as well as early clinical trials of bevacizumab, and appropriately focus on the randomized evidence. In summary, the three large first-line trials comparing chemotherapy alone with chemotherapy plus bevacizumab—Eastern Cooperative Oncology Group (ECOG) 2100, AVADO (Avastin and Docetaxel), and RIBBON-1 (Regimens in Bevacizumab for Breast Oncology)—met their primary endpoints and showed a statistically significant longer progression-free survival (PFS) duration. Pooled results demonstrated PFS intervals of 9.2 months and 6.7 months for patients treated with and without bevacizumab, respectively (hazard ratio, 0.64; 95% confidence interval [CI], 0.48–0.69). The results were not homogenous, however, with median differences of 5.5 months in ECOG 2100 and 1.2–2.9 months in the other studies.

The median, 1-year, and overall survival outcomes did not differ between the control and treatment arms in any of the individual trials or in the combined individual patient data meta-analysis [2]. Furthermore, there were no differences in any of the subgroups analyzed. The authors and the oncology community have raised potential hypotheses to explain this phenomenon, including the use of multiple further treatments upon progression, patients on placebo crossing over to receive bevacizumab, different interactions and potentials for synergism with each chemotherapy backbone, heterogeneous biology and sample populations, and the modest benefits of bevacizumab, among others [1, 3, 4].

The activity of bevacizumab described here must be balanced with its adverse event profile. A meta-analysis of five randomized trials [5] showed the following to be more common when bevacizumab was added to chemotherapy in the treatment of breast cancer (all differences were statistically significant): proteinuria (odds ratio [OR], 27.68), hypertension (OR, 12.76), left ventricular dysfunction (OR, 2.25), and hemorrhagic events (OR, 4.07). Although these adverse events have the potential to cause complications, most patients do not seem to have a negative impact on their quality of life (QOL) with the addition of bevacizumab, and in the same meta-analysis there were no statistically significant differences for gastrointestinal perforation, vascular events, fatal events, or febrile neutropenia. A larger meta-analysis of 16 randomized trials [6] with 10,217 patients, which included patients with other cancers, however, showed the addition of bevacizumab to be associated with a higher risk for fatal events (relative risk [RR], 1.33; 95% CI, 1.02–1.73; $p = .04$; incidence, 2.9% versus 2.2% for bevacizumab versus chemotherapy alone). There was a higher risk for fatal events for individuals receiving taxanes or platinum agents (RR, 3.49; 95% CI, 1.82–6.66; incidence, 3.3% versus 1.0%) but not for those treated with other agents (RR, 0.83; 95% CI, 0.37–1.85; incidence, 1.6% versus 1.6%). Although the authors of this second meta-analysis did not show any significant differences by diagnosis, most clinicians believe that toxic deaths with bevacizumab occur in pa-

Correspondence: Rebecca Dent, M.D., F.R.C.P.(C)., National Cancer Center Singapore, Department of Medical Oncology, 11 Hospital Drive, Singapore 169610. Telephone: 65-6601-1890; Fax: 65-6601-1890; e-mail: rebecca.dent@sunnybrook.ca, rebecca.dent@duke-nus.edu.sg Received November 16, 2011; accepted for publication November 18, 2011; first published online in ***The Oncologist*** *Express* on December 8, 2011. 1083-7159/2011/$40.00/0 doi: 10.1634/theoncologist.2011-0403

tients with colon and lung cancer but not in breast cancer patients, as shown in the breast cancer–specific meta-analysis discussed above.

Much has been discussed about the ideal primary clinical endpoint for advanced breast cancer trials and the acceptable balance and tradeoff between efficacy and toxicity [4, 7]. The controversy goes on nevertheless. The U.S. Food and Drug Administration (FDA) withdrew its approval of bevacizumab for patients with mammary malignancies (with a vote of 12 to one by the Oncologic Drug Advisory Committee) and on November 18, 2011, the FDA officially removed the breast cancer indication from the Avastin label. In contrast, the National Comprehensive Cancer Network recently ratified the use of bevacizumab in combination with paclitaxel, with 24 votes for and one abstention, and the European Medicines Agency maintained its approval (albeit qualified in combination with paclitaxel or capecitabine only) [8–10]. A recent worldwide survey of 564 oncologists (14.6% from the U.S., 7.8% from Canada, and 31.1% from Europe) showed that 52% of physicians did not think it was justified to withdraw bevacizumab's approval based on a smaller PFS benefit in the AVADO and RIBBON-1 trials than in the ECOG 2100 trial, whereas 48% believed it was [11]. Following the FDA's decision, Blue Shield of California was the first large insurer to declare that it will stop coverage for bevacizumab for breast cancer patients [12].

In this editorial, we would like to focus on another area of research, in which the evidence is less convoluted and mostly speaks against the use of bevacizumab in the treatment of unselected patients with advanced breast cancer: pharmacoeconomics. We expect many readers may stop reading at this point, but we urge all to take a deep breath, and keep on reading. The greatest challenge we face in oncology today is how to continue rewarding innovation while increasing access to new cancer treatments: we see exponentially rising costs for each small, but clearly statistically significant and incremental, improvement in survival. It is only through an honest and informed discussion that we can fulfill our larger roles as clinicians and researchers helping society frame health care issues and make difficult but important and long-due collective decisions. Our current levels of health care spending (at nearly 18% of all economic activity in the U.S. and reaching and passing 10% in many other countries) are unlikely to be sustainable for long, and oncology drugs are some of the fastest rising items in overall medical costs [13, 14].

The fundamental premise of economics is that societies have limited resources and the human spirit has unbounded needs and wants. In perfectly competitive markets, prices are a function of supply and demand, and through them Adam Smith's "invisible hand" leads to the most efficient distribution of those scarce resources. Health care markets are far from perfect however [15] due in part to uncertainties in diagnosis, prognosis, and treatment; asymmetric information; and agency and insurance issues. Pharmacoeconomic studies are used in multiple countries and regions to decide on coverage for new drugs, aiming to disburse public and insured persons' resources in the most efficient way possible. Typical cost-effectiveness and cost-utility studies (in which a clinical outcome is adjusted to reflect the gain or loss in QOL) assess incremental clinical gains and their relationship to increasing costs through a measure known as the incremental cost-effectiveness ratio (ICER). Quality-adjusted life years (QALYs) are the usual measure of clinical benefit in health economic evaluations and researchers determine this by multiplying the length of survival by the utility reached with a treatment. For instance, a new technology that costs US$50,000 in addition to current or comparative treatment, and that adds 1 year of life with a utility of 0.5, would lead to an ICER of US$100,000 per QALY; that is, the incremental cost is divided by 1 year of survival multiplied by a utility of 0.5 (US$50,000/1 year*0.5). These evaluations are fraught with methodological and philosophical difficulties but there is a broad consensus that they are useful tools for policymakers and societies in the difficult and unforgiving task to rationalize health care spending.

Several health economic studies have been conducted assessing the cost-effectiveness of bevacizumab in the treatment of advanced breast cancer. A Swiss study [16] showed an ICER of €189,427/QALY (approximately US$260,000/QALY). These results were corroborated by a comprehensive evaluation conducted for the U.K. National Institute for Health and Clinical Excellence (NICE) [17] in which the cost per QALY for bevacizumab in addition to docetaxel or paclitaxel fell in the range of £110,000–£259,000 (US$174,000–$411,000). Finally, one study used costs and perspective from the U.S. Medicare program [18]. Those investigators (one of the authors of this editorial included) calculated a cost of US$204,000 per year of PFS time gained and a cost of US$750,000 per QALY. These studies reached the conclusion that the drug is not cost-effective for unselected patients.

Because no clinical or epidemiological factors have surfaced as potential rational ways to individualize therapy, biomarkers are urgently needed to identify which patients with breast cancer benefit from or have the potential for serious adverse events with bevacizumab. The pharmacoeconomic literature has several examples in which the use of biomarkers not only improves clinical outcomes and therapeutic selection but also makes treatments more cost-effective. The treatment of unselected refractory metastatic colon cancer patients with cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor pathway, leads to a cost of nearly US$300,000 per QALY [19]. If we restrict its use to patients with wild-type *KRAS*, the ICER decreases to ~US$187,000. Finally, the ICER for the first-line treatment of patients with liver-only metastasis with chemotherapy plus cetuximab was in the range of £23,400–£30,000 (US$37,00–$47,800), which was considered cost-effective and led NICE to recommend covering the monoclonal antibody for this specific indication [20].

In the realm of public policymaking and insurance coverage, we need to give serious thought to the use of value-based insurance design as a means to not only reward health care innovation but to also nudge industry to develop treatments that improve clinical outcomes and at the same time are cost-effective. Here, the main caveat is in how we arrive at a defi-

nition of value. Should it be determined by policymakers, for whom an improvement of 2 months in lifespan or progression might be seen as minimal? Or by patients, who actually might like to have the choice of living a bit longer, even if it's only for a day? The oncology community should spearhead these efforts and discussions, starting with further studies to assess the willingness to pay of patients for each month or year of PFS time added, adjusted and unadjusted by QOL, which is likely to become a new and potentially more accurate economic indicator in metastatic solid tumor trials.

In conclusion, clinical experience clearly tells us that some women with advanced breast cancer have benefited enormously from combined antiangiogenic and systemic therapy. However, the absence of a biomarker has bedeviled the development of this class of agent. Future strategic directions would best serve patients by combining Bayesian adaptive clinical trial models in combination with cost-effectiveness analyses to identify subgroups of patients who benefit from antiangiogenic drugs.

Author Contributions

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