Refocusing the Debate: Evidence-Based Clinical Cancer Research Versus Marketplace Reality

By Maurie Markman, MD

The results of a recently reported randomized phase III trial examining the clinical utility of adding bevacizumab to a standard chemotherapy program (single-agent paclitaxel) in the management of metastatic breast cancer,¹ and the ensuing highly public debate regarding the implications of these findings for regulatory agency approval of the antiangiogenesis agent for this clinical indication, have raised a

critically important issue that, in the opinion of this commentator, has not found its proper place in this complex discussion.

The finding that the time to disease progression was substantially delayed but overall survival was not improved forced investigators, clinicians, patients, regulatory agencies, and third-party medical care payors to confront the fundamental and difficult issue of the valid goals of antineoplastic drug therapy.

Some people believe that unless a new drug/regimen is documented to improve overall survival, the strategy should not receive regulatory approval. Others argue that lengthening the time until the disease progresses will allow a patient to maintain an acceptable quality of life without the development or worsening of symptoms (eg, pain), and this outcome should be considered an acceptable primary goal of the use of antineoplastic agents, independent of their impact on the individual's ultimate survival.

Though this debate will surely continue, the focus of this commentary is not on the question of the legitimate primary end point of a trial, but rather on the issue of the considerable cost of the therapy being debated. In fact, one can rationally argue that a major component of the entire controversy regarding the relative clinical utility associated with extending progression-free survival arises from the truly vexing issue of the cost of the therapy in question (eg, bevacizumab).

Assuming for a moment that cost was not an overriding issue, would those who question the end point of progression-free survival be concerned if a patient elected to receive treatment that may substantially prolong the time until there is objective (or subjective) evidence of progression of the disease process? (Of course, this also assumes the patient will be informed of the data that both support its demonstrated utility, as well as its potential toxicity).

References

1. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 357:2666-2676, 2007

In this discussion, it is critical to note that the decision to accept the demonstrated utility of bevacizumab in this setting comes principally from the strength of the data; the results of an evidence-based, well-designed and conducted, 700-patient randomized phase III trial,¹ rather than merely the opinion of experts or a report of a phase II study whose outcome has been compared with an investigator-selected historical control. The fundamental point is that the evidence of benefit of bevacizumab has been obtained through an essentially universally accepted, objective, rigorous, and scientifically-valid process.

In striking contrast, the cost of a drug or product is determined largely, if not exclusively, by existing economic forces present within the health care market.² Or, as noted by others, the price of a drug is set at "the maximum of what the market (third-party payors) will currently permit." Though a business analysis is performed before a price tag is assigned to a new antineoplastic agent, this process is certainly not evidence-based, as that terminology is recognized by the medical community.

For a variety of reasons, a pharmaceutical or biotechnology company may elect to increase or decrease the price of a novel antineoplastic agent. However, although such a change may have a major impact (either negative or positive) on the willingness of a third-party payor to permit use of an antineoplastic drug, it must be clearly understood that what may be a highly rational fiscal decision has absolutely nothing to do with, nor does it alter, the scientifically-determined evidence for the clinical utility of that agent in a particular setting.

In conclusion, excellent clinical science should drive and document the benefits of new cancer treatments. Though a variety of often complex economic factors will surely influence what a new or novel antineoplastic strategy will cost, and the level of profit that may be generated from use of that approach, the current method of establishing price is profoundly different from what should be a rigorously objective and openly debated scientific process that will determine the evidence of the utility of that therapy.

Price does not define clinical benefit, but this economic factor may increasingly determine whether an individual patient will be given the opportunity to experience the objective (and subjective) benefits documented though the conduct of evidence-based clinical trials.

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2. Schrag D: The price tag on progress: Chemotherapy for colorectal cancer. *N Engl J Med* 351:317-319, 2004