

## Big Costs for Little Gain in Ovarian Cancer

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The results of the GOG 218 (Gynecologic Oncology Group) study were reported in abstract form at the 46th Annual Meeting of the American Society of Clinical Oncology in June 2010.<sup>1</sup> In this three-arm randomized phase III study, women with advanced epithelial ovarian cancer (stage III or IV, after maximal attempt at surgical debulking) were assigned to treatment with paclitaxel plus carboplatin followed by placebo (PC), paclitaxel plus carboplatin plus bevacizumab followed by placebo (PCB), or paclitaxel plus carboplatin plus bevacizumab followed by bevacizumab maintenance (PCB-B). Bevacizumab or placebo was administered at 15 mg/kg every 3 weeks, with the first five cycles administered concurrently with cycles two to six of chemotherapy and an additional 17 cycles delivered as single-agent maintenance treatment. Progression-free survival (PFS) was 10.3 months in the PC arm; 11.2 months, PCB; and 14.1 months, PCB-B. The 3.8-month improvement in PFS came at the cost (in terms of patient inconvenience and toxicity) of women receiving treatment every 3 weeks for an additional 51 weeks beyond the standard duration, a 23% risk for developing grade 2 hypertension, 10% risk for grades 3 to 4 hypertension, and 2.3% risk for grade 3 or worse GI perforation, hemorrhage, or fistula formation. At present, there seems to be no difference in overall survival among the treatment arms, although data are not yet mature.

In this issue of *Journal of Clinical Oncology*, Cohn et al<sup>2</sup> report on the potential cost effectiveness of adding bevacizumab to first-line treatment of advanced epithelial ovarian cancer. Here, cost refers only to the additional monetary expenditure incurred by adding bevacizumab to standard paclitaxel/carboplatin treatment. The authors provide a simplified cost-effectiveness analysis using standard methodology. No actual cost data were collected in GOG 218. The authors use estimates of drug costs using Medicare reimbursement rates. The model does not include any indirect costs (patient out-of-pocket expenses, time lost from work for 51 weeks of maintenance treatment, and so on). The only costs of toxicity that are included are the estimated costs for management of intestinal perforation. Specifically, the model does not include the costs of management of grade 2 or worse hypertension or other chemotherapy- or bevacizumab-associated morbidities. Including direct and indirect costs of managing hypertension would only increase the size of the numerator and worsen the cost-effectiveness ratio.

Results of the model reported by Cohn et al<sup>2</sup> show that PCB-B costs \$78.3 million (\$1,305,000 per patient) and has an incremental cost-effectiveness ratio (compared with referent PC) of \$401,088 per

progression-free year of life saved. It should be noted that most cost-effectiveness analyses model the costs of improvements in overall survival or quality-adjusted overall survival (true effectiveness) and compare the results with a traditional bar for what may be considered cost effective: \$50,000 per year of life saved<sup>3</sup> or, more recently, \$100,000 per year of life saved. The choice by Cohn et al to model PFS was presumably a practical one; they simply did not have any mature overall-survival data to model. However, it is worth considering the implications of this choice. In basic terms, when we provide health care to patients (in frank terms, when we buy chemotherapy or pain medications or vaccinations against measles), there should be a gain in the patient experience (ie, longer life, relief of suffering, or prevention of widespread morbid disease among children). Modeling PFS presumes that those 3.8 months of progression-free time yield a tangible improvement in the patient experience. This may not be the case. The use of cancer antigen 125 and periodic computed tomography imaging means that most recurrences in ovarian cancer are found while patients are asymptomatic. It is not a given that remaining radiographically progression free for an extra 3.8 months would improve a patient's quality of life. It is rather unlikely that it would translate into a quality-adjusted improvement in overall survival. If GOG 218 shows that PCB-B yields no improvement in overall survival, then the cost effectiveness of PCB-B will be even farther from the bar of acceptability.

Sensitivity analyses constitute a standard part of cost-effectiveness analyses, permitting researchers to vary the assumptions in the model to determine the weight and size of the drivers of cost and necessary magnitude of benefit that would be required to approach the acceptable cost-effectiveness bar. Only when PFS with PCB-B was hypothetically extended to 32.1 months (observed PFS in GOG 218 was 14.1 months) did the incremental cost-effectiveness ratio approach \$100,000 per progression-free year of life saved. The data for bevacizumab in ovarian cancer to date would suggest that PFS of 32.1 months is unlikely to be achieved.<sup>4</sup> Even among better-risk patients with optimally debulked stage III ovarian cancer treated with intraperitoneal-based platinum/taxane therapy, median PFS is just 24 months.<sup>5</sup>

Although the denominator of the cost-effectiveness ratio (PFS or overall survival) may not be something that can plausibly be prolonged beyond what is observed in GOG 218, the numerator (drug costs) is a potentially alterable parameter. Cohn et al<sup>2</sup> test differing bevacizumab prices to determine how low the cost would need to be to

approach cost effectiveness; only at a price point that is 25% of the actual bevacizumab cost does the incremental cost-effectiveness ratio dip below \$100,000 per progression-free year of life. This is the same magnitude of bevacizumab price reduction required for the addition of bevacizumab to paclitaxel/carboplatin in the treatment of advanced non-small-cell lung cancer to result in a cost less than \$100,000 per year of life saved.<sup>6</sup>

There are other potentially malleable parameters in the numerator to consider. The Gynaecologic Cancer Intergroup also conducted a phase III randomized trial of paclitaxel/carboplatin with or without bevacizumab and bevacizumab maintenance (ICON7).<sup>7</sup> In this study, the dose of bevacizumab was only half that used in GOG 218 (7.5 mg/kg rather than 15 mg/kg), and the duration of maintenance was 12 cycles instead of 17 (36 weeks of continued treatment rather than 51 weeks). Preliminary efficacy results show a PFS advantage with the addition of bevacizumab similar to that reported in GOG 218. Use of lower-dose and shorter-duration bevacizumab would likely serve to whittle down the size of the cost numerator in the cost-effectiveness equation. It will be of interest to see if the incidence of grade 2 or worse hypertension is less frequent with lower dose/shorter duration, a possibility that could further reduce overall costs.

Although there is a certain wow factor in just seeing the magnitude of the cost of PCB-B for the treatment of ovarian cancer (\$78.3 million), and it is perhaps not surprising that even generous sensitivity analyses show that bevacizumab use is highly unlikely to achieve generally accepted standards of cost effectiveness, perhaps the real question is whether anyone cares. Consumers are said to be price inelastic when an incremental change in price does not alter demand for the product. When health care costs are borne only indirectly by patients (ie, costs are covered by third-party payers), it is relatively easy for individual patients to be price inelastic regarding health care. Costs may rise, but demand does not fall. Unfortunately, this is not a sustainable health care delivery system. No matter who is paying, buying one thing comes at the opportunity cost of not buying another. Buying bevacizumab at \$78.3 million for 3.8 progression-free months for 600 women means not buying something else, such as basic clinical research to find better compounds that improve overall survival by a meaningful magnitude. It will require the (likely unpleasant) interface of medicine and policy to decide where and how the ultimately finite number of health care dollars will be spent.

In the meantime, are there intermediate steps to be taken to help us put the role and costs of bevacizumab for first-line treatment of ovarian cancer in perspective? Yes. We need the answers to the following critical questions: First, is there a clinically meaningful overall survival advantage to PCB-B over PC? If PCB-B is not effective, then it cannot be cost effective. Second, are the data from the Gynaecologic Cancer Intergroup study<sup>7</sup> sufficiently robust to permit treatment at half the dose for 9 months instead of 12 months? If so, total costs would be substantially lower. Third, is there a subset of patients who

benefit dramatically from PCB-B? In other words, is there a fat tail to the overall survival curve? Fourth, if there is a subset of patients who benefit, we need to study these women and their cancers to determine potential biomarkers that will identify which patients will or will not benefit from the addition of bevacizumab (similar to *KRAS* mutations predicting poor response to cetuximab treatment in colorectal cancer<sup>8,9</sup>). Such biologic triage of patients has high potential for helping achieve cost effectiveness with expensive drugs. Identifying biomarkers that can predict response means a commitment to conducting correlative studies in large clinical trials.

It is likely that novel drugs for cancer coming to market will continue to have stratospheric price tags.<sup>10</sup> It is also likely that novel agents will achieve, at best, incremental improvements in PFS that often will not translate into improvements in overall survival. We will serve our patients best by designing trials that permit us to identify which patients have the highest likelihood of deriving a meaningful survival benefit from a novel agent. Correlative science for effective patient selection may be the key to cost-effective treatment of cancer in the biologic therapy era.

#### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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