Considering Efficacy and Cost, Where Does Ramucirumab Fit in the Management of Metastatic Colorectal Cancer?

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Disclosures of potential conflicts of interest may be found at the end of this article.

Ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR2) recently gained approval by the U.S. Food and Drug Administration (FDA) for use in gastric and lung cancer [1–3]. Based on safety and efficacy, it was subsequently approved in April 2015 by the FDA for use in metastatic colorectal cancer.

The RAISE trial, a randomized phase III trial, confirmed the benefit from ramucirumab in colorectal cancer after progression on bevacizumab, oxaliplatin, and a fluoropyrimidine [4]. A total of 1,072 patients with metastatic colorectal cancer who had progressed on FOLFOX plus bevacizumab were randomized to receive either FOLFIRI plus ramucirumab or FOLFIRI plus placebo. The trial demonstrated a median overall survival (OS) benefit of 1.6 months (hazard ratio [HR]: 0.84) with the use of ramucirumab.

The control arm of the study (FOLFIRI) is not the current standard of care in the U.S. The ML18147 trial previously demonstrated a median OS benefit of 1.4 months (HR: 0.81) when bevacizumab was continued beyond progression in combination with second-line 5-fluorouracil-based chemotherapy [5]. The VELOR study previously demonstrated a median OS benefit of 1.4 months (HR: 0.82) when ziv-aflibercept was added to second-line FOLFIRI [6]. In addition to the antiangiogenic therapeutic options, patients whose tumors are RAS wild type are also eligible for EGFR-targeted therapy in combination with standard chemotherapy in this setting [7–12].

Oncologists now have three options for antiangiogenic agents that can be added to the chemotherapy backbone in patients with colorectal cancer refractory to FOLFOX plus bevacizumab. Although all three agents have not been compared in a head-to-head trial, they appear to have similar efficacy and toxicity profiles in randomized trials. If cost is incorporated into the decision-making process, there are major differences. We have made calculations of the monthly drug cost using a mean U.S. body weight of 82 kg [13]. We used the Medicare average sale price to calculate the monthly costs of each drug [14]. Table 1 provides further details.

We propose that there are two types of low-value cancer treatments. Type 1 is a new therapy that has a statistically significant but clinically modest benefit at a high cost. In this scenario, the precise value can be formally determined by a cost-effectiveness analysis. If the incremental cost-effectiveness ratio is above a certain threshold, the treatment can be described as a low-value treatment. Type 2 is a treatment that adds no additional benefit in terms of efficacy or toxicity compared with the current standard of care options and has a higher cost. In this situation, a formal cost-effectiveness analysis is not required. A perfect example is ziv-aflibercept in the second-line setting of metastatic colorectal cancer. In 2012, ziv-aflibercept was approved by the FDA, and the drug price was significantly higher than bevacizumab. At that time, there was a public protest by physicians at Memorial Sloan Kettering Cancer Center [15], and the price was subsequently decreased by the manufacturer. Ramucirumab in metastatic colorectal cancer falls into the second category of a low-value treatment.

Health care cost is a huge social and economic challenge in the U.S. Drug costs represent a sizable portion of health care costs. Unfortunately, at this time, there is no formal process to regulate the cost of new therapeutic agents and to ensure that the cost justifies the added benefit of new therapies. The FDA evaluates clinical trial data regarding safety and efficacy of a drug prior to granting approval. The FDA has no mandate to consider the cost of a drug prior to approval. Furthermore, Medicare is prevented from negotiating the cost of a drug with pharmaceutical companies as a result of the Medicare Modernization Act of 2003. Both policy makers and physicians in the U.S. usually are not willing to deny a particular treatment in the case of a type 1 low-value treatment. Policy makers are reluctant to address this issue to avoid criticism relating to rationing of care. Physicians consider their prime objective to be bringing the best possible care to their patients regardless of cost. In the case of a type 2 low-value treatment, however, both policy makers and physicians should be willing to deny such a therapy, given the presence of comparable and cheaper alternatives. At our institution, ramucirumab is currently on the formulary for use in advanced gastric cancer. The gastrointestinal oncology group has decided not to use ramucirumab for colorectal cancer at the current price. In our opinion, health care institutions, physicians, and patients can—and should—be more involved in evaluating the role of...
new therapies based on their value, especially in the case of a type 2 low-value treatment.

REFERENCES


EDITOR’S NOTE: See the related article, “Ramucirumab for Colon Cancer and the Problem of Rising Prices Independent of Benefits,” on page 983 of this issue.