Quality of Life and Targeted Treatment for Metastatic Renal Cell Carcinoma

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In a recent issue of *The Oncologist*, Beaumont and colleagues reported on quality of life analyses [1] from their pivotal, randomized, placebo-controlled, phase III trial of everolimus for metastatic renal cell carcinoma progressing after treatment with sunitinib and/or sorafenib [2]. They reported that disease-related symptoms were similar for participants allocated to the everolimus group and participants allocated to the placebo group, but that physical functioning and global quality of life deteriorated somewhat quicker in those allocated everolimus. They conclude that the “delay in tumor progression demonstrated by everolimus is associated with minimal impact on symptoms, physical functioning or quality of life.”

These conclusions may seem disappointingly negative for those accustomed to seeing symptoms of metastatic cancer improve with effective treatment. They warrant closer scrutiny and highlight three important questions for clinicians considering the results of quality of life analyses in cancer clinical trials: *who* was asked about their quality of life, *what* were they asked, and *when* were they asked it?

Most participants had good functional status, negligible symptoms, and reasonable quality of life at baseline. Karnofsky performance status scores were 90 or 100 in about 65% of participants, and none were <70. Mean

scores at baseline were about 28 for symptoms (on a scale of 0 = worst to 36 = best) [3], 75 for physical function, and 60 for global quality of life (both on scales of 0 = worst to 100 = best) [4].

Participants were asked questions about symptoms, physical function, and global quality of life. The specific symptoms were selected because they were “predominantly attributable to kidney cancer itself,” including pain, fatigue, shortness of breath, fevers, weight loss, coughing, and blood in the urine [3]. However, all but the first and last of these symptoms are listed as common adverse effects of everolimus. Physical function ratings assessed trouble doing strenuous activities and walking, restriction to a bed or chair, and needing help with activities of daily living [4]. Global quality of life comprised single items rating “overall health” and “overall quality of life” [4]. Given the participants’ characteristics, it is no surprise that their baseline ratings on these aspects were generally high and fell slowly over time.

Participants rated their quality of life from randomization until objective tumor progression. Imaging was repeated every 8 weeks, or earlier if progression was suspected, so progression was likely to be documented before participants developed troublesome cancer-related

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symptoms. At each time point, the results reflect the quality of life of participants who had not yet progressed and were well enough to complete questionnaires. Participants allocated to the placebo group progressed about three times faster than participants allocated to everolimus (hazard ratio for progression, 0.31) [2], so at each successive assessment, there were progressively more participants remaining on everolimus than on placebo. So by 8 months, for example, the quality of life results tell us that the remaining 4% of participants allocated placebo (six of 139) had a somewhat better physical function and global quality of life than the remaining 20% of participants allocated everolimus (54 of 277).

The authors confirmed that the missing quality of life ratings were likely to be systematically worse than those that were completed, and used modern statistical methods

to account for these missing data. Although it is clear that missing data will make the results in both treatment groups look better than they really are, there is no satisfactory way to determine how missing data alter the result we are really interested in: the estimated difference between the two groups.

The investigators should be congratulated for carefully collecting and analyzing quality of life data from a rigorous, pivotal, placebo-controlled trial addressing an important question. Their findings reassure us that the adverse effects of everolimus on symptoms and quality of life are probably relatively modest for relatively well people having second-line treatment for metastatic kidney cancer. Unfortunately, however, for most people considering this treatment, the results tell us little about its net effect on the quality of their remaining lives.

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EDITOR'S NOTE:

The article by Beaumont et al. is available online at <http://theoncologist.alphamedpress.org/content/16/5/632>.