Is more better than less? Caveats from bevacizumab and cetuximab combination in colorectal cancer

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In the past few years, impressive improvements have been made in the treatment of advanced colorectal cancer. Following decades of modest achievements, in which it was just a matter of dose and schedule for 5-FU and leucovorin—the only treatment then available—first, the development of irinotecan and oxaliplatin, and then the use of the two biologicals, bevacizumab and cetuximab, have dramatically improved the life expectancy of our colorectal cancer patients [1].

Therefore, a lot of expectations surrounded the first trial in which a combination of chemotherapy with both biologicals was tested. Such a combination was also supported by preclinical studies in animal models suggesting that combining a drug that targets vascular endothelial growth factor (VEGF) with a drug that targets epidermal growth factor receptor (EGFR) may be more effective than either drug alone; furthermore, single case reports suggested that such an increase in activity could also be observed in the clinical setting [2].

The idea was to demonstrate that we can obtain a better and longer disease control targeting two different, but nevertheless key, mechanisms responsible for tumor growth and spread, i.e., VEGF-driven angiogenesis, as well as the EGFR pathway.

This randomized clinical trial, testing chemotherapy combined with the VEGF-neutralizing monoclonal antibody Bevacizumab and the anti-EGFR monoclonal antibody cetuximab, and comparing this with chemotherapy and

bevacizumab alone, found that the addition of cetuximab actually shortened patients' recurrence-free and median survival, as reported in the February 5 issue of the *New England Journal of Medicine* [3].

Investigators from the Netherlands enrolled 755 patients with metastatic, inoperable colon or rectal cancer into this trial, continuing treatment until disease progression, death, or unacceptable toxicity.

Unfortunately, they found that "... the addition of Cetuximab significantly decreased the median progression-free survival ..." from 10.7 to 9.4 months; furthermore, median overall survival was 20.3 months for patients receiving chemotherapy and bevacizumab, versus 19.4 months for patients receiving chemotherapy, bevacizumab and cetuximab; finally, patients who received cetuximab reported less improvement in overall quality of life during treatment [3].

The investigators analyzed these results considering the status of *KRAS*, either wild type or mutated. A number of studies have indeed shown that only patients with normal *KRAS* benefit from drugs targeting EGFR [4]. Patients with mutant *KRAS* who were given cetuximab had a significantly shorter progression-free survival than patients treated with chemotherapy and bevacizumab, while, for patients with normal *KRAS*, cetuximab had no effect on progression-free survival [3].

The cause of these unexpected negative results are presently not clear, although a negative interaction between the two biologicals has been postulated as a possible mechanism responsible for such unexpectedly unsatisfactory results.

These results clearly open relevant questions on the real, biological and clinical, significance of trying to combine different molecularly targeted agents for the treatment of cancer, either in a horizontal, or a vertical fashion. Besides

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the problems of toxicities and economical issues, once again the question is: is more better than less?

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