Bevacizumab in colorectal cancer: it should have worked

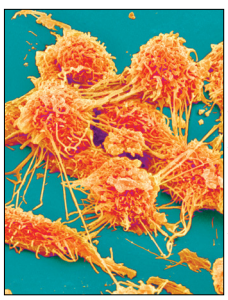
We've heard the message before: until we do the trial, we don't know the result, and negative trials, unwelcome as they are, are just as important as positive ones. In *The Lancet Oncology*, Rachel Kerr and colleagues present the results of the QUASAR 2 trial,[1] which now joins the NSABP C-08[2] and AVANT[3] trials as an important negative study of bevacizumab. Kerr and coworkers assessed capecitabine alone versus capecitabine plus bevacizumab as adjuvant treatment after potentially curative surgery for histologically proven stage III or high-risk stage II colorectal cancer. 3-year disease-free survival did not differ between the groups (capecitabine and bevacizumab 75·4% *vs* capacitabine alone 78·4%, hazard ratio 1·06, 95% CI 0·89–1·25, p=0·54). Post-hoc biomarker analyses suggested potential benefits in some subgroups of patients, but these were purely exploratory. Serious adverse events were reported in 221 patients who received capecitabine and in 350 who received capecitabine and bevacizumab.

Collectively, the QUASAR 2, NSABP C-08, and AVANT trials have assessed bevacizumab for the treatment of colorectal cancer in more than 8000 patients, and together tell us several things about this drug, most of which we wish were not so. The first inescapable message, confirmed in triplicate, is that the addition of bevacizumb to adjuvant chemotherapy does not improve the outcome for patients with stage II or III colorectal cancer. The second is that we can do actual harm in terms of cancer-specific outcomes and fatal toxic effects. The third is that there might be a subgroup of patients who would benefit from treatment, but that is not entirely clear, and we must be respectful of the first two points before too quickly embracing the third.

These three negative trials, along with the four negative trials of adjuvant irinotecan[4-7] and one of adjuvant cetuximab,[8] force us to accept that just because an agent has antitumour activity against macroscopic metastatic cancer does not mean that it has activity against that same cancer in the microscopic metastatic setting. The fact that three different agents, working by three totally different mechanisms, illustrate this issue suggests that how antineoplastic agents kill macrometastatic and micrometastatic tumour cells differs fundamentally. We must, therefore, be cautious when proposing a mechanistic hypothesis for a putative marker for bevacizumab susceptibility, such as microsatellite instability or CD31 expression. In QUASAR 2, these markers were identified in a retrospective analysis not planned as part of the study protocol. Thus, as noted by Kerr and colleagues, the findings are bases only for hypothesis generation and should not be viewed as actionable.

What other questions might be informed by these negative trials? Is it reasonable to assume that other anti-VEGF agents, such as aflibercept, ramucirumab, or anti-VEGF tyrosine kinase inhibitors, will have similar profiles of inactivity and negative effects in the adjuvant setting as bevacizumab? Given what is known about the similarities in mechanisms and metastatic activities, the answer seems to be yes. Any further adjuvant trials of anti-VEGF agents in colorectal cancer should, therefore, be limited to rigorously defined subsets of patients who are rationally selected to be most likely to benefit. The results of QUASAR 2 and the other negative trials can probably also be extrapolated to inform treatment decisions in the adjuvant setting of resected stage IV colorectal cancer. That micrometastases left after resection of stage IV tumours should differ biologically from those of stage II or III tumours, which these agents could not eradicate, seems unlikely. Indeed, the negative trial of irintoecan after resection of colorectal cancer liver metastases directly supports this concept.[7] Finally, the findings of these trials must force physicians to confront what they wished would not be so—not only do these drugs not help in the adjuvant setting, they can also do harm.

Kerr and colleagues[1] raised the issue in their discussion of the much longer use of bevacizumab than of standard adjuvant chemotherapy. In all three trials of this drug, treatment with bevacizumab was administered for 24 weeks longer than standard chemotherapy, yet none provided either supportive data or a meaningful rationale for this duration. Excess treatment-related deaths occurred in the QUASAR 2 bevacizumab group compared with the capecitabine alone group (15 *vs* eight within 6 months of randomisation),[1] and toxic effects from bevacizumab alone were reported in NSABP C-08.[9] Had these trials shown benefit, we probably would never have known whether the additional nearly 6 months of bevacizumab were useful or necessary. Rather, the



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toxic effects, including of the non-trivial so-called financial toxicity, would have been ensconced in our practice. This is a mistake that should not be further repeated. That the addition of an agent would have no meaningful benefit when given for 6 months, but would be useful when given for 12, strains credibility. Any future adjuvant trials, whether of bevacizumab in molecularly selected populations or of any other novel agents, should first show efficacy and safety without lengthening the course of treatment.

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