Failure of bevacizumab in early-stage colon cancer

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A randomised phase III trial of patients with stage II and III colon cancer showed no benefit of adding bevacizumab to standard adjuvant oxaliplatin plus fluorouracil and leucovorin. Despite suggestive evidence of a short-term benefit, these data and other similar findings dictate that adjuvant bevacizumab should not be used in colon cancer.

The first definitive evidence of clinical benefit of bevacizumab in metastatic colon cancer was reported in 2001.[1] Since then, this agent has become a standard component of the treatment of multiple tumour types in the setting of advanced cancer. Although bevacizumab has produced variable success across disease entities, its clear activity in patients with stage IV colon cancer logically warranted an evaluation of its efficacy in patients with earlier-stage disease. Adjuvant therapy with fluorouracil-based regimens following surgical resection of stage III colon cancer has been the standard of care for approximately 20 years;[2] in 2003 the addition of oxaliplatin to fluorouracil and leucovorin (a combination called FOLFOX) became the current standard of care in adjuvant colon cancer.[3] Now, Allegra et al.[4] report the first trial testing the addition of bevacizumab to the FOLFOX regimen for patients with stage II and III colon cancer.

In the randomised, multicentre trial of 2672 evaluable patients, no benefit was observed for the addition of bevacizumab to standard FOLFOX for the primary endpoint of disease-free survival.[4] The endpoint chosen was appropriate, as results based on disease-free survival have been demonstrated to be highly predictive of later overall survival findings.[5] The overall trial results are definitive; the possible benefit suggested by the hazard ratio of 0.89 is clearly non-significant (P=0.15). Any modest possible benefit in the initial phase of the trial was attenuated over time; in the period from 2 to 3.5 years of follow-up, the recurrence rate in the bevacizumab arm was in fact higher than in the control arm. In addition, the results of a second trial of bevacizumab in the setting of stage III colon cancer were announced in September 2010.[6] In that trial, the results at three years numerically favoured the control arm (FOLFOX alone). Thus, on the basis of these two trials, bevacizumab is clearly not recommended for the adjuvant treatment of stage II and III colon cancer.

In an exploratory analysis, Allegra et al.[4] identified a possible short-term disease-free survival benefit of bevacizumab in the first 15 months following randomisation. This finding is intriguing, given that the bevacizumab treatment was administered for 12 months. Owing to the potential bias induced by unequal time to imaging between the two arms of the trial (imaging frequency was not protocol mandated), a sensitivity analysis was conducted attempting to adjust for the differential time to first imaging that

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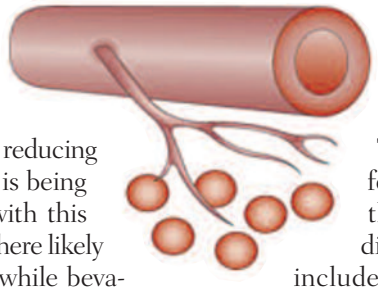
was observed. In this analysis, the short-term benefit of bevacizumab remained, with some attenuation of the first 15 month hazard ratio, from 0.61 to 0.71. Allegra et al.[4] conclude that, all factors considered, this finding likely represents a true biological effect of bevacizumab in reducing recurrence risk while it is being administered. I agree with this conclusion that indeed there likely is a short-term benefit while bevacizumab is being delivered. Whether longer-term bevacizumab exposure would further delay recurrence, eventually eradicate tumour cells and thus prevent recurrence, or have no further effect can only be tested through a subsequent randomised trial. However, given that most stage II and III patients are cured by surgery alone, and considering the adverse effects and inconvenience associated with bevacizumab and the cost, it is unclear whether such a trial could succeed (or even be appropriate) in the stage III setting. A trial of extended-duration bevacizumab in the alternative setting of maintenance therapy for patients with resected stage IV disease, where the recurrence risk is much higher (50%–70% risk of recurrence within two years) may be a more promising alternative.



On the basis of the results reported by Allegra et al.,[4] FOLFOX following surgical resection remains the standard of care for stage III colon cancer. This finding is clearly disappointing, as it represents the third agent with demonstrated activity in stage IV disease that has failed to improve outcomes in earlier-stage disease. Specifically, in addition to bevacizumab, the proven activity of both irinotecan and cetuximab in patients with advanced disease has not translated into benefit in patients with stage III disease.[7,8] As such, it seems the standard paradigm for drug development in this setting is broken: activity in metastatic disease is not a reliable predictor of adjuvant therapy benefit. The biological reasons for this discordance are the subject of intense discussion, possibilities include a different biology between existing visible versus micrometastatic disease (including the concept of epithelial–mesenchymal transition of tumour cells) and the presence of therapy-resistant cancer stem cells. However, the fact remains that we currently do not have an accurate predictor of efficacy for a new proposed adjuvant therapy. A possible alternative approach, the use of neoadjuvant chemotherapy in early-stage disease, seems worthy of exploration. Rectal cancer therapy has moved primarily to the neoadjuvant paradigm (as has much research in breast cancer). The ability to test a therapy's impact in an intact tumour (as well as obtaining pre-treatment and post-treatment biospecimens) is very attractive. Clinical trials of neoadjuvant therapy for colon cancer are ongoing.[9] In the setting of stage II disease, given the high cure rate (approximately 20% recurrence risk), very modest benefit of fluorouracil[10] and no benefit of oxaliplatin,[3] research is focused on strategies for risk assessment to identify patients who are at high risk of recurrence and thus may be considered for adjuvant therapy.

Even if the paradigm of advanced disease testing before adjuvant trials remained appropriate, at the present time there is a dearth of agents in later-stage (phase III) testing in advanced colon cancer. Currently, the most pressing adjuvant therapy question seems to be that of the optimal duration of therapy. On the basis of the cumulative neurological toxic effects of oxaliplatin, reducing the treatment time to three months (from the current six months) would be highly advantageous. This question is being tested in four ongoing trials and one planned randomised trial that are being conducted throughout the world (including the TOSCA trial in Italy, the SCOT trial headquartered in the UK, the C80702 trial in the USA and the PRODIGE/GERCOR trial in France). These trials have prospectively agreed to pool their data for a definitive noninferiority analysis with at least 10,500 patients through the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration.

In conclusion, the primary clinical implications of the study by Allegra et al.[4] are clear – bevacizumab should not be used in the adjuvant setting in colon cancer outside clinical trials – and at the same time raise many new questions of how to best develop new agents before adjuvant testing. Innovative strategies are needed to assess new agents and treatment strategies, as colon cancer remains a major cause of cancer death worldwide.

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

The use of adjuvant bevacizumab in the setting of stage II or III colon cancer is not recommended.

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