EDITORIAL

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HORIZON I: Is there a future for oral anti-angiogenics on the horizon of colorectal cancer therapy?

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In this issue of *BJC*, Cunningham *et al* (2013) report on a randomised phase II study of the VEGF receptor tyrosine kinase inhibitor cediranib (AZ 2171), given at 20 and 30 mg once daily compared with bevacizumab 10 mg kg^{-1} given with FOLFOX chemotherapy (Cunningham *et al*, 2013). The study was conducted as a second line trial, for patients with previously treated metastatic colorectal cancer. The study is noteworthy in directly comparing the novel anti-angiogenic to the antibody bevacizumab, rather than FOLFOX plus placebo, particularly in absence (at the time) of a randomised trial showing the benefit of second line bevacizumab or an FDA-approved indication in this setting. The study was part of a dose selection strategy for the HORIZON II and HORIZON III trials (Hoff *et al*, 2012; Schmoll *et al*, 2012), which resulted in the 20 mg cediranib dose selection for the large randomised trials.

The results of this study show statistical equivalence of the two cediranib arms to bevacizumab for PFS and OS, though the higher dose (30 mg) was somewhat more active and closer to the bevacizumab arm. However the study is rather small, at ~70 patients per arm, to rule out a moderate difference between the arms. The study was successful in showing statistical equivalence of the arms and a signal to move forward with the larger phase 3 trials, such as HORIZON III, with 1400 patients and a non-inferiority design. This trial also showed the statistical equivalence of cediranib to bevacizumab in first line therapy with FOLFOX, for PFS, OS and response rate. Nonetheless, the trial did not reach the regulatory bar of 'non-inferiority' with the upper limit of the PFS hazard ratio 95% confidence interval being outside the acceptable range (1.25 instead of <1.2, implying as much as a 25% chance of being truly inferior). The toxicity profile for cediranib was not favourable, additionally, with increased diarrhoea, neutropenia and an shorter time to occurrence of significant symptoms by the FACT-C outcome index. In the HORIZON II study FOLFOX or CapeOX with cediranib was compared with placebo. The results were remarkably similar to the NO196966 study with bevacizumab compared with placebo (Saltz *et al*, 2008). Because of these findings the development of cediranib in colorectal cancer was abandoned.

In the context of anti-angiogenic therapy for colorectal cancer, the cediranib studies add another chapter to the unfortunate history of oral anti-VEGFR drugs. Cediranib, like vatalanib, inhibits the tyrosine kinase of all three VEGFR enzymes. Like vatalanib, this agent showed PFS advantage compared with placebo but could not effect OS. Bevacizumab (in E3200 (Giantonio *et al*, 2007) and the TML trials (Bennouna *et al*, 2013)) and aflibercept (in the VELOUR trial (Van Cutsem *et al*, 2012)) both show survival advantages in second line therapy of colorectal cancer.

In the end, is this a question of oral drugs *vs* intravenous? Oral agents certainly present additional pharmacological challenges of absorption and inter-patient variability. This may be particularly important for angiogenesis where consistent inhibition could be essential for clinical benefit. The half-life of bevacizumab is almost 3 weeks and aflibercept about 1 week. In contrast, the median half-life for cediranib is about 24 h (Drevs *et al*, 2007; Ryan *et al*, 2007), and for vatalanib only 8 h. This may be compounded by compliance issues as with any oral drug. Does a less consistent complete blockade of VEGF stimulation result in less benefit? This view receives some support from the NSABP C-08 adjuvant trial of colon cancer (Allegra *et al*, 2011), which showed very substantial improvement in time to recurrence for the 1 year of bevacizumab administration, but this benefit was quickly lost once the drug was stopped.

Another problematic aspect of oral VEGFR TKIs when given with chemotherapy is the adverse event profile. In the current HORIZON I trial, the authors report greater incidence of diarrhoea and overall grade 3–4 adverse events in the cediranib arms. This also translated to more dose reductions and fewer chemotherapy cycles administered for cediranib and chemotherapy. This finding was also predictive of the HORIZON III results. In the larger study, significantly greater diarrhoea and neutropenia was observed with cediranib. Lesser chemotherapy dose intensity was achieved with the cediranib arms. Would selection of the 30 mg cediranib dose have been more effective in HORIZON III? More anti-angiogenic effects as well as more adverse effects were seen at the higher dose. We can only speculate that this dose would have resulted in even

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greater dose attenuation and again lack of benefit compared with bevacizumab. As with many oral TKIs, toxicity is quite low for cediranib as single agent. However, these drugs do not play well with the multiple chemotherapy agents used for colorectal cancer therapy and drug interactions continue to plague such combination regimens in the practice.

All in all the experience of oral VEGFR TKIs in colon cancer has been fraught with failure; after all, these drugs are pharmacologically and pharmacodynamically inferior. It is difficult to beat a low toxicity antibody with a very long half-life. When the toxicity of the oral TKI agents is added to chemotherapy, it invariably has resulted in lower drug intensity and earlier discontinuation. Some of these agents are active as single agents, as we now know for regorafenib in the refractory situation (Grothey *et al*, 2012). The ideal oral VEGFR TKI for use with chemotherapy remains to be developed. In the meantime we have the choice of combining intravenous bevacizumab in the first or second lines of therapy or switching to aflibercept in the second line when wishing to deploy and anti-angiogenic in combination with chemotherapy for the treatment of metastatic colorectal cancer.

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