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I have served on advisory boards for Blue Earth and Janssen.

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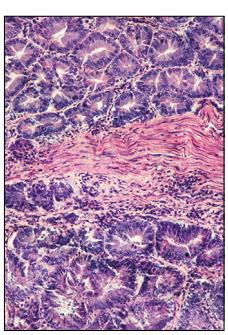
No clear role for angiogenesis inhibitors in first-line therapy for stomach cancer

In this century, anti-angiogenic therapy has played a part in the treatment of multiple solid cancers. Possible strategies to inhibit the angiogenic VEGF–VEGFR signalling axis include targeted therapy against VEGF ligand, VEGFR-2, and VEGFR tyrosine kinases. These approaches have identified ramucirumab, a recombinant, fully human IgG1 monoclonal antibody specific for VEGFR-2, as the most successful anti-angiogenic compound in gastric cancer treatment.[1,2] This finding has led to approval by the US Food and Drug Administration and European Medicines Agency of ramucirumab (in combination with paclitaxel or as monotherapy) for second-line treatment of patients with advanced gastric or gastro-oesophageal junction adenocarcinoma with disease progression after previous platinum and fluoropyrimidine chemotherapy.

In *The Lancet Oncology*, Charles Fuchs and colleagues[3] now report results of the placebo-controlled, phase 3 RAINFALL trial, investigating the role of ramucirumab in combination with standard first-line cisplatin and capecitabine (or 5-fluorouracil) chemotherapy. The primary endpoint was met: the addition of ramucirumab improved investigator-assessed progression-free survival, analysed by intention-to-treat in the first 508 eligible patients (HR 0·753, 95% CI 0·607–0·935). However, this finding was not accompanied by a clinically meaningful improvement in median progression-free survival: 5·7 months (95% CI 5·5–6·5) in the ramucirumab group versus 5·4 months (4·5–5·7) in the placebo group. Moreover, this difference in progression-free survival was not confirmed in a sensitivity analysis based on central independent review (0·961, 0·768–1·203, p=0·74). With a study population of 645 patients, the study was also powered to investigate overall survival as a secondary endpoint, but there was no difference between groups (HR 0·962, 95% CI 0·801–1·156), with median survival of 11·2 months (9·9–11·9) in the ramucirumab group versus 10·7 months (9·5–11·9) in the placebo group.

A clear question is why ramucirumab, as a single agent in the REGARD study[1] and in combination with paclitaxel in the RAINBOW study,[2] showed improved progression-free and overall survival in the second-line setting, but not as first-line therapy. Study populations and dose schedules vary slightly between the different studies and it is unclear whether this has influenced findings. For example, RAINFALL only included metastatic cancers, whereas RAINBOW also included locally advanced tumours. However, the proportion of locally advanced tumours in RAINBOW was probably low.[4,5] Furthermore, HER2-positive tumours were excluded from RAINFALL because anti-HER compounds are standard of care in patients with these tumours. In vitro, HER2 overexpression has been associated with increased angiogenesis and VEGF expression,[6] which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might imply a better responsiveness to anti-angiogenic inhibitors. However, in a retrospective analysis of the small number of HER2-positive tumours in the REGARD study, outcomes did not seem to differ between patients with HER2-positive and HER2-negative tumours.[7]

The results of the RAINFALL study do not stand alone. AVAGAST[4] and AVATAR[5] also showed no benefit of bevacizumab in first-line in combination with cisplatin and fluoropyrimidine. In the curative setting, bevacizumab also did not improve survival when added to perioperative chemotherapy with epirubicin, cisplatin, and capecitabine.[8] To date, only second and later-line studies have demonstrated benefit of angiogenesis inhibition.[1,2,9] The RAINFALL study authors found that 93 (14%) of the study population receiving ramucirumab in subsequent lines had a better prognosis, irrespective of study group. Although this finding is from an exploratory analysis of surviving patients who have disease progression after first-line treatment, but are well enough to continue treatment, it is consistent with previous findings. The authors hypothesise that the angiogenic pathway might promote tumour growth mainly in metastatic gastric cancer, or that a natural selection of angiogenic sensitive tumours occurs after systemic treatment.

Another possible explanation is that the chemotherapy backbone affects anti-angiogenic therapy. So far, all studies using cisplatin and fluoropyrimidine have underperformed compared with those with paclitaxel or ramucirumab as monotherapy. Taxanes, in particular, have been linked to inhibition of endothelial cell proliferation in vitro and disruption of tumour vascularity in vivo, and the latter process is found to be enhanced by anti-mouse VEGFR-2 monoclonal antibody. Paclitaxel and, to a lesser extent, docetaxel and fluorouracil, increased circulating endothelial progenitors, whereas cisplatin did not.[10] In this context, the results of the ongoing RAMSES trial (NCT02661971), in which ramucirumab is combined perioperatively with FLOT chemotherapy in patients with resectable gastric cancer, are eagerly awaited

Global inclusion, which allowed rapid patient accrual within 2 years, also raises concerns of masking outcome differences because of the inclusion of heterogeneous populations with different genetic backgrounds and locoregional diagnostic or therapeutic strategies in a highly heterogeneous disease. Predictive biomarkers that can overcome this issue are urgently needed. In RAINFALL, efforts to validate VEGF ligands, VEGFR-1, and VEGFR-3 as reliable biomarkers were unfortunately unsuccessful.

There is currently no role for inhibition of angiogenesis in first-line gastric cancer treatment with standard platinum and fluoropyrimidine derivatives. The RAINFALL trial once again shows that understanding the evolutionary biology of gastric cancer against the background of patients' genetic make-up, and the effect these factors have on the complex interaction between anti-cancer drugs and the tumour and vascular microenvironment, is crucial for the personalisation of future gastric cancer treatment.

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I was involved in the initiation of the RAINFALL study at the Netherlands Cancer Institute, but was not involved in the conduct of the study.

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