RESEARCH HIGHLIGHT

Targeting angiogenesis in advanced gastric cancer: Is this end of the road?

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Despite recent advances in the management of several solid tumour types, gastric cancer remains a challenging disease to treat. In 2008, gastric cancer accounted for almost one million new cases and over 738,000 deaths, making it the fourth most common malignancy and second most common cause of cancer-related death in the world (1). The majority of cases (713,000) occur in developing countries, predominantly in Eastern Asia, with a male:female ratio of approximately 2:1. In the Western world, most patients with gastric cancer have advanced inoperable disease at presentation which contrasts sharply with countries such as Japan where an established screening program permits frequent diagnosis of early-stage disease (2). The prognosis for advanced gastric cancer is particularly dismal, with a median survival of less than one year (3). There is no single global standard regimen for first line treatment and patients are often treated with a platinum and fluoropyrimidine-based doublet or triplet regimen. The UK multicentre REAL-2 study demonstrated that infusional 5-fluorouracil and cisplatin can be safely replaced by capecitabine and oxaliplatin respectively, thereby improving tolerability and patient convenience (3). However, there remains a significant unmet need for more effective treatment strategies and therapeutics targeted against crucial survival pathways within the cancer cells and tumour micro-environment.

Angiogenesis is the process by which new blood vessels arise from the pre-existing vascular bed, and is known to play an important role during embryogenesis and wound healing, as well as being well recognised as an important hallmark of cancer development (4). The possibility of targeting tumour angiogenesis as a therapeutic strategy was postulated almost 40 years ago, though the development of anti-angiogenic agents has only reached fruition with the past decade. Bevacizumab is a humanised recombinant monoclonal antibody against vascular endothelial growth factor A (VEGF-A) which is a major regulator of normal and pathological angiogenesis (5). Although the exact mechanism of action of bevacizumab is poorly understood, it is postulated that bevacizumab sensitises the endothelial cells to chemotherapy-induced apoptosis, leading to a normalization of tumour vasculature and improved chemotherapy and oxygen delivery (14). Bevacizumab and other targeted therapies directed against the angiogenesis pathway have now been shown to be of clinical benefit across many cancer types, including colorectal, breast, lung and ovarian cancers (6-9). In gastric cancer, initial studies demonstrated that increased VEGF-A expression was present in a proportion of tumours and correlated with poor prognosis due to a more aggressive tumour phenotype (10,11). Following this finding, early phase trials of bevacizumab in advanced gastric cancer demonstrated encouraging results (12), and prompted further evaluation in a large phase III study.

The randomised phase III Avastin in Gastric Cancer (AVAGAST) study was designed to evaluate the efficacy of bevacizumab in advanced gastric cancer (13). In this double-blind, placebo-controlled study, 774 patients with advanced gastric or gastro-esophageal cancer were treated with a cisplatin-capecitabine chemotherapy doublet and were randomised between the addition of bevacizumab or placebo. Cisplatin was given for six cycles, and capecitabine and bevacizumab were continued until disease progression or unacceptable toxicity. Addition of bevacizumab to chemotherapy resulted in a significant improvement in progression-free survival (PFS) (6.7 months versus 5.3 months; hazard ratio, 0.80; 95% CI, 0.68-0.93; P=0.0037) and overall response rate (ORR) (46.0% versus 37.4%; P=0.0315) but was

not associated with significant improvements in overall survival (OS) and the study therefore failed to meet its primary end-point (12.1 months versus 10.1 months; hazard ratio, 0.87; 95% CI, 0.73-1.03; P=0.1002). Safety data revealed comparable toxicity profiles between the two arms, with no increase in chemotherapy related toxicity from the addition of bevacizumab.

The AVAGAST study is the largest study of bevacizumab in advanced gastric cancer. Disappointingly, the trial was negative however these data do raise several important questions about the use of anti-angiogenic agents in gastric cancer: Why there was no OS benefit demonstrated? Is bevacizumab the right drug for targeting angiogenesis? Are there definable subsets of patients who do derive meaningful survival benefit from use of bevacizumab? Is a 1.5 months PFS benefit of sufficient importance to justify further evaluation of bevacizumab in gastric cancer? Will other anti-angiogenic therapies be similarly ineffective?

Although a benefit has been demonstrated from use of bevacizumab in other tumour types, recent data suggest that the approach of targeting only the VEGF-A ligand with bevacizumab, is vulnerable to subversion via activation of the other ligands in the angiogenesis pathway (14), and it is therefore possible that a more multi-targeted approach may be needed to effectively target angiogenesis in gastric cancer and other tumour types. This may partly explain the discrepancy between the pre-clinical and the clinical studies of bevacizumab in gastric cancer and in other cancer types, many of which also demonstrate improved RR and PFS without OS benefit. Indeed, alternative anti-angiogenic strategies with agents targeting the VEGF receptor and other components of the angiogenesis pathway are currently undergoing evaluation in clinical trials. Pre-clinical studies have also raised concerns regarding disease rebound after stopping anti-angiogenic agents, although this phenomenon has not been reported in clinical studies, and it is unlikely that this was responsible for the lack of benefit in overall survival in the AVAGAST study.

In the AVAGAST study, there was no survival benefit in the intention-to-treat population however a pre-planned subgroup analysis demonstrated a significant OS benefit with the addition of bevacizumab in the pan-American subgroup, with no benefit being found in patients from the Asian subcontinent. This is most likely due to inherent global differences in disease biology and host or tumour-related genetic factors, as well as differences in clinical practice such as use of second-line chemotherapy. Taken together, these factors probably explain the regional difference in outcomes, reaffirming that gastric cancer trials data are not readily applicable worldwide and that 'East versus West' does matter in gastric cancer.

Although there were demonstrated improvements in the secondary end point of RR and PFS from the addition of bevacizumab, given the negative OS result in the ITT analysis, the use of bevacizumab in advanced gastric cancer cannot be justified currently. However, these data do confirm some activity for bevacizumab in advanced gastric cancer. The improved response rate may be of particular importance in the setting of operable gastric cancer where a higher response rate to preoperative chemotherapy may potentially facilitate a greater rate of R0 resection and hence lead to long-term survival benefit. The ongoing phase III UK MRC ST03 study is evaluating the benefit of adding bevacizumab to perioperative chemotherapy in operable gastro-oesophageal cancer (15).

Given the above data which provide some evidence of activity of bevacizumab in an unselected population, it remains distinctly possible that a subgroup of patients may derive more significant benefit than can be detected in a trial such as AVAGAST. Indeed, there are now ample data with other targeted agents which suggest efficacy in only a subgroup of patients with specific tumour charactesitics (16,17). Extensive research is currently ongoing to identify patients who will benefit from bevacizumab, though at present, there are no established predictive biomarkers for either bevacizumab or other anti-angiogenic drugs. Nevertheless, the established benefits of anti-angiogenic therapies in other cancer types, plus the improvements in RR and PFS in the AVAGAST trial, provide sufficient support for further evaluation in this setting, and these results should certainly not be considered as the end of the road for anti-angiogenic agents in gastric cancer. Indeed, it is imperative that we undertake focussed research in this area, including current and future trials of anti-angiogenic agents, in order to answer many of the outstanding questions surrounding this therapeutic strategy. This will be a difficult task with many potential pitfalls and challenges, but these are precisely the challenges which scientists and oncologists of today must overcome if we are to achieve personalized therapy for our patients and improve outcomes from this aggressive disease.

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