Targeting Angiogenesis in Gastroesophageal Cancer: Industry-Sponsored Trials are not the Answer

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Angiogenesis is a dynamic process essential for tumor growth. Maeda et al. first reported its association with poor prognosis in gastric cancer in 1996 and, since then, there have been numerous similar studies examining various factors that mediate angiogenesis such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor [1]. It is therefore surprising that a decade and a half later there is still no clear consensus on the role of anti-angiogenic agents in the treatment of gastroesophageal cancer and, more importantly, recognition of the patient subset who are most likely to benefit from these expensive agents.

In this issue of the *Journal*, Liu et al. [2] report that VEGF expression is an independent prognostic factor for tumor recurrence and decreased survival in patients with node-negative gastric cancer. Unlike prior studies, the authors excluded all node-positive patients in the hopes of stratifying node-negative patients into low- and high-risk groups for tumor recurrence. This is an important step in identifying patients most likely to benefit from adjuvant therapy, but the manner in which patients were deemed node-negative is particularly relevant.

What was the median number of nodes resected, and how were the nodes examined? It seems unusual that 11 patients with pT4 tumors were node-negative. If we presume all nodes were examined using a single section and conventional [hematoxylin-eosin (H&E)] staining, then this means that only about 1% of the lymph node tissue was examined, and some node-positive patients almost

certainly were missed. In a retrospective study last year, we found that almost one-third of esophageal cancer patients who were node-negative by conventional histology proved to have occult tumor deposits in their lymph nodes after serial sectioning and immunohistochemical evaluation [3]. In other words, until standardized and more stringent histopathology is performed on lymph nodes, it is difficult for the reader to be confident that all patients were truly node-negative. Also, in Liu et al.'s study, it is possible that 24 of 55 (44%) patients who were VEGF-positive and had a worse survival were those who might have been node-positive with more stringent histopathologic testing.

Nevertheless, their study raises an interesting question. Should patients with early gastric cancer and positive VEGF staining be given an antiangiogenic agent to reduce their risk of tumor recurrence? Bevacizumab (Avastin), a recombinant humanized monoclonal antibody directed against VEGF-A, was approved for patients with metastatic colorectal cancer in 2004, in combination with 5-fluorouracil chemotherapy, after a Phase III (randomized controlled multicenter) study showed an increase in survival of 4.7 months with the inclusion of this agent in the treatment regimen [4]. This study paved the way for a myriad of other clinical trials evaluating more than 40 antiangiogenesis agents in various solid tumors. In gastric cancer, a Phase III trial called AVAGAST (Avastin in Gastric Cancer) has just been published in the *Journal of Clinical Oncology* on the back of three Phase II (nonrandomized) trials evaluating the addition of bevacizumab to chemotherapy in patients with unresectable or metastatic gastroesophageal cancer [5]. Although the smaller Phase II trials reported response rates of 65 to 68% with encouraging progression-free survival [6], the Phase III trial found only a 2 month survival benefit between groups, which was not significant [5]. Subsequently, bevacizumab has not been

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approved for routine use in patients with gastroesophageal cancer.

Perhaps the most controversial agent with antiangiogenesis properties on the market today is trastuzumab (Herceptin), a humanized monoclonal antibody that binds to the HER2/*neu* receptor. The recently published Phase III ToGA (Trastuzumab for Gastric Cancer) study found a 2.7 month survival benefit in favor of patients with advanced gastroesophageal cancer who were randomized to trastuzumab plus combination chemotherapy [7]. However, the cost/benefit ratio of instituting HER2-targeted therapy in gastric cancer is much less clear. First, several studies have failed to find a significant association between HER2 overexpression/amplification and decreased survival (particularly on multivariate analysis). A recent systematic review found that of 35 studies reporting the impact of HER2 overexpression on survival in gastric cancer only a small number found a significant association with poorer overall survival (13 vs. 22 studies) [8]. In two of the 22 studies, the opposite finding was found (i.e., significantly longer overall survival in patients with HER2 overexpression). This raises the possibility that “...HER2 overexpression might already be conferring a better prognosis across both groups of this population of patients,” as written by the ToGA trial authors in their recent publication [7]. Second, trastuzumab costs on average \$19,431 Australian dollars per person (as per the ToGA trial methodology), and carries with it a significant risk of cardiac dysfunction (2–7%) [9]. Who pays for this treatment and at the detriment of what other government services and/or treatments?

Despite our greater understanding of the role of angiogenesis in upper gastrointestinal cancer, the successful and cost-effective integration of antiangiogenic agents into clinical practice remains somewhat elusive. Okines et al., in a recent review [6], pleaded for “parallel prospective translational research in current trials” to “bridge” gaps in our knowledge. I would argue that translational or benchside research, such as the current study by Liu et al., is an essential first step prior to the institution of further

industry-sponsored clinical trials because of the tendency of such trials, even when randomized, to produce biased results [10]. Until we fully understand the mechanisms of tumor angiogenesis, including the recognition of validated biomarkers that can indicate the efficacy of these high-cost treatments, it is unlikely that we will have a major impact on disease-free progression and overall survival rates in patients with early and advanced gastric cancer.

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