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COMMENTARY

VEGF and EGFR Antagonists for Gastric Cancer

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The idea of the dependence of tumor growth and metastasis on blood vessels was published for the first in the 1970s [1]. Tumor anti-angiogenesis is a rational target for therapy. Although accumulating preclinical evidence supports this hypothesis there is still moderate overall survival benefit in patients with metastatic colorectal and lung cancer, No positive adjuvant trial has reported improved cure by adding anti-angiogenic agents to cytotoxic chemotherapy for any cancer type.

The fact that nearly four decades later, despite major advances in biotechnology and molecular research there is only moderate or less clinical success reveals that cancer is much more complicated that we have supposed [2,3]. Cure for metastatic disease is major goal but it will probably remain an elusion for this century. Even in the adjuvant setting despite novel combinations with surgery, radiotherapy and new systemic therapies, cure rates of patients with advanced solid cancers will moderately be improved in the near future.

Bevacizumab (Avastin) --a humanized monoclonal antibody directed against vascular endothelial growth factor A (VEGF-A), is currently approved by the US Food and Drug Administration (US FDA) for the treatment of metastatic colorectal cancer and non–small-cell lung cancer. However, FDA recommended against approval of bevacizumab for patients with metastatic breast cancer, largely because a large-scale phase III trial showed no overall survival advantage for patients who received bevacizumab [4]. This case highlights the shifting sands on which investigators and drug developers stand when the results of extremely complicated and expensive clinical trials are reported.

Could the addition of bevacizumab to chemotherapy improve survival of patients with operable gastric cancer? The results of the ongoing United Kingdom National Cancer Research Institute ST03 trial of perioperative epirubicin, cisplatin, and capecitabine — with or without bevacizumab [5] will elucidate this critical question. Nevertheless, in the absence of a phase III positive trial in the metastatic gastric cancer, the contrasting results from trials for various other solid tumors, and Jain [2] prediction that cure by

combining anti-VEGF and cytotoxic agents in the adjuvant setting should be expected in the more distant future. There are some concerns whether a generalization for anti-VEGF therapy in all patients with stage II/III gastric cancer can ever be proven effective to increase cure rates.

Instead, molecular biomarkers to predict response to anti-VEGF and other combined targeted agents are urgently needed for various solid tumors including gastric [2,3,6-10].

Recently, Lieto et al [11] correctly focused their efforts to identify gastric cancer patients who might mostly benefit by inhibiting VEGF/EGFR pathways. Although the authors found that about half of patients expressed VEGF and EGFR, there is no correlation of VEGF and EGFR levels and response to anti-VEGF and anti-EGFR agents [3]. Larger number of patients is required to assess whether these markers could more accurate than TNM stage predict the outcomes of patients.

Prognosis of gastric cancer still remains poor despite advances in locoregional tumor control with D2 surgery, D1 surgery plus radiotherapy and systemic treatment with adjuvant chemotherapy [12]. Adjuvant chemotherapy irrespective of extent of surgery and timing of administration has become standard [13,14] following the results of pivotal adjuvant trials [15-17]. Despite these improvements, cure rates for stages II/III disease are still low.

As reported above the MAGIC Trial 2 in the UK [5] has launched a large-scale phase III randomized trial with enrollment of more than 1000 patients with resectable adenocarcinoma of the stomach and gastroesophageal junction. The patients are randomly assigned to receive perioperative chemotherapy with or without bevacizumab. Given that there is no adjuvant trial testing the efficacy and safety of bevacizumab for any solid cancer, the results of this study are awaited with great interest. There are however some concerns considering the contrasting results of bevacizumab efficacy in metastatic setting for colorectal, lung and breast cancer [2,3]. Perhaps, a priority would be given in developing biomarkers to predict response to VEGF antagonists under the light of rapidly growing technological advances and biomedical research progress. Guided clinical trials selecting for enrollment only responder patients might be an optimal process.

Tailoring the best treatment in individuals with gastric cancer can dramatically alter poor outcomes of patients with localized advanced gastric cancer. Currently, a comprehensive step-by-step, bench-to-bedside protocol [6]. Perhaps, instead of major clinical trials with combination of targeted and cytotoxic agents, priority should be given on biomarkers research to guide the design of randomized trials only among responder patients to specific therapies. The era of personalized medicine has been started.

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