Editorial

Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in epidermal growth factor receptor-2-negative, mesenchymal-epithelial transition-positive gastroesophageal adenocarcinoma: is it a real failure?

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Gastric cancer (GC) is the sixth most common cancer worldwide and the fourth leading cause of cancer-related deaths. The median overall survival is between 8–16 months but varies for different geographical locations. Because of its asymptomatic nature, GC is usually diagnosed at an advanced stage, mostly with metastasis (1,2).

The prognosis of patients with HER_2^- GC is generally poor (<10% survival at 5 years), with marginal treatment options. The approval of targeted bivalent therapies such as trastuzumab and ramucirumab by the Food and Drug Administration (FDA) for the treatment of GC has prompted interest in onartuzumab (3,4). This compound is a monovalent monoclonal humanized antibody, which inhibits expression of the mesenchymal-epithelial transition (MET) oncogene (5).

The lacklustre results of a recent phase III clinical trial examining the safety and efficacy of onartuzumab in the treatment of advanced-stage GC is a disappointing setback (4). We appreciate the sponsor's decision to terminate the study early, in light of similar findings from a Phase II trial assessing onartuzumab plus MFOLFOX6 (4). Onartuzumab also has been shown to be ineffective in a phase III clinical trial of stage IIIB and IV non-small cell lung carcinoma (NSCLC) (6).

Previous research has shown that the over-expression/mutations/alternate gene splicing/amplification of MET results in poor prognosis and in a more severe form of disease for various cancers including breast cancer, colorectal cancer, GC and NSCLC (7-10). MET, also known as N-methyl-N'-nitroso-guanidine human osteosarcoma transforming gene, is an oncogene, which plays an important role in tumor progression, angiogenesis, tumor cell motility, invasion, and metastasis.

MET encodes hepatocyte growth factor (HGF) receptor, which activates key tumor progression molecules including mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), retrovirus-associated DNA sequences (RAS) and phosphatidylinositol 3-kinase (P13K). These molecules regulate different tumor progression steps and their increased expression is associated with a more aggressive form of GC (11-13). In particular, HGF plays an important role in cell mobility and the separation of cancerous cells from the primary tumor site, facilitating their translocation to other organs. This is the first and essential step of metastatic disease (13).

In more than 50% cases of GC, the peritoneal is the predominant site of metastasis, followed by lymphatic and haematogenous targets (14). The number of metastatic sites, location of metastasis, and nodal status are significantly associated with disease prognosis.

Key factors in understanding the clinical aspects of GC are its asymptomatic nature, varying tumor biology, as well as regional and demographic differences. The majority of patients with GC are diagnosed in China, Japan, South/Central America, and Eastern Europe (15). Although GC is less prevalent in other parts of the world, such as the United States and Western Europe, more than 80–90% of cases are diagnosed at an advanced stage, when the possibility of a cure is low. Finding an effective treatment for early-stage GC is similarly challenging in these countries, given its low incidence rate. Additionally, intestinal versus diffuse histologic-subtype is more common in higher prevalent countries, with the latter conveying greater risk. Race, age at diagnosis and tumor location (proximal/distal) are other important determinants of GC incidence and progression that may differ by geography and global health care systems (2,16).

An infectious aetiology [*Helicobacter pylori* (*H. pylori*)] for GC, in contrast to a more sporadic form of the disease, is commonly observed in the aforementioned regions of the world with a high prevalence rate (17-22). *H. pylori* infection, which is classified as a group 1 carcinogen for GC by World Health Organization (WHO), is associated with increased expression of MET protein and GC progression.

Treatment for stage IV GC is predominantly palliative rather than curative. The current study of onartuzumab, as well as other phase II and III clinical trials of NSCLC and breast cancer, have mainly enrolled patients with metastatic disease (6,23). A more successful study design for onartuzumab may entail selecting patients with early-stage GC from regions of the world that have a history of *H. pylori* infection. However, such a study design will need to be carefully evaluated from a pharmacoeconomic perspective. The management of embolic and thrombotic events also may pose a concern when healthcare resources are limited. Specifically, these and other medically serious adverse events (MSAE) may lead to an increased mortality rate when not adequately monitored and treated in a timely fashion (24).

MET expression is not limited to HER_2^- GC, although the prognosis of this group is poor. Future studies of onartuzumab will benefit by including patients with HER_2^+ GC. Furthermore, early side effects such as peripheral edema, local swelling, and fluid overload are more frequently observed for onartuzumab versus placebo (24). Because this differential effect may lead to unintentional unblinding and study bias, it will be important to use a permuted block design with "randomly chosen block sizes", when randomizing patients in a new study involving onartuzumab (25).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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