Pharmacoeconomic studies of targeted agents in gastric cancer: ready for prime time?

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Gastric or gastroesophageal junction (GEJ) cancer represents a major health public issue. This disease is the second leading cause of cancer related death among men and the fourth among women (1). In China, the well known decline of incidence was less dramatic than other countries; in fact, an increase has been observed in the oldest and the youngest age subgroup, and a less remarkable decline has been observed among women than in men (2). Of note is that the age of onset of developing gastric cancer in Chinese population is younger than that in the West. The high mortality rate from gastric cancer is a result of the high incidence of metastatic disease, the aggressive clinical course and lack of effective systemic therapies. The frustrating lack of significant advancements in the treatment of advanced gastric cancer remains one of medical oncology's biggest disappointments. This has resulted in regulators, investigators, and practicing oncologists gradually lowering their standards/expectations with regard to interpreting clinical trials. Moreover, with the exception of trastuzumab, the combination of target agents with standard chemotherapy has failed to produce any added benefit to patients with advanced gastric cancer.

HER2 overexpression can be determined by immunohistochemistry (IHC) using a monoclonal antibody or by the detection of HER2 gene amplification through fluorescent *in situ* hybridization (FISH). Increased expression of HER2 has been detected in 13-23% of patients with gastric cancer. In Asians, most gastric tumors arise distally to the GEJ. Large, unselected Asian population series show lower HER2 positivity rates (ranging from 6% to 15%) than those from Western countries (ranging from 10% to 23%) (3). Because of its observed overexpression and/or amplification in a significant percentage of gastric cancers and its association with poor prognosis, the human epidermal growth factor receptor 2 (HER-2) signalling cascade has been treated with targeted agents in recent trials.

Trastuzumab (Herceptin), a humanized monoclonal antibody directed against the extracellular domain of HER2, was approved by the US Food and Drug Administration (FDA), and by the European authorities, for treatment of metastatic breast cancer (MBC) overexpressing HER-2, as detected either by immunohistochemistry (IHC) or by fluorescence in situ hybridization (FISH). Based on the phase III, randomized, ToGA trial, trastuzumab in combination with standard cisplatin and fluoropyrimidine (either 5-fluorouracil or capecitabine) received FDA approval as first-line treatment for advanced gastric or gastroesophageal junction cancer. The addition of trastuzumab to chemotherapy improved median overall survival from 11.1 months (95% CI, 12-16 months) in the control arm to 13.8 months (95% CI, 10-13 months) in those assigned to chemotherapy alone (hazard ratio 0.74; 95% CI, 0.60-0.91; P=0.0046) (4). One relevant problem with the ToGA study is that the economic impact of the incremental survival benefit is still unknown. Indeed, there is a growing consensus world-wide that cost-effectiveness considerations should be taken into account when making private or public health insurance decisions for coverage of innovative and costly medical procedures. Medical decision makers need information on the economic value of the new treatment for medical resource optimisation.

In gastric cancer, tumor heterogeneity of the HER2 genotype, which can lead to discrepancies in the results

from IHC and FISH testing, is more prominent than what was experienced in breast cancer (5). Incomplete basolateral membrane HER2 IHC staining is also more common in gastric cancer, due to the higher frequency of glandular formations that occur in gastric tissue. According to FDA, a patient with an IHC score of 3+ and/or positive FISH (with any IHC result) could be treated with a trastuzumab-based regimen. In fact, HER2 testing in the ToGA trial required both IHC and FISH and only one positive test was needed to indicate eligibility for HER2-targeted therapy (IHC 3+ or FISH+). Of the randomized patients included in the ToGA trial, 25% (146/584) of the population could have been missed using the current FDA approved breast cancer HER2 testing algorithm if only one HER2 test was used (i.e. IHC 0/FISH+, IHC 1+/FISH+, IHC 3+/FISH-). However, the National Comprehensive Cancer Network (NCCN) guidelines panel recommended that less than 3+ overexpression of HER2 by IHC should be additionally examined by FISH or other *in situ* hybridization methods.

In this issue of Translational Gastrointestinal Oncology, Wu and Colleagues provided a pharmacoeconomic assessment of the use of trastuzumab in the Chinese patients population with advanced gastric cancer. In this analysis, the direct costs were estimated from the perspective of Chinese health care system. Secondly, the Markov model simulated the natural progression of advanced gastric and closely matched the reported PFS curve and mortality. The Authors demonstrate that the incremental cost-effectiveness of trastuzumab is dramatically unsatisfactory, i.e. quality-adjusted life-years (QALYs) was far less than 1 (0.18) and the incremental cost-effectiveness ratio (ICER) was $ 251,667,10/QALY gain.

It is very important to highlight that a discount plan for trastuzumab would certainly decrease the ICER of the combination of trastuzumab with chemotherapy in gastric cancer. However, some remarks should be addressed. The exploratory retrospective analysis of the ToGA trial revealed that treatment with trastuzumab in combination with chemotherapy improved in a statistically and clinically meaningful manner the median OS in patients with IHC2+/FISH+ and IHC3+ gastric or gastroesophageal junction adenocarcinoma. Thus, the European board, EMEA, approved trastuzumab for the treatment of metastasized adenocarcinomas of the stomach and immunohistochemical testing is the primary method of choice to determine HER2 status in gastric cancer, while FISH is restricted to those cases that have equivocal (IHC2+) HER2 expression. Specifically, in the post-hoc identified subgroups with IHC2+/FISH+ and IHC3+, median OS increased from 11.8 months for the chemotherapy treatment arm to the encouraging 16.0 months for the chemotherapy with trastuzumab arm (hazard ratio 0.65; 95% CI, 0.51-0.83). Conversely, in patients with gastric tumors with low HER2 expression (0/1+) and FISH+, the addition of trastuzumab to chemotherapy was not associated with an evident benefit (hazard ratio 1.07; 95% CI, 0.70-1.62). There was evidence of a significant interaction test (P=0.036) between treatment and the high HER2 expression versus low HER2 expression groups. The hazard ratio of OS for patients with IHC 2+/FISH+ was 0.75 (95% CI, 0.51-1.11). In the pre-planned subgroup analysis of patients with IHC3+/FISH+, the median OS reached 17.9 months with trastuzumab-based chemotherapy and the hazard ratio was 0.58 (95% CI, 0.41-0.81). Thus, the administration of trastuzumab in patients with HER2 3+ gastric cancer could be cost-effective. This evidence was previously demonstrated by the pharmacoeconomic evaluation of the U.K. Authority (NICE) (6) and by a subgroup analysis of Japanese and Korean patients enrolled in the ToGA trial (7).

In our opinion, one of the most important ways to improve the value of trastuzumab in gastric cancer is to further develop the validation of biomarkers to improve the selection of patients benefiting from treatment. Active research is ongoing to improve the knowledge of molecular biology of gastric cancer and to identify reliable prognostic and predictive factors that may improve the cost-effectiveness of targeted agents.

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