Costs of trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or gastroesophageal junction cancer: does one "Analysis" fit all?

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Abstract: New cancer treatments are posing a significant financial burden on health-care systems worldwide. Cost effectiveness analyses of novel cancer treatments have received increased attention in oncology and are being used to make reimbursement decisions. In this article, we review a recently published economic evaluation of adding Trastuzumab to chemotherapy for HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer in China. The study suggests that the addition of trastuzumab to conventional chemotherapy might not be cost-effective based on incremental cost-effectiveness ratios of $251,667.10/QALY gained. Although highlighting an opportunity for efficient investment in cancer care, we believe that the results of this analysis are not generalizable to other health care system. While the incremental cost-effectiveness is likely to remain quite large in any context, it is known that cost-effectiveness is heavily dependent on a ceiling ratio and a decision maker's willingness to pay for a unit of quality of life gained.

Key Words: Cost effectiveness analysis; trastuzumab; gastric cancer; QALY. ToGA trial

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While increased survival is needed for patients with Gastric cancer, new treatments are posing a significant economic burden on health care systems worldwide. The Trastuzumab for Gastric Cancer (ToGA) study (1) reported a statistically significant overall survival benefit of 11 weeks for trastuzumab plus chemotherapy compared with chemotherapy alone for first-line treatment of advanced gastric and gastroesophageal cancer. However, Bin Wu *et al*. (2) suggested in an economic evaluation in a Chinese population that the addition of trastuzumab to conventional chemotherapy might not be cost effective in patients with HER-2 positive advanced Gastric and GE junction cancer. In their analysis, they concluded that poor overall survival time has the largest impact on cost.

Trastuzumab has been approved for HER-2 positive breast cancer for several years in the adjuvant and metastatic setting. Several cost-effectiveness analyses have been performed to assess the clinical and economic implication of adding trastuzumab to the treatment of breast cancer. In a US based analysis published in 2007, the projected additional lifetime cost of adjuvant trastuzumab per quality-adjusted life year (QALY) gained was $26,417 (3). Discounted incremental lifetime cost was $44,923, and projected life expectancy was 3 years longer for patients who received trastuzumab. The projected cost of adding trastuzumab to chemotherapy during a 20 year horizon was $34,201 per QALY gained.

Similar results were reported in an Australian analysis where adjuvant trastuzumab for early breast cancer was found to be cost effective when given over either 52 or

9 weeks (4). Another Italian/American analysis (5) concluded that adjuvant trastuzumab increases life expectancy by 1.54 (1.18 discounted) QALYs, and trastuzumab achieves its clinical benefit at a cost of 14,861 Euros and 18,970 dollars per QALY gained. The incremental cost effectiveness was higher than 50,000 Euros/QALY (or 60,000 dollars/QALY) at time horizons shorter than 7.8 years and for patients older than 76 years or with a 10-year risk of relapse lower than 15%. In a different analysis from the United Kingdom (6), the cost effectiveness of adjuvant trastuzumab was thought to be uncertain and dependent on assumptions regarding its clinical effect. Uncertainty around cost effectiveness was mostly related to the length of treatment and late toxicities.

Similar analyses have been reported in metastatic breast cancer (MBC); in a French analysis published in 2009 (7), the cost of adding trastuzumab to the treatment was 3 times higher (€39,608 *vs*. €12,795). The cost per additional life-year gained was estimated to be €27,492/year of life. The study concluded that despite the high price, trastuzumab is cost-effective in MBC patients to the extent that its incremental cost per life-year saved remains lower than the per capita gross domestic product, a commonly used threshold. Another analysis from France showed similar results where the mean overall cost was 33,271 euro per patient treated with trastuzumab versus 11,191 euro per patient treat it without it. The additional cost was 15,370 euros per QALYS gained (8).

This study we are reviewing here investigated the cost-effectiveness of adding trastuzumab to chemotherapy for patients with HER-2 positive advanced gastric or gastro-esophageal junction cancer in China (2). The time horizon for this analysis was 5 years. Relative to chemotherapy alone, the addition of trastuzumab increased cost and effectiveness by $56,004 and 0.18 QALYs, respectively, resulting in an ICER of $251,667/QALY gained. The study concluded that, for the Chinese health care system, adding trastuzumab was not cost-effective in this population. The methods of the study were appropriate. However, there is a risk of bias due to the key variables coming from an open label study. On the other hand, gastric cancer is a heterogeneous disease and it has been suggested that outcomes in an Asian population are better than in other populations. In the ToGA trial, only 50% of the patients were from Asia, making it difficult to generalize the results to other populations. This is especially true since the utility value for the control group was taken from a Chinese study. This study assumed that the additional trastuzumab had no impact on quality of life beyond the impact of the underlying chemotherapy regimen. Consideration of this impact would only make trastuzumab even less cost-effective than in the baseline analysis.

Generalizing this data to other countries with different health care systems, costs and utilization patterns requires further investigation. The authors reported a number of limitations, including not considering other chemotherapy regimens for the treatment of gastric cancer, which was not feasible since such trials have not yet been reported. The major limitation of this model is the lack of long-term survival data. Some factors were omitted entirely, such as HER-2 testing cost and non-treatment related supportive care cost including nutrition, pain management, doctor visits, etc. The latter costs may be quite significant after disease progression and changing to second line treatment.

An important subgroup, not examined in the study by Wu *et al*., are patients with high HER-2 expression. Patients in the ToGA trials with high HER-2 expression on immunohistochemistry (IHC 3+) had a better overall outcome, and a Korean and Japanese sub-group population of the ToGA trial were analyzed based on their IHC staining (9). In this base-case analysis, the incremental cost-effectiveness ratio was JPY 6.1 million (€55,000) per QALY gained and JPY 4.3 million (€39,000) per life-year gained concluding that trastuzumab treatment for the IHC 3+ population is cost effective.

The results of the analysis must be considered within the context of the study, including the population and time horizon. The impact of other adverse event and supportive care cost were not captured because of the small number of patients who were alive at the time of the analysis. Patients and caregiver's time cost and out-of-pocket expenses were not included as well. In order to increase the value derived from adding trastuzumab similar to breast cancer, the survival benefit must be significantly greater. The results of this analysis are clearly distinct from the breast cancer literature where trastuzumab has been demonstrated to be cost-effective and been approved for years in the metastatic and adjuvant setting. While the improvement in survival in the ToGA trial was statistically significant, it was very small.

The cost-effectiveness analysis by Wu *et al*. in the Chinese population is not generalizable to non-Asian populations with different health care systems. While the incremental cost-effectiveness is likely to remain quite large, many developed countries have shown a willingness to accept much higher thresholds of cost-effectiveness in oncology.

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