An Economic Evaluation of Adjuvant Trastuzumab Therapy in HER2-Positive Early Breast Cancer

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ABSTRACT

Objective: One-year adjuvant trastuzumab therapy increases disease-free and overall survival in the adjuvant treatment of early HER2-positive breast cancer. This study aims to assess the long-term cost-effectiveness of adjuvant trastuzumab treatment in Beijing, Shanghai, and Guangzhou.

Methods: A Markov health-state transition model was constructed to simulate the natural development of breast cancer based on HERceptin Adjuvant (HERA) trial, estimate costs and disease progression over a lifetime perspective with annual transition cycles, and evaluate the cost-effectiveness of 1-year adjuvant trastuzumab treatment group compared with the standard adjuvant chemotherapy. From the perspective of a China health insurance system, cost was calculated based on a survey from clinical expert panels.

Results: On the basis of HERA data, the model results showed that the utilization of adjuvant trastuzumab treatment in early breast cancer can prolong 2.87 life years, compared with the standard chemotherapy group. The incremental cost for an additional life-year gained (LYG) was US$7364, US$7933, and US$7929 in Beijing, Shanghai, and Guangzhou, respectively. If measured by quality-adjusted life-year, the incremental cost-effectiveness ratio was US$7676, US$8049, and US$8046, respectively.

Conclusion: The results suggest that the 1-year adjuvant trastuzumab treatment is cost-effective. Both clinical and economic benefits were superior for the 1-year adjuvant trastuzumab treatment group compared with the standard adjuvant chemotherapy group.

Keywords: adjuvant treatment, breast cancer, cost-effectiveness, trastuzumab.

Introduction

According to the National Cancer Deaths Retrospective Survey, the mortality rate of breast cancer was 3.37 and 3.53 per 100,000 females in 1973 to 1975 and 1985 to 1992, respectively, and it increased to 5.90 per 100,000 females in 2004 to 2005 in China [1]. There was an uptrend either in the morbidity and mortality, or in absolute number, during 2000 and 2005. The number of new cases has increased by 38.5% and death toll rose by 37.1% [2]. Breast cancer has already become one of the most common cancers for the women in Beijing, Shanghai, and other developed regions [3]. The deaths due to breast cancer were estimated as 37,595 per year in China [4]. Reducing the deaths caused by breast cancer is one of the most important issues for Chinese women’s public health.

Oncogene erb B-2, called HER-2/neu, is an important molecule marker and curing target of breast cancer because of close correlation between its abnormal amplification and expression and the occurrence and progression of breast cancer [5]. Trastuzumab (Herceptin), a recombinant, humanized, monoclonal antibody targeting HER2 is well established as an effective treatment for HER2-positive breast cancer. Many studies have proven the obvious effects of trastuzumab in treating metastatic breast cancer. It was notable that trastuzumab significantly reduced the risks of cancer local recurrence and metastasis and can prolong survival time of the patients [6–8].

Though the cost of adjuvant trastuzumab treatment is high, the National Institute for Health and Clinical Excellence (NICE) has recommended adjuvant trastuzumab treatment for HER2-positive breast cancer patients [9,10]; and the evidence from other countries showed that trastuzumab was of high cost-effectiveness in adjuvant treatment for early breast cancer [11,12], there is still no evidence of this kind in China. With its high treatment cost, it is a concern whether trastuzumab is of economic value for the patients. With the development of China’s health insurance system, cost-effectiveness and outcomes evidence tends to be vital for the policymaking to make a tradeoff between limited financial resources and equitable access, especially in urban China where there exists higher demand for high quality health care. Therefore, this cost-effectiveness analysis is designed to examine the economic value of adjuvant trastuzumab therapy based on the HERceptin Adjuvant (HERA) trial to support health insurance decision-making.

Materials and Methods

A Markov health-state transition model was constructed to assess the cost-effectiveness of 1-year adjuvant trastuzumab treatment for women with HER2-positive early breast cancer. Two treatment scenarios were examined: 1-year adjuvant trastuzumab treatment after surgical therapy of early breast cancer and standard adjuvant chemotherapy (combination of docetaxel, doxorubicin, and cyclophosphamide) after surgical therapy. Clinical data and the treatment protocol were based on the results of the HERA trial. Five key health states were identified in the progression of breast cancer, including disease-free state (representing the health state after the completion of surgery and chemotherapy, disease-free state [DFS]), recurrence (local and contralateral recurrence), metastasis, cardiac event, and death (see Fig. S1 at An Economic Evaluation Of Adjuvant Trastuzumab Therapy In HER2-Positive Early Breast Cancer Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH11x3_WChen2.asp). The model was simulated from lifetime perspective. The cycle length was 1 year and the maximum cycle number was 45. For modeling purposes, it was assumed that each patient can experience only one locoregional or contralateral breast cancer recurrence. After a single year in the locoregional/
contralateral recurrence state, the patients returned to the recurrence health state and remained there until they die or experience metastasis.

**Clinical Data**

According to the HERA study, it was assumed that there were two groups each having 100 50-year-old patients in the DFS after surgery followed by adjuvant therapy. In the trastuzumab group, all patients were treated with adjuvant trastuzumab for 1 year and followed by standard chemotherapy. In the observation group, all patients were treated with standard adjuvant chemotherapy. The specific transition probabilities of disease progression for the two groups were retrieved from the HERA study and literature (see Table S1 at An Economic Evaluation Of Adjuvant Trastuzumab Therapy In HER2-Positive Early Breast Cancer Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_WChen2.asp) [9,13].

The impact of trastuzumab on disease progression is estimated by applying the hazard ratio (HR) observed in the HERA study, i.e., the unadjusted HR for the risk of recurrence in the trastuzumab group, as compared with the comparator group, was 0.54 (95% confidence interval, 0.43 to 0.67) [9]. We assumed a constant yearly risk for local and distant recurrences during the first 5 years after treatment before decreasing in a stepwise function at 5 and 10 years, i.e., the adjustment of baseline risk due to the time elapsed because surgery without a recurrence is divided into three different categories: 0–5 years, 6–10 years, over 11 years. This adjustment of baseline risks takes into account that the probability to develop a recurrence is reduced among long-term survivors who have not experienced any recurrences. The clinical benefit of trastuzumab was assumed to last for the first 5 years [13]. Thereafter, the relative risk for recurrent and metastatic disease in the trastuzumab group was assumed to be the same as in the observation group. Population-based utilities associated with different health states were derived from published literature (see Table S2 at An Economic Evaluation Of Adjuvant Trastuzumab Therapy In HER2-Positive Early Breast Cancer Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_WChen2.asp) [13–17]. The age-specific death rates for DFS and recurrence states were assumed to be the same as that of the whole population, taken from the China National Population Statistics [18].

**Cost Data**

The evaluation was considered from the perspective of China’s health insurance system and includes only direct medical expenditures.

The loading dose of trastuzumab in the model was 4 mg per kilogram weight and 2 mg per kilogram weekly. The average weight of patients with breast cancer was 58 kg in the model and assumed to be the same as that of general population [19].

To estimate the resource utilization and related costs, a survey of clinical expert panels was conducted with a structured questionnaire. The survey questionnaire was designed to understand the detailed treatment choices in the DFS, local and contralateral recurrence, advanced breast cancer, and cardiac events. In total, 28 famous clinical experts in breast cancer specialty chosen in the whole country have been investigated to inquire the proportion of the average follow-up patients who take outpatient visit and hospitalization and the frequency of medical care utilization including examination, lab tests, and all kinds of treatments (surgery, hormonal therapy, chemotherapy, radiotherapy, special interventions). All clinical experts were required to give the second estimate based on the feedback of the average of every item derived from the first round survey. The average of every item based on the second round survey was calculated and employed to measure the annual medical expenditure burden under different health states according to the fee schedule of medical services and pharmaceuticals related in Beijing, Shanghai, and Guangzhou cities as representatives of urban China. A discounting rate at 3% was used to discount medical expenditures that happened at different years.

**Sensitivity Analysis**

We conducted univariate sensitivity analyses with Monte-Carlo simulation method to understand the key drivers and general sensitivity of the model. The following variables were assessed: discounting rate of medical expenditure, discount rate of life years, the probabilities of DFS progressed to recurrence and metastasis, the price of trastuzumab, and the cost of first year in recurrence and metastatic state.

**Results**

**Annual Medical Expenditure in Different Health States**

The annual medical expenditure except trastuzumab cost was assumed to be the same in different health states for trastuzumab and observation group (see Table S3 at An Economic Evaluation Of Adjuvant Trastuzumab Therapy In HER2-Positive Early Breast Cancer Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_WChen2.asp). The trastuzumab cost was calculated according to an average patient with the weight of 58 kg and reached US$54,043 for 1-year treatment. The results showed that there was higher medical expenditure burden in first year in local and contralateral recurrence state and metastatic state.

**Cost-Effectiveness Analysis**

The total life years obtained for the treatment with trastuzumab are 18.17 years and 15.30 years for the treatment without trastuzumab, meaning the incremental life years of 2.87 years for the patients treated with trastuzumab. According to the measurement of quality-adjusted life-years (QALY), the incremental QALY of 2.83 years are generated with trastuzumab treatment (see Table S4 at An Economic Evaluation Of Adjuvant Trastuzumab Therapy In HER2-Positive Early Breast Cancer Value in Health Supporting Information at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_WChen2.asp).

The discounted lifetime medical expenditure for trastuzumab treatment reached US$83,960 to US$89,800, increasing by US$21,700 to US$22,760 compared with that without trastuzumab treatment.

The results showed that the incremental cost-effectiveness ratio (ICER) for trastuzumab treatment ranged from US$7564 to US$7933 per QALY. If measured by QALY, the ICER was estimated to be US$7676 to US$8049 per QALY gained.

**Sensitivity Analysis**

The cost-effectiveness of trastuzumab depends on some key parameters, including the discounting rate of medical expenditure and life-year, the probabilities of DFS progressed to recurrence and metastasis, the price of trastuzumab, and the cost of first year in recurrence and metastatic state. Figure S2 (found at An Economic Evaluation Of Adjuvant Trastuzumab Therapy In HER2-Positive Early Breast Cancer Value in Health Supporting Information at: http://www.ispor.org/Publications/value/
VIIHSupplementary/ViH12s3_WChen2.asp) presents the various incremental costs per QALY gained when these parameters are changed. The results highlight the sensitivity of the model to these parameters but also demonstrate that they remain cost-effective even with the most conservative assumptions as showed by the cost-effectiveness acceptability curve for Beijing case (see Fig. S3 at An Economic Evaluation Of Adjuvant Trastuzumab Therapy In HER2-Positive Early Breast Cancer Value in Health Supporting Information at: http://www.ispor.org/Publications/value/VIIHSupplementary/ViH12s3_WChen2.asp).

Discussion

Adjuvant trastuzumab has been proven to be a cost-effective regimen for HER-2 positive early breast cancer in many counties. In Switzerland, Dedes et al. found that adjuvant trastuzumab is a cost-effective regimen based on the clinical data from HERA trial, and ICER was about €17,000 to €38,000 per LYG [20]. In UK, a cost-effectiveness analysis submitted to NICE presented that the ICER of adjuvant trastuzumab treatment was £2396 and NICE has recommended adjuvant trastuzumab treatment for HER2-positive breast cancer patients [10,21]. In Japan, a cost-effectiveness model based on HERA trial showed that the ICER of adjuvant trastuzumab was JPY2,600,000 (€17,000) and concluded that adjuvant trastuzumab treatment was superior to the comparator [22].

Our model yielded a similar result as mentioned previously. In this comparison of observation after standard adjuvant chemotherapy, 1-year adjuvant trastuzumab treatment yielded an ICER of US$7564, US$7933, and US$7929 in Beijing, Shanghai, and Guangzhou, respectively. If measured by QALY, the ICER was US$7676, US$8049, and US$8046, respectively. According to the definition of WHO cost-effectiveness threshold [23], the adjuvant trastuzumab treatment for HER2-positive early breast cancer in developed urban China is cost-effective using gross domestic product (GDP) per capita (2006) as threshold [24].

Nevertheless, the major limitation of our analysis is the absence of long-term clinical evidence with adjuvant trastuzumab, leading to uncertainty about efficacy and toxicity of the alternative approaches to care over the years. Our model is based on the clinical data of one 1-year randomized clinical trial. The long-term clinical benefit had to be estimated by modeling techniques. More evidences on the effectiveness of adjuvant trastuzumab therapy are needed. Nevertheless, adjuvant trastuzumab regimen has been approved in many countries based on this short-term clinical data. The another limitation is that we used UK utilities in the model confirmed by Chinese clinical experts through Delphi method, because in China there are no health-related quality of life data for breast cancer patients applied to our analysis.

Based on the HERA trial and our economic analysis, we can conclude that 1-year adjuvant trastuzumab treatment is cost-effective compared with observation in a long-term perspective.

Source of financial support: This study was supported by a grant from Shanghai Roche Pharmaceutical Ltd, China.

Wen Chen, Zefei Jiang, Zhimin Shao, Qiang Sun, and Kunwei Shen have no conflicts to declare.

References