MaHTAS
Malaysian Health Technology Assessment Section

TRASTUZUMAB AS AN ADJUVANT THERAPY FOR EARLY BREAST CANCER AND ECONOMIC EVALUATION

Executive Summary

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Introduction

In Malaysia, breast cancer is the most common cancer in females and also the first most common cancer among population regardless of gender. According to the National Cancer Registry Report 2007, the age pattern showed a peak age-standardised rate (ASR) at the 50-59 age groups.

Human epidermal growth factor receptor 2 (HER2) is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family. Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer. Trastuzumab is used for the treatment of early-stage breast cancer that is HER2 positive, has or has not spread into the lymph nodes. Although this treatment has been routinely used, there are still controversial on the timing of the addition of trastuzumab to the chemotherapy regimen (simultaneously or sequentially).

In Malaysia, trastuzumab 440mg injection has been approved by Ministry of Health Formulary to be used only in adjuvant setting for patients with HER2 over-expressed breast cancer, which is HER2 3+ by immunohistochemistry and over-expressed by Fluorescence in situ hybridization (FISH) and high risk group. Oncologist suggested that Echocardiogram (ECHO) should be performed prior to first dose and every three months during treatment.

This review was requested by clinical oncologist from Hospital Kuala Lumpur to review the safety, efficacy/effectiveness and cost-effectiveness of trastuzumab as an adjunct in early breast cancer patients either concurrently or sequentially to chemotherapy.

Objective/Aim

i. To assess the safety, efficacy/effectiveness and cost-effectiveness of trastuzumab as an adjunct in early breast cancer patients either concurrently or sequentially to chemotherapy through a systematic review of literatures. The optimal duration for the usage of trastuzumab will also be reviewed.
ii. To calculate the incremental cost-effectiveness ratio (ICER) between chemotherapy + trastuzumab and chemotherapy alone as adjuvant treatment for early breast cancer.

Results and Conclusions

A total of 901 titles were identified from the OVID interface. One Cochrane systematic reviews, one systematic review and meta-analysis, two recent randomised controlled trials and four economic evaluations were included in this review.

Safety

There was high level of evidence to suggest that the risk of CHF was significantly higher in patients treated with trastuzumab compared to non-trastuzumab control group. Evidence also suggest that the risk was significantly higher with longer duration of treatment (> 6 months) and also with higher loading dose of treatment (8mg/kg).

Effectiveness

Overall Survival (OS)

The OS significantly favoured trastuzumab containing regimen over non-trastuzumab control group. In terms of duration, subgroup analysis reported that the OS significantly favoured trastuzumab containing regimen over non-

trastuzumab control group trials where trastuzumab was given longer (> 6 months). In the trials that gave trastuzumab and chemotherapy concurrently, the outcomes significantly favoured trastuzumab-containing regimens.

Disease Free Survival (DFS)
The evidence from Cochrane systematic review suggests that DFS favoured trastuzumab containing regimen over non-trastuzumab control group. There was no significant difference in DFS when trastuzumab was used for less than six months, or more than six months. Limited evidence to suggest that two years duration of adjuvant trastuzumab was not more effective than one year of treatment. However, six months treatment with trastuzumab failed to show that it was non-inferior to twelve months of trastuzumab. Despite the higher rates of cardiac events, twelve months of adjuvant trastuzumab should remain the standard of care.

Cost/Cost-effectiveness
Systematic review of cost-effectiveness evaluation reported a wide range of ICER/QALY ranging from USD 7,676 to USD 71,491.

Local economic evaluation
From the decision analytic modelling that has been conducted, addition of 1-year treatment with trastuzumab on top of standard adjuvant chemotherapy is considered as a cost-effective strategy for early breast cancer with HER2 positive, yielding an ICER of RM 83,544.59 per QALY gained, which is within the suggested value of cost-effectiveness threshold by WHO (1-3 times GDP per capita). However, if suggested cost-effectiveness threshold for Malaysia is taken into consideration which is ≤1 GDP per capita, this treatment may not be a cost-effective strategy.

Based on one-way sensitivity analysis performed, these components have shown to be a sensitive parameter for ICER determination: discount rate, disease-free state utility values, route of trastuzumab administration and cost of trastuzumab.

Methods for systematic review
Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1948 to present, EBM Reviews – Cochrane Central Register of Controlled Trials – July 2016, EBM Reviews – Cochrane Database of Systematic Reviews – 2009 to Jun 2016, EBM Reviews – Health Technology Assessment – 2nd Quarter 2016, EBM Reviews – Database of Abstracts of Reviews of Effects – 2nd Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 2nd Quarter 2016, Embase – 1988 to 2016 week 33. Searched were also run in PubMed. Google was used to search for additional web-based materials and information.

Methods for local economic evaluation
A state transition model (Markov cohort simulation) was developed using Microsoft Excel Workbook 2007 to estimate the cost-utility of adjuvant trastuzumab compared with chemotherapy alone for treatment of early breast cancer with HER2 positive status. A hypothetical cohort of women with HER2 positive early breast cancer was simulated in two treatment strategies: chemotherapy + trastuzumab as adjuvant treatment and chemotherapy alone as adjuvant treatment. This Markov model included six health states which were projected to lifetime horizon and the cycle length was one year. All costs and outcomes were discounted at 3% and the cost-effectiveness result was expressed in ICER.