TARGETED THERAPIES IN COMBINATION WITH NEOADJUVANT CHEMOTHERAPYFOR HER2-POSITIVE BREAST CANCER AND ECONOMIC EVALUATION

EXECUTIVE SUMMARY

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Background

Breast cancer is the most prevalent type of malignancy in females. It is a heterogeneous disease which can be divided into several subtypes. Based on severity, breast cancer is broadly categorised into three groups which are early breast cancer (EBC), locally advanced breast cancer (LABC) and metastatic breast cancer (MBC). Human epidermal growth factor receptor 2 (HER2) is a growth-promoting protein on the outside of all breast cells. About 15 to 20% women with breast cancer have overexpression of HER2 and called as HER2-positive. HER2-positive is an aggressive subtype that exhibits unique epidemiological, clinical and prognostic differences with poor response to standard chemotherapy regimens compared with HER2-negative. The treatment of breast cancer generally depends on the stage of disease and characteristics of the tumour which involves surgery, chemotherapy, radiotherapy and hormonal therapy. Neoadjuvant therapy in breast cancer refers to the administration of treatment with the intent of down staging the tumour and improves operability and surgical outcomes. The current practices in Malaysia for management of EBC include neoadjuvant chemotherapy only while management of LABC include neoadjuvant chemotherapy and anti-HER2 therapy for operable and inoperable conditions. In Ministry of Health Medicines Formulary (MHMF) Malaysia, trastuzumab injection was approved in adjuvant setting only for patients with HER2-positive, over-expressed by FISH (Fluorescence in situ hybridization) and high risk group (>30% lifetime risk but no known genetic variant). Both drugs (pertuzumab and lapatinib) are registered under National Pharmaceutical Regulatory Agency (NPRA) but not included in the MHMF. Pertuzumab injection is indicated for neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either >2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer and indicated in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for metastatic breast cancer. While, lapatinib is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab or in combination with letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer. As these agents may play an important role in neoadjuvant therapy setting, their effectiveness and economic implications need to be assessed. This HTA was requested by a Clinical Oncologist from Hospital Kuala Lumpur (HKL).

Objective

i-To assess the effectiveness, safety, cost-effectiveness, organisational or societal implication of trastuzumab, pertuzumab, lapatinib in combination with chemotherapy in neoadjuvant setting for patient with HER2-positive breast cancer.
ii-To determine whether to use one or dual targeted therapies in combination with chemotherapy in neoadjuvant setting for HER2-positive breast cancer.

Methods

The following electronic databases were searched through the Ovid interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-

Data-Review & Other Non-Indexed Citations, Daily and Versions(R)-1946 to March 26, 2021. Google Scholar was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. The references of retrieved articles were scrutinised for additional articles. No limits were applied. Last search was conducted on 5th of August 2021. A literature-based hybrid model (Decision tree and Markov cohort simulation) was developed using Microsoft 365 Excel Workbook® to estimate the lifetime costs and quality adjusted life years (QALYs) of using targeted agents in combination with neoadjuvant chemotherapy in early HER2+ breast cancer. This type of model was chosen for its ability to extrapolate efficacy data from short-term clinical trials in early HER2+ breast cancer to longer term cost-effectiveness results.
The epidemiological and disease-related data were obtained from local sources of data whenever available, or literature review when local data was not available.

Results and conclusion:
A total of 1019 records were identified through Ovid interface and 12 records were identified from other sources. Nineteen studies included in this review: two systematic review (SR) and network meta-analysis (NMA), nine randomised controlled trials (RCTs), three cohort studies, one cross-sectional study and four economic analyses.

Effectiveness
Based on retrievable evidence, targeted therapy had shown to improve the pathologic complete response rates in HER2-positive early and locally advanced breast cancer population particularly with the treatment of dual-targeted therapy. Combination of pertuzumab plus trastuzumab plus chemotherapy (with or without anthracyclines) significantly improved pCR compared with single-targeted therapy followed by combination of lapatinib plus trastuzumab plus chemotherapy (with or without anthracyclines). In addition, for both types of interventions (addition of pertuzumab or lapatinib), combination chemotherapy (with or without anthracyclines) was significantly better than mono chemotherapy. From indirect meta-analysis, they found that there was no difference in pCR between the two groups with and without anthracyclines. However, according to the SUCRA rank, the group without anthracyclines took the highest percentage of pCR for both additions of pertuzumab or lapatinib. The used of trastuzumab biosimilar plus chemotherapy (with or without anthracyclines) was also ranked higher than combination of pertuzumab plus trastuzumab plus docetaxel. There was a good level of retrievable evidence that showed the rates of Progression Free Survival, Disease Free Survival, Event Free Survival and Overall Survival were higher in dual-targeted therapy (for addition of pertuzumab or lapatinib) than single-targeted therapy.

Safety
In terms of safety, grade 3 to 5 treatment-related side effects were significantly higher in patients who received pertuzumab-arms (neutropenia), lapatinib-arms (diarrhea and skin disorders) and chemotherapy with commonly reported side effects of diarrhea and skin disorders. For incidence of cardiac events, there was no significant difference observed in all treatment arms. Trastuzumab biosimilar had comparable side-effects to trastuzumab.

Cost-effectiveness

Based on two cost-effectiveness analyses studies, mono chemotherapy (pertuzumab plus trastuzumab plus taxol) was more effective with the highest health benefits (10.73 QALYs) and less costly (US $ 415 833) compared to combination chemotherapy (taxol plus carboplatin plus pertuzumab plus trastuzumab or taxol plus pertuzumab plus trastuzumab plus anthracyclines). However, de-escalated strategies found that combination of trastuzumab plus taxol became the most cost-effective option in both HR-positive and HR-negative patients. One cost minimisation analysis showed SC trastuzumab resulted in savings of RM7561 every patient to the MOH and RM7820 every patient to the society in comparison with IV trastuzumab.

Local Economic Evaluation

From the decision analytic modelling that has been conducted, addition of six cycles of neoadjuvant trastuzumab biosimilar (Herzuma) or neoadjuvant Pertuzumab/ Trastuzumab on top of standard neoadjuvant chemotherapy considered as a cost-effective strategy for high-risk early breast cancer with HER2 positive, yielding an ICER of RM 16,471.59 and RM 96,013.20 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, addition of single targeted therapy may be the most cost-effective strategy. Definition of one Malaysian GDP per capita per QALY gained is USD10, 500 ~ RM 43, 884.75.

Based on one-way sensitivity analysis performed, these components have shown to be sensitive parameters for ICER determination: discount rate, recurrence state transitional probability values, and cost of targeted therapies.