Cost-minimisation analysis of intravenous versus subcutaneous trastuzumab regimen for breast cancer management in Hong Kong

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A B S T R A C T

Introduction: In 2017, breast cancer was the most common cancer and third leading cause of cancer death among women in Hong Kong. Approximately 20% of patients were human epidermal growth factor receptor-2 (HER2)-positive. This study was conducted to investigate cost differences between intravenous and subcutaneous trastuzumab regimens in Hong Kong using medical resources utilisation data from other countries.

Methods: A cost-minimisation model was developed to compare the cost of total care, including direct medical cost and full-time equivalent (FTE) hours. The drug acquisition cost was obtained from the manufacturer, whereas the costs for hospitalisation and clinic visits were acquired from the Hong Kong Gazette. Time (in FTE hours) was determined by literature review. All costs were expressed in US dollars (US$1 = HK$7.8). Costs were not discounted because of the short time horizon. One-way deterministic sensitivity analysis was performed to identify the effects of changes in drug acquisition cost, changes in FTE hours (based on confidence intervals reported), and changes in body weight (±20%).

Results: Literature review indicated that 0.18 FTE hour of nursing time (7.9 hours) and 0.14 FTE hour of pharmacist time (6.2 hours) could be saved each week if the subcutaneous formulation was used. Using data in 2017, after 18 cycles of treatment with subcutaneous trastuzumab, the drug acquisition and healthcare professional time costs were reduced by US$9451.28 and US$566.16, respectively, yielding an annual savings of over US$8 million.

Conclusion: The subcutaneous formulation of trastuzumab is a potential cost-saving therapy for HER2-positive breast cancer patients in Hong Kong. The drug acquisition cost was the parameter with the greatest effect on the total cost of treatment.

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New knowledge added by this study

- The results of this study suggest that the subcutaneous formulation of trastuzumab would be a cost-saving therapy for HER2-positive breast cancer patients in Hong Kong.
- The drug acquisition cost was the parameter with the greatest effect on the total cost of treatment.

Implications for clinical practice or policy

- The high drug acquisition cost of trastuzumab may prevent patients from receiving effective treatment.
- The subcutaneous formulation of trastuzumab is expected to remain more cost-effective, despite the potential emergence of biosimilar trastuzumab.

Introduction

In 2017, breast cancer was the most common cancer and third leading cause of cancer death among women in Hong Kong.[1] Additionally, an estimated 20% of breast cancers in Hong Kong were human epidermal growth factor receptor-2 (HER2)-positive.[2,3]

Intravenous (IV) trastuzumab, in combination with chemotherapy, is licensed for the treatment of HER2-positive early-stage breast cancer and metastatic breast cancer. It must be reconstituted into solution for loading dose infusion over a duration of 90 minutes, followed by maintenance dose infusion over a duration of 30 minutes.[4] Additionally, IV trastuzumab is dosed according to each patient's body weight, with a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every 3 weeks.[4] This regimen consumes considerable healthcare resources, including drug preparation and administration time, clinic and chair time, and physician time dedicated to patient interaction.[5]

A fixed-dose subcutaneous (SC) formulation of trastuzumab was developed to allow drug administration over approximately 5 minutes, which

is much shorter than the duration of IV infusion. The 600-mg dose of SC trastuzumab every 3 weeks is non-inferior to the IV formulation with respect to efficacy and tolerability.[6,7] Furthermore, approximately 90% of patients preferred SC over IV administration of trastuzumab in the PrefHer (Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer) randomised crossover trials,[8,9] which were designed to assess patient preference and healthcare professional satisfaction with both treatment options.

Data from other countries have demonstrated that for SC formulation of trastuzumab, less time is required for drug preparation and administration; moreover, fewer consumables are used.[10-13] A cost-minimisation analysis (CMA) study in Greece demonstrated that the total cost of therapy per patient was 21 870 euros (€) when using the SC formulation of trastuzumab, whereas it was €23 118 when using the IV formation of trastuzumab. The investigators concluded that use of the SC formulation of trastuzumab would provide cost savings for the Greek healthcare system.[10] A study in Spain revealed similar findings: the use of the SC formulation of trastuzumab led to a 19.4 to 28.8% cost savings in the hospital.[11] Additionally, a time-and-motion study in New Zealand compared medical resource utilisation between the IV and SC formulations of trastuzumab in patients with HER2-positive breast cancer. The potential cost saving was NZ$96.94 per patient per cycle.[12] Furthermore, a time-and-motion sub-study[13] from the PrefHer trials involving eight countries (Canada, France, Switzerland, Denmark, Italy, Russia, Spain, and Turkey) demonstrated time savings for patient chair, administration by healthcare professionals, and drug preparation.

The SC formulation of trastuzumab is expected to provide cost savings in other countries. However, healthcare systems and modes of clinical services differ between Hong Kong and other countries. Therefore, this study was conducted to investigate cost differences between IV and SC trastuzumab regimens in Hong Kong medical settings, using medical resources utilisation data from other countries.

香港的乳癌管理：皮下注射曲妥珠單抗方案的最低成本分析

李詠恩、鄭永德

引言：乳癌是2017年香港女性最常見的癌症和第三大癌症死因。大約20%患者的第二型人類上皮成長因子受體（HER2）為陽性。本研究旨在利用其他國家的醫療數據，調查香港靜脈注射和皮下注射曲妥珠單抗方案的成本差異。

方法：我們建立了一個模型來比較總護理成本，包括直接醫療成本和全職等效（FTE）時數。藥品購置成本是從製造商處獲得，住院和門診費用是從香港特區政府憲報獲得，而時間（以FTE時數為單位）則從文獻取得。所有成本均以美元表示（1美元 = 7.8港元）。由於時間跨度短，模型並未有考慮折現。我們亦透過單向敏感度分析以確定藥品購置價格變化、FTE變化（根據研究所得的置信區間得出）和體重變化（±20%）的影響。

結果：過往文獻顯示，如果使用皮下製劑，每周可節省0.18 FTE時數護理時間（7.9小時）及0.14 FTE時數藥劑師時間（6.2小時）。以2017年數據計算，在使用皮下曲妥珠單抗治療18個週期後，藥品購置成本和醫療保健專業人員的時間成本分別減少了9451.28美元和566.16 美元，而每年則共可節省超過800萬美元。

結論：對於香港的HER2陽性乳癌患者來說，皮下注射曲妥珠單抗是一種節省成本的療法。藥品購置成本是對治療總成本影響最大的參數。

Methods

Cost methods and data sources

A CMA model was developed to compare the cost of total care. The CMA approach was used because the clinical efficacy and safety profiles of IV and SC trastuzumab regimens are similar, as demonstrated in the previous studies[7,14,15]; this fulfils the CMA requirement for two treatments to demonstrate similar efficacy. The following steps were followed in the CMA. We compared direct medical costs related to the IV and SC trastuzumab regimens that produced equivalent health outcomes. The CMA solely focuses on selection of the least costly option. In this study, the CMA was conducted from a hospital perspective. All direct medical costs and full-time equivalent (FTE) hours were included in this study. Drugs, clinic visits for drug administration, specialist out-patient clinic visits, and consumables were regarded as direct medical costs. The time horizon was 18 cycles of treatment, which mimics the duration of treatment for early-stage HER2-positive breast cancer. Drug acquisition cost data were obtained from the manufacturer, whereas costs for hospitalisation and clinic visits were acquired from the 2017 Hong Kong Gazette.[16] The drug acquisition cost was based on the dose used in previous clinical trials: IV loading dose of 8 mg/kg and maintenance dose of 6 mg/kg every 3 weeks versus SC fixed dose of 600 mg every 3 weeks. A mean body weight of 57.3 kg was used, based on data from the 2016 Hong Kong Cancer Registry.[3]

Estimated FTE hour values were obtained from previous literature. These values were regarded as the time (in hours) required for drug preparation and administration, divided by 44 hours, the weekly average working hours for such tasks. The FTE hour values were then converted to monetary values, calculated as the median hourly rate received by

individuals in each position. In Hong Kong, nurses and pharmacists are mainly involved in drug preparation and administration; thus, the salaries of these positions were used for estimation of FTE hour values.

All costs were expressed in US dollars (US$1 = HK$7.8), using 2016 as the fiscal year. Because of the short time horizon in the study, no costs were discounted.

Literature review

Medical resources and FTE hour values were determined by literature review in Embase and MEDLINE, using the key words 'subcutaneous', 'trastuzumab', 'time', 'cost', and 'medical resources'.

Statistical analyses

The CMA was conducted from the healthcare payer perspective. All continuous variables were described as means ± standard deviations and medians with ranges.

A drug budget impact forecast analysis was performed to determine how changes in the total cost of treatment regimens, including direct medical costs and FTE hours, would impact healthcare expenditures in Hong Kong. Each individual parameter, namely drug acquisition cost for each formulation (±20%), patient body weight (±20%), and time and consumables reported in the literature (based on confidence intervals reported) were analysed independently within specified ranges, whereas other factors were fixed at base-case values. The analysis parameters were chosen based on the findings in previous cost-effectiveness studies.[17] A simulation model was used to run 10 000 iterations of the forecast model; for each iteration, model parameters were input as shown in Table 1. We assumed that cost changes were consistent with the beta distribution around the mean. One-way deterministic sensitivity analysis was also performed to evaluate the extent to which the total cost would be affected by changes in the drug acquisition cost for each formulation (±20%), changes in times and consumables obtained from literature (based on confidence intervals reported), and changes in body weight (±20%); this approach is consistent with the methodology used in another cost-effectiveness analysis focused on trastuzumab.[17] Figure 1 summarises the analysis process of this study.

TABLE 1. Parameters and costs of the drug budget impact forecast model

Model parameter	Cost (US$)*
Intravenous trastuzumab	150 mg: $797.44 300 mg: $2307.69
Subcutaneous trastuzumab	$32 884.62
Nurses	$0.52/min
Pharmacists	$1.03/min

* US$1 = HK$7.8
Drug acquisition cost data were obtained from the manufacturer, while the costs of human resources were calculated as the median hourly rate received by individuals in each position

Results

In total, 11 studies were identified, eight of which were eligible for analysis.[12,18-24] Three studies were excluded because they did not report the time required for administration or preparation. There are a total of six studies with information on pharmacist time on preparation and nursing time on administration for IV and SC trastuzumab; the remaining two only reported time differences between the two formulations. Among the six studies that reported the time for preparation, four reported the total drug preparation time required for IV and SC trastuzumab, whereas the remaining two only reported time differences. If the SC formulation was used, 0.18 FTE hour of nursing time (7.9 hours) and 0.14 FTE hour of pharmacist time (6.2 hours) could be saved each week. Table 2 summarises the findings from these studies.

After 18 cycles of treatment with SC trastuzumab, the drug acquisition and healthcare professional time costs were reduced by US$9451.28 and US$566.16, respectively, compared with IV trastuzumab. Therefore, US$10 017.44 could be saved for each patient who completed 18 cycles of treatment. The cost of consumables was excluded because only two studies reported this information,

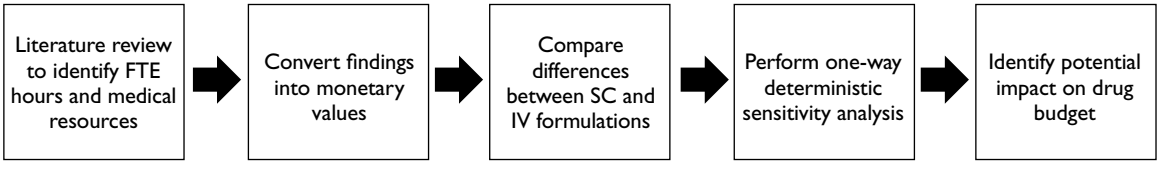

FIG 1. Flowchart of the analysis process
Abbreviations: FTE = full-time equivalent; IV = intravenous; SC = subcutaneous

TABLE 2. Summary of findings on healthcare professional time

	IV formulation[12,18-22]	SC formulation[12,18-22]	Difference[12,18-24]
Total nursing time, min			
Mean ± standard deviation	797.6 ± 709.0	364.6 ± 380.0	437.5 ± 464.8
Median (range)	489.2 (180.5-1725.6)	254.3 (124.2-1123.2)	226.1 (54.5-1378.8)
	IV formulation[12,19,20,22]	**SC formulation[12,19,20,22]**	**Difference[12,19,20,22-24]**
Total pharmacist time, min			
Mean ± standard deviation	377.5 ± 158.6	105.5 ± 75.1	326.8 ± 189.4
Median (range)	320.0 (265.5-604.8)	124.6 (0-172.8)	305.2 (130.6-630.5)

Abbreviations: IV = intravenous; SC = subcutaneous

and the contributions to overall costs were minimal (NZ$15.27[12] and GBP0.64[21], respectively). Table 3 summarises the direct medical costs of IV and SC formulations.

Sensitivity analysis

The drug budget impact forecast model was most affected by body weight and drug acquisition cost. Cost differences between the IV and SC formulations were reduced by decreases in body weight and IV trastuzumab cost, as well as an increase in SC trastuzumab cost. The effects of changes in nursing time and pharmacist time were smaller. Table 1 summarises the model parameters, and Figure 2 illustrates the effects of each variable on cost differences.

Drug budget impact forecast

In 2017, 4373 women were diagnosed with invasive breast cancer,[1] and approximately 20% of them were HER2-positive.[2,3] Furthermore, trastuzumab was the most commonly used targeted therapy (95.3%).[3] Assuming that the SC formulation was used (instead of the IV formulation) for all HER2-positive patients receiving trastuzumab and using the 2017 data stated here, an annual saving of over US$8.3 million could be achieved in Hong Kong.

Discussion

The results of this study suggest that SC trastuzumab would be more cost-effective than its IV counterpart in Hong Kong. Even if lower-cost biosimilar trastuzumab becomes available, the SC formulation will remain less expensive unless there is a substantial reduction in the acquisition cost of IV trastuzumab.

As body weight decreases, the necessary dosage and corresponding expenditures are expected to decrease. Paradoxically, ≤20% increases in body weight had a neutral effect in the analysis. This result could be related to a substantial amount of drug wastage when using weight-based IV trastuzumab, which is consistent with previous findings.[19,25] Therefore, further studies are needed to determine

TABLE 3. Total cost of care for 18 cycles of treatment with intravenous trastuzumab versus subcutaneous trastuzumab*

Type of cost	IV formulation	SC formulation	Difference
Drug acquisition†	$42 335.90	$32 884.62	$9451.28
Nursing	$416.10[12,18-22]	$190.21[12,18-22]	$228.21[12,18-24]
Pharmacist	$390.33[12,19,20,22]	$109.05[12,19,20,22]	$337.95[12,19,20,22-24]
Clinic visits	$1846.15[16]	$1846.15[16]	0.00
Chemotherapy	$1650.00[16]	$1650.00[16]	0.00
Consumables‡	N/A	N/A	N/A
Total	$46 638.48	$36 680.03	$10 017.44

Abbreviations: IV = intravenous; N/A = not available; SC = subcutaneous

* Expressed in US dollars (US$1 = HK$7.8)

† Data obtained directly from the manufacturer

‡ Excluded as only two studies reported such cost and the contributions to overall costs were minimal

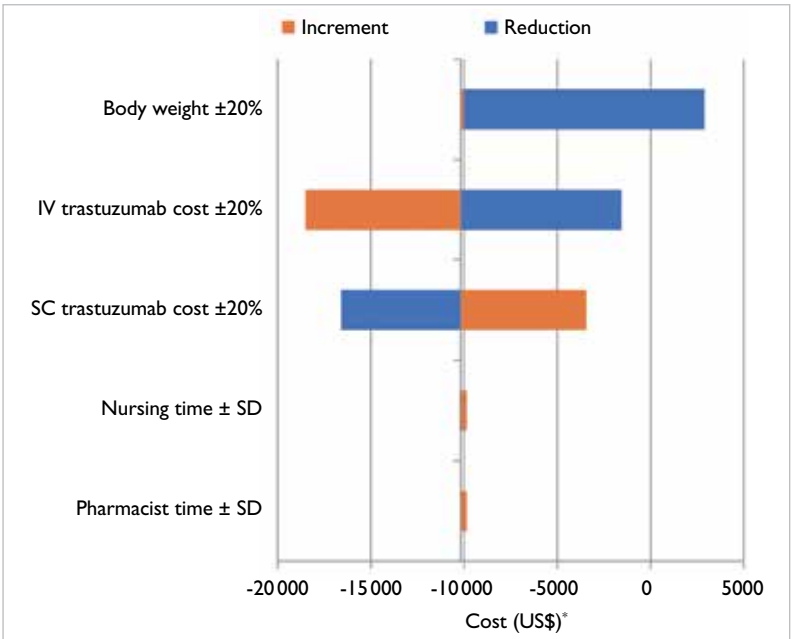

FIG 2. Tornado diagram of factors affecting total cost of treatment

Abbreviations: IV = intravenous; SC = subcutaneous; SD = standard deviation

* US$1 = HK$7.8

For each factor on the vertical axis, base case values are listed (-US$10 017.44) followed by the range considered in sensitivity analysis. The importance of each factor affecting total cost of treatment is ordered according to the spread of variation of the resulting model output value, with the widest variation on top

the optimal route of administration for patients who are underweight or do not require full doses of trastuzumab because of their clinical conditions.

Although the SC formulation is expected to save time for healthcare professionals,[26-28] the present analysis suggests that its contribution to the total cost of care is minimal. The cost of drug acquisition has the greatest effect on financial burden.

The use of data from previous time-and-motion studies in other countries may not be appropriate for medical settings in Hong Kong. Further studies should be conducted in Hong Kong to estimate the actual cost savings with respect to healthcare professional time, although theoretical time savings may not accurately represent actual time savings because of clinical activities conducted during administration of trastuzumab.[29] Furthermore, data from other countries exhibited wide distributions in terms of standard deviation and range. Nevertheless, the influence of the SC formulation on the total cost-saving effect may be limited, as demonstrated in the sensitivity analysis.

Although the costs of clinic visits and chemotherapy were assumed to be identical throughout 18 cycles of treatment between the two formulations, some patients can receive SC trastuzumab in ambulatory care settings. Thus, the mean savings may have been underestimated in our model.

There were several limitations in this study. First, because of the small number of studies identified in the literature review, consumables could not be included in the CMA. Second, societal cost and patient preferences were not considered because such information is unavailable in Hong Kong. A more patient-centred approach would provide greater insights. Third, time-and-motion analysis and waste handling in Hong Kong were not considered; these factors may have specific impact on drug preparation time and administration time and costs. Fourth, costs for adverse drug reactions were not included because these costs were assumed to be equal for IV and SC trastuzumab regimens. However, this assumption may be incorrect, particularly with regard to infusion-related reactions.

Conclusion

The results of this study suggest that the SC formulation of trastuzumab would be a cost-saving therapy for HER2-positive breast cancer patients in Hong Kong. The drug acquisition cost was the parameter with the greatest effect on the total cost of treatment.

Author contributions

Concept or design: VWY Lee.
Acquisition of data: FWT Cheng.
Analysis or interpretation of data: Both authors.
Drafting of the manuscript: FWT Cheng.
Critical revision of the manuscript for important intellectual content: VWY Lee.

Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

Both authors disclosed no conflicts of interest.

Declaration

The datasets generated and/or analysed in this study are available from the corresponding author on reasonable request.

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Ethics approval

Not applicable because this study did not involve human participants.

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