Economic burden of patients with inoperable advanced breast cancer receiving early or late capecitabine or trastuzumab as second-line treatment: A population-based study

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Abstract: This study investigates the economic burden and healthcare resource utilization of receiving early or late capecitabine and trastuzumab as second-line anthracycline- or taxane-based treatments for inoperable advanced breast cancer (IABC). Data was retrieved from the National Health Insurance Research Database of Taiwan. The demographic characteristics, healthcare resource utilization, and economic burden of patients with IABC receiving capecitabine and trastuzumab for 0–3, 3–6, 6–9 and 9–12 months after anthracycline- or taxane-based treatments were analyzed. 1,629 women newly diagnosed with IABC were recruited. IABC incidence rates reduced from 9.75% in 2004 to 7.35% in 2006. However, the proportion of patients receiving capecitabine or trastuzumab after anthracycline- or taxane-based treatments increased. Inpatient admissions (times/year), length of hospital stay (days/year), and outpatient visits (visits/year) did not differ significantly for the 2004–2005, 2005–2006 and 2006–2007 cohorts of patients with IABC receiving capecitabine and trastuzumab at different time points. The 1-year healthcare cost and outpatient, inpatient, and total costs (USD/year) differed significantly for trastuzumab but not for capecitabine. The conclusion indicated that early or late capecitabine or trastuzumab administration after first-line anthracycline or taxane-based treatments did not exhibit a change in healthcare resource utilization. In addition, the 1-year healthcare costs did not differ significantly for patients with IABC receiving early or late capecitabine. However, patients with IABC receiving trastuzumab continue to face an economic burden.

Keywords: inoperable breast cancer; capecitabine; trastuzumab; healthcare resources; economic burden

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Globally, breast cancer is the most prevalent malignanct cancer among women. Although new therapies have been proposed in recent years for possibly prolonging survival, studies regarding economic burden are scant, particularly for inoperable advanced breast cancer (IABC). Capecitabine and trastuzumab have been widely used in advanced breast cancer (ABC) treatments[1]. Capecitabine (trade name: Xeloda®), an orally administered fluoropyrimidine carbamate, has been proven effective in monotherapy for metastatic breast cancer, metastatic colorectal cancer, and adjuvant colon cancer in recent years[2-4]. In addition, trastuzumab (trade names: Herclon®, Herceptin®), a monoclonal antibody that interferes with the HER2/neu receptor, has been proven to improve clinical outcome and prolong the survival of patients with HER2-positive breast cancer and is
the standard drug for both adjuvant and metastatic cancers\(^5\)-\(^7\). However, irrespective of whether patients with IABC receive targeted therapies, the economic burden has always been a critical concern for patients with breast cancer as well as for healthcare policy makers and health insurance providers\(^8\).

The economic burden of patients with ABC has now been recognized and widely investigated in the United States and the European countries\(^9\)-\(^11\). However, few studies have focused on the economic burden of IABC, probably because the IABC population is smaller than that of operable ABC. Patients with IABC may require several conventional cytotoxic treatments, and if these treatments fail, the patients may receive targeted therapies, which further increased their economic burden\(^12\)-\(^14\). Sixteen-week intense chemotherapy has been reported to be safe and is well-tolerated by patients with IABC\(^15\) and similar results were obtained in a Phase II study on dose-dense sequential doxorubicin and docetaxel for such patients\(^16\). With the failure of conventional cytotoxic treatments, the economic burden and healthcare resource utilization of early or late second-line targeted therapies are crucial. However, this concern has rarely been addressed.

In Taiwan, breast cancer has been the most prevalent cancer among females since 2007\(^17\). The Bureau of National Health Insurance (BNHI) reimburses the costs of capecitabine and trastuzumab only when the first-line treatment using anthracycline-plus-taxane-based treatment fails. Therefore, the economic burden and healthcare resource utilization for patients with IABC receiving first-line cytotoxic treatments can be estimated. Although numerous studies have investigated the economic burden for early-stage breast cancer\(^18\)-\(^20\), only a few have investigated the economic burden of patients with newly diagnosed IABC. Furthermore, few studies have reported the economic burden and healthcare resource utilization of early or late targeted therapy after first-line cytotoxic treatments. Anthracyclines and taxanes are frequently used in treating adjuvant and first-line metastatic or advanced cancers\(^21\)-\(^22\), and capecitabine and trastuzumab are frequently used in monotherapy and in combination for ABC\(^6\),\(^23\)-\(^25\). In this study, the demographic characteristics, healthcare resource utilization, and economic burden of patients with IABC receiving capecitabine and trastuzumab at 0–3, 3–6, 6–9, and 9–12 months after anthracycline- or taxane-based treatments were investigated using the population-based BNHI database in Taiwan.

Materials and methods

Data

The data used in this study were retrieved from the National Health Insurance Research Database (NHIRD) of Taiwan on the basis of the following inclusion and exclusion criteria.

Inclusion criteria:

1. Age: patients aged ≥18 years.
2. IABC diagnosis: At least two eligible ABC diagnoses (or one ABC-related hospitalization) occurring on different days between 1\(^{\text{st}}\) January 2004 and 31\(^{\text{st}}\) December 2006. ABC was identified using the International Classification of Diseases, 9\(^{\text{th}}\) Revision, Clinical Modification (ICD-9-CM) with diagnosis code 174.xx. Among these patients, only those recently diagnosed with cancer, not having any cancer diagnosis in the previous year (clean period), and possessing a catastrophic illness card (CIC) issued by the BNHI for breast cancer were included in this study.

Exclusion criteria

Excluded are patients who received any form of breast surgery within one year of being recently diagnosed with ABC.

A retrospective cohort study was conducted on the basis of the NHIRD claims data to estimate the medical costs and the healthcare resource utilization of patients with IABC. Six cohorts were formed according to their year of diagnosis: cohorts A, B, and C were the capecitabine cohorts and D, E, and F were the trastuzumab cohorts for 2004–2005, 2005–2006, and 2006–2007, respectively. For each year’s cohort, we further classified patients with IABC into 4 groups: receiving capecitabine or trastuzumab subsequently to anthracycline- or taxane-based treatments for 0–3, 3–6, 6–9, and 9–12 months. All patients with IABC were identified, except those who did not enroll in the BNHI or those making out-of-pocket healthcare payments.

Statistical analysis

Descriptive profiles were used for estimating the average annual direct medical costs for patients receiving capecitabine and trastuzumab after anthracycline- and taxane-based treatments. Continuous and other numeric
variables are presented as means and standard deviation. Categorical variables are presented as the number of observations and frequency (%). In addition, a Charlson comorbidity index (CCI) score was computed for evaluating the concurrent illnesses in each patient during the study period and was used for adjusting the expected medical resource utilization and medical costs associated with major comorbidities. A general linear model (GLM) was employed for comparing the differences in the medical costs and medical resource utilization in patients receiving capecitabine and trastuzumab at different time points. The outcome variables in this study were inpatient hospital admissions (IPD admissions, times/year), length of hospital stay (LOS, d/year), the number of outpatient hospital admissions (IPD admissions, times/year), medical resource utilization and medical costs associated with the concurrent illnesses in each patient during the study period and was used for adjusting the expected medical costs. The outcome variables in this study were inpatient hospital admissions (IPD admissions, times/year), length of hospital stay (LOS, d/year), the number of outpatient hospital admissions (OPD visits, times/year), inpatient medical costs (IPD costs, USD), outpatient medical costs (OPD costs, USD), and total medical costs (USD). The covariates were age, CCI scores, and radiotherapy (RT) administration. In addition, statistical models of healthcare expenditure, as an outcome or response variable, were estimated using log-transformed dollars [26,27]. All statistical analyses were conducted using SAS (Version 8.1, SAS Institute Incorporation). Two-tailed tests of hypotheses were considered, and p < 0.05 was considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of the School of Nursing, National Taipei University of Nursing and Health Sciences (CN-IRB-2011-063). The data in this study was retrieved from the NHIRD, which is maintained and managed by the National Health Research Institutes. The NHIRD contains de-identified secondary data of patients and medical facilities, and these data were scrambled twice to protect patient privacy. The informed consent requirement was waived by the review board as only secondary data were analyzed in this study.

Results

We identified and adopted 1,629 women who were recently diagnosed with IABC and sequentially received chemotherapies in 2004, 2005, and 2006 for more than 8 months after the initial diagnosis (N = 602, 520, 507 for 2004, 2005, and 2006, respectively as shown in Table 1). The IABC incidence rates reduced from 9.75% in 2004 to 7.35% in 2006. However, the proportion of patients receiving capecitabine sequential to anthracycline-plus-taxane-based regimens (ATC) and trastuzumab sequential to anthracycline-plus-taxane-based regimens (ATT) increased in the recent years (from 25.42% in 2004 to 57.79% in 2006). For patients with IABC on ATC at different time points (0–3, 3–6, 6–9 and 9–12 months as shown in Table 2), the age and CCI score distribution did not differ significantly among cohorts of A, B, and C. A borderline significant difference was observed in patients receiving RT in cohort A (p = 0.05). However, no such differences were observed for cohorts B and C. Meanwhile, for patients with IABC on ATT at different time points (0–3, 3–6, 6–9 and 9–12 months as shown in Table 2), the distribution of age, RT administration, and CCI scores did not significantly differ among cohorts of D, E, and F.

Regarding healthcare resource utilization, patients on ATC at different time points (0–3, 3–6, 6–9 and 9–12 months as shown in Table 3) were analyzed using GLM after adjustment for age, RT administration, and CCI scores. IPD admissions, LOS, and OPD visits did not significantly differ among cohorts of A, B, and C. Similarly, for patients on ATT, the IPD admissions, LOS, and OPD visits did not differ significantly among cohorts of D, E and F. Furthermore, the 1-year healthcare cost for patients on ATC at different time points (0–3, 3–6, 6–9 and 9–12 months as shown in Table 4) were evaluated using GLM after an adjustment of age, RT administration, and CCI scores. The OPD, IPD, and total costs did not

<table>
<thead>
<tr>
<th>Year</th>
<th>Women all cancer incidence1 (N)</th>
<th>BC incidence2 (N)</th>
<th>IABC incidence2 (N)</th>
<th>IABC BC Incidence (%)</th>
<th>ATC3 N (%)</th>
<th>ATT4 N (%)</th>
<th>(ATC+ATT) IABC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>28821</td>
<td>6176</td>
<td>602</td>
<td>9.75</td>
<td>88 (14.6%)</td>
<td>65 (10.8%)</td>
<td>25.42</td>
</tr>
<tr>
<td>2005</td>
<td>29476</td>
<td>6593</td>
<td>520</td>
<td>7.89</td>
<td>134 (25.8%)</td>
<td>96 (18.5%)</td>
<td>44.23</td>
</tr>
<tr>
<td>2006</td>
<td>31276</td>
<td>6895</td>
<td>507</td>
<td>7.35</td>
<td>129 (25.4%)</td>
<td>164 (32.3%)</td>
<td>57.79</td>
</tr>
<tr>
<td>Total</td>
<td>89573</td>
<td>19664</td>
<td>1629</td>
<td>8.28</td>
<td>351 (21.5%)</td>
<td>325 (20.0%)</td>
<td>41.50</td>
</tr>
</tbody>
</table>

1The incidence data were from the Taiwan Cancer Registration System, Bureau of Health Promotion, Department of Health, Executive Yuan, Taiwan, Republic of China
2Data estimated from this study
3ATC: IABC patients receiving capecitabine subsequent to anthracycline and taxane
4ATT: IABC patients receiving trastuzumab subsequent to anthracycline and taxane

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Table 2 Demographic information of study sample (arranged by time of receiving capecitabine/trastuzumab)

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<tr>
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<tr>
<td></td>
<td>Time of receiving capecitabine</td>
<td>Time of receiving trastuzumab</td>
</tr>
<tr>
<td></td>
<td>N  0–3 mo  3–6 mo  6–9 mo  9–12 mo</td>
<td>p value  N  0–3 mo  3–6 mo  6–9 mo  9–12 mo</td>
</tr>
<tr>
<td>Age 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥50</td>
<td>42 23 7 7 5</td>
<td>35 20 7 7 1</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>46 24 14 4 4</td>
<td>30 17 9 3 1</td>
</tr>
<tr>
<td>Receiving RT 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 20 13 3 1</td>
<td>36 22 9 4 1</td>
</tr>
<tr>
<td>No</td>
<td>51 27 8 8 8</td>
<td>29 15 7 6 1</td>
</tr>
<tr>
<td>CCI score (X ± SD) 2</td>
<td>42 ± 23 43 ± 15 48 ± 38 48 ± 22</td>
<td>40 ± 18 41 ± 18 40 ± 14 41 ± 27 57 ± 15</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td></td>
<td>Age 1</td>
<td></td>
<td>Age 1</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>92 57 20 6 9</td>
<td>60 38 11 4 7</td>
<td>0.6191</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>42 26 9 5 2</td>
<td>36 21 4 3 8</td>
<td></td>
</tr>
<tr>
<td>Receiving RT 1</td>
<td></td>
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<tr>
<td>Yes</td>
<td>42 33 5 2 2</td>
<td>43 28 5 3 7</td>
<td>0.0790</td>
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<tr>
<td>No</td>
<td>92 50 24 9 9</td>
<td>63 31 10 4 8</td>
<td></td>
</tr>
<tr>
<td>CCI score (X ± SD) 2</td>
<td>46 ± 26 46 ± 29 51 ± 25 35 ± 19 41 ± 17</td>
<td>52 ± 25 54 ± 28 58 ± 23 45 ± 21 44 ± 18</td>
<td>0.3612</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Cohort (C)</th>
<th>2006–2007 (N = 129)</th>
<th>Cohort (F)</th>
<th>2006–2007 (N = 164)</th>
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<tbody>
<tr>
<td></td>
<td>Age 1</td>
<td></td>
<td>Age 1</td>
</tr>
<tr>
<td>Age ≥50</td>
<td>75 39 21 11 4</td>
<td>76 71 12 7 6</td>
<td>0.5261</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>54 35 11 5 3</td>
<td>68 49 12 2 5</td>
<td></td>
</tr>
<tr>
<td>Receiving RT 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 15 6 4 1</td>
<td>49 41 5 2 1</td>
<td>0.9615</td>
</tr>
<tr>
<td>No</td>
<td>103 59 26 12 6</td>
<td>115 79 19 7 10</td>
<td></td>
</tr>
<tr>
<td>CCI score (X ± SD) 2</td>
<td>50 ± 27 51 ± 29 47 ± 21 55 ± 31 49 ± 27</td>
<td>50 ± 30 50 ± 31 52 ± 23 53 ± 35 52 ± 25</td>
<td>0.7697</td>
</tr>
</tbody>
</table>

1analyzed by χ² test, 2analyzed by one-way ANOVA

significantly differ among cohorts A, B, and C. However, for patients on ATT at different time points (0–3, 3–6, 6–9, and 9–12 months as shown in Table 4), the IPDs costs of cohort D were significantly higher in the ‘9–12 months’ group than that in the other groups (Scheffe post-hoc comparison p < 0.05). Similarly, OPD and total costs of cohort F differed significantly in the 0–3 and 3–6 months groups compared with the other groups (Scheffe post-hoc comparison p < 0.05). OPD, IPD, and total costs did not significantly differ in cohort E.

Discussion

In this study, we used data of a population-representative database for estimating the incidence of IABC and proportion of patients receiving capecitabine and trastuzumab after anthracycline- or taxane-based treatments between 2004 and 2006. Furthermore, we investigated whether demographic characteristics, healthcare resource utilization, and healthcare differed for the different time points of receiving second-line capecitabine and trastuzumab. A review of relevant literature revealed that this is the first study to investigate the economic burden of patients with IABC.

The obtained results showed that the IABC incidence rates reduced from 2004 to 2006, possibly because of the annual increase in early screening and detection

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| Table 3: Health care utilization of inoperable breast cancer patients receiving capecitabine and trastuzumab...
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<tr>
<td>Capcitabine</td>
<td>Trastuzumab</td>
</tr>
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<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Cohort (C): 2004-2005 (N = 88)</strong></td>
<td><strong>Cohort (D): 2006-2007 (N = 144)</strong></td>
</tr>
<tr>
<td><strong>Cohort (E): 2006-2007 (N = 86)</strong></td>
<td><strong>Cohort (F): 2006-2007 (N = 86)</strong></td>
</tr>
<tr>
<td><strong>Length of hospital stay (days/year)</strong></td>
<td><strong>Length of hospital stay (days/year)</strong></td>
</tr>
<tr>
<td>8.1 ± 0.5</td>
<td>6.7 ± 1.2</td>
</tr>
<tr>
<td>8.2 ± 0.2</td>
<td>6.3 ± 0.9</td>
</tr>
<tr>
<td>8.9 ± 0.2</td>
<td>8.4 ± 1.5</td>
</tr>
<tr>
<td>8.8 ± 0.4</td>
<td>9.3 ± 1.2</td>
</tr>
<tr>
<td>8.1 ± 0.9</td>
<td>9.2 ± 1.5</td>
</tr>
<tr>
<td>8.0 ± 0.2</td>
<td>8.5 ± 1.2</td>
</tr>
<tr>
<td>0.038</td>
<td>0.023</td>
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<tr>
<td>0.185</td>
<td>0.097</td>
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<tr>
<td>0.095</td>
<td>0.073</td>
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<tr>
<td>0.053</td>
<td>0.021</td>
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<tr>
<td>0.048</td>
<td>0.014</td>
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<tr>
<td>0.038</td>
<td>0.014</td>
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<tr>
<td><strong>OPD visits (times/year)</strong></td>
<td><strong>OPD visits (times/year)</strong></td>
</tr>
<tr>
<td>0.038</td>
<td>0.023</td>
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<tr>
<td>0.185</td>
<td>0.097</td>
</tr>
<tr>
<td>0.095</td>
<td>0.073</td>
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<td>0.053</td>
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<td>0.048</td>
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<td>0.038</td>
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<td>0.048</td>
<td>0.014</td>
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<tr>
<td>0.038</td>
<td>0.014</td>
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</table>

**Note:** All estimates have been adjusted for age, receiving radiotherapy or not and Charlson comorbidity index (CCI).
not significantly differ among the 0–3, 3–6, 6–9, and 9–12 months subgroups. In this study, we classified patients into two subgroups (≥50 and <50 years) according to their age. The results indicated that early or late capecitabine or trastuzumab administration did not significantly differ between these two subgroups. Regarding healthcare resource utilization, the IPD admissions, LOS, and OPD visits did not significantly differ among those receiving early or late capecitabine or trastuzumab, implies that early or late second-line treatment in patients with IABC did not increase the healthcare service utilization. The mean of total 1-year healthcare costs of patients with IABC receiving ATC and ATT ranged from USD22,634 (cohort B) to USD39,003 (cohort D) and these values were higher than the mean of annual cost of patients with general breast cancer (approximately USD16,364) in Taiwan[30]. However, no significant differences in OPD, IPD, and total costs were observed in cohorts A, B, and C at different time points which implies that early or late administration of capecitabine did not affect the healthcare costs. For patients receiving trastuzumab, the IPD cost was significantly higher for the late-use group (9–12 months, cohort D as shown in Table 4) compared with the other groups. However, the OPD and total costs were significantly higher for the early-use groups (0–3 and 3–6 months in cohort F as shown in Table 4). This implies that physicians may prescribe trastuzumab for aggressive treatment or that the patients may prefer to receive trastuzumab combined with other chemotherapeutic treatments if first-line anthracycline- or taxane-based treatments fail.

The results in this study should be interpreted with caution. Although this study was mainly to study the economic burden of IABC patients receiving capecitabine or trastuzumab followed by anthracycline-plus-taxane-based treatments for 0–3, 3–6, 6–9, and 9–12 months, other treatments such as eribulin[31], vinorelbine and gemcitabine[32] were also proposed in recent years. Due to lack of studies, it is difficult to collect economic burden data of such treatments, which can be done in the future studies. Besides, due to the nature of secondary database study, the side effects and corresponding additional cost to the disease management and hospital stay were not recorded in NHIRD database, which can be regarded as a study limitation. This study is a parallel group study of healthcare resource utilization and the economic burden of patients with IABC receiving capecitabine and trastuzumab and whether any differences exist between early or late capecitabine and trastuzumab administration. The definition of IABC was based on the operational definition coined using the ICD-9-CM codes and BNHI drug codes for capecitabine and trastuzumab. The BNHI programme in Taiwan reimbursed capecitabine and trastuzumab as the second- or third-line treatments only if the first-line anthracycline- or taxane-based treatments have failed. In addition, every patient with breast cancer was issued a CIC based on pathological and imaging evidences. Therefore, the definition of IABC employed for patient recruitment is valid. In addition, the OPD, IPD, and total costs were calculated on the basis of the 1-year healthcare cost of receiving second-line capecitabine and trastuzumab, not for 5 years[33] or for lifetime[18], which is usually used for healthcare cost estimation. In addition, the cost estimates in this study may be conservative because the healthcare costs were estimated using NHIRD data, which is a claim-based database. Moreover, we did not consider the ‘out-of-pocket’ healthcare costs. The economic burden of IABC on patients receiving early or late second-line capecitabine or trastuzumab after the first-line anthracycline- or taxane-based treatments substantially influences the overall cost of breast cancer care. Therefore, our results facilitate the development of cost-effective evaluations of breast cancer therapies. Furthermore, this study serves as a valuable reference for framing reimbursement policies for patients availing IABC treatment.

**Conclusion**

Early or late capecitabine or trastuzumab administration after the failure of first-line anthracycline- or taxane-based treatments did not affect healthcare resource utilization. The one-year healthcare costs of early or late capecitabine administration did not differ significantly for patients with IABC. However, the economic burden remains a concern for patients receiving early or late trastuzumab.

**Author contributions**

Liu CY planned the study design, performed data application and statistical analysis, and authored the manuscript.

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Conflict of interest

The author declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

References


