Drug Use Evaluation of Letrozole in Breast Cancer Patients at Regional Cancer Hospitals in Thailand

Chaninun Ketkaew*, Niyada Kiatying-Angsulee

Abstract

**Background:** Medication policy development in Thailand is continually promoting rational drug use. Letrozole, an endocrine therapy drug, is usually prescribed for post-menopausal status early and advanced stage breast cancer. After Ministry of Public Health announced Letrozole as compulsory licensed drug in 2009, more breast cancer patients can access to this drug at low cost especially those within universal coverage schemes. To ensure that Letrozole is rationally prescribed, the drug utilization study was conducted. **Objectives:** The aim of this study was to describe the appropriate use of Letrozole in breast cancer and the relationship between appropriate use and health benefit schemes. **Materials and Methods:** A retrospective study to evaluate use of Letrozole in breast cancer patients was performed for six months between January - June 2010 in seven regional cancer hospitals, Thailand. All prescriptions of Letrozole were identified from pharmacy dispensing databases and prescription papers. A medical record review was also performed to evaluate appropriate use referring to the drug use evaluation criteria. The approved criterion of this study was referred from the guideline of Thai National Formulary version 2010. **Results:** There were 681 prescriptions of Letrozole for 254 breast cancer patients with an average age of 58.6 ± 10.0 years. The patients in universal coverage scheme (UCS), civil servant medication benefit scheme (CSMBS) and social security scheme (SSS) were 77.7%, 18.5% and 8.7% respectively. 10.6% were prescribed Letrozole for the first time. Letrozole were prescribed by oncologists (82.8%). The average number of tablets per prescription was 58 ± 10. Calcium supplements were prescribed concomitant with Letrozole for 19.4%. To assess drug use evaluation criteria, 45 prescriptions were excluded because of uncompleted clinical data, 636 prescriptions were evaluated. The study showed 86 prescriptions (13.5%) with inappropriate use including 6 (0.9%) not prescribed for estrogen receptor (ER) and/or progesterone receptor (PR) positive, 31 (4.9%) not prescribed for post-menopausal and 49 (7.7%) not prescribed for an appropriate duration. Appropriate use percentages in different health benefit schemes were similar, 85.7% of CSMBS, 86.4% of SSS and 86.7% of UCS. The relationship between health benefit scheme and appropriate use of Letrozole was not significantly different, \( \chi^2 (2, N = 636) = 0.081, p > 0.05 \). **Conclusions:** The study showed inappropriate use in breast cancer patients because of non-compliance with duration, menopausal status and hormone receptor requirements. To prescribe appropriate indication did not referred to the appropriate practice along the treatment. Drug use evaluation proved very useful for detecting the sign of inappropriate use and allows immediate feedback to the stakeholder for developing medication policy in the future. Importantly, there was no significantly difference in appropriate use of Letrozole across health benefit schemes.

Keywords: Rational drug use - drug use evaluation - breast cancer - letrozole
drugs because of its expensive and high risk in adverse
drug reaction (Delpeuch, Leveque, Rob, & Bergerat,
2011; Gulam Muhammad Khan, 2013; Joerger et al.,
2014; Krzyzanowska, 2013; Lerose, Musto, Aiesta, Papa,
&Tartarone, 2012; Pasqualetti et al., 2012; Siddiqua A.,
2014; Tartarone, Lerose, & Aiesta, 2012; Wang et al., 2013).
Few studies focused on evaluation of endocrine therapy
in breast cancer, for example, Kahan N.R. et al. showed
5.8% off-label use of Tamoxifen in Israel(Kahan, Waitman,
Blackman, & Vardy, 2010). This study aimed to describe
the appropriate use of Letrozole referred to the treatment
guideline by Thai National Formulary (TNF) version
2010 (National List of Essential Medicine Development
Subcommittee, 2010; National List of Essential Medicines,
2009) and describe the pattern of use between three health
benefit schemes. Letrozole is endocrine therapy drug for
breast cancer as inhibit hormone action and stop tumor cell
growth (Barnadas et al., 2011; Cohen, Johnson, Justice,
&Pazdur, 2011; Lee, Armstrong, & Wardley, 2012;
Shaw & Ellis, 2002). It was launched in Thailand more
than ten years ago but not listed in the National Essential
Drug List until 2010. Because of expensive drug, sale
price of original drug was 256 Baht/tablet in 2009 (7 – 8
US$/tablet, 1 US$=35 Baht) and major health schemes
was not covered. In 2010, The Ministry of Public Health
announced Letrozole as compulsory licensed drugs that
was centrally procured and distributed by The Government
Pharmaceutical Organization (GPO). After that Letrozole
was listed in the National Essential Drug List of Thailand
2010 in J-2 category and its sale price was only 7 Baht/
tablet (0.20 US$/tablet). To ensure that breast cancer
patients can appropriately access to Letrozole, DUE
process should be performed.

Materials and Methods

Retrospective research was performed at seven
regional cancer hospitals in Chonburi, Lopburi, Lumpang,
Pathumthani, Ubonrachathani, Udonthani and Suraththani.
Regional cancer hospitals were referral hospital for cancer.
All hospitals should be met four system criteria.
1) The hospitals were tertiary care in cancer treatment
due to the National Health Security Organization (NHSO)
guideline.
2) The hospital must be registered in NHSO hospital
lists
3) The specialists of each hospital must be registered
as Letrozole’s prescriber
4) The patients of each hospital must be registered
as breast cancer patients
5) The patients of each hospital must be registered
as breast cancer patients

All prescriptions of Letrozole between January – June
2010 were collected from prescription paper and pharmacy
dispensing database. The information obtained from
prescriptions were prescriptions’ date, hospital number
(HN), ages, health benefit schemes, specialty of physician,
dose and administration, amount of Letrozole tablet and
calcium supplement prescribing data. Those data were
recorded in data collection form by trained pharmacists.
The medical record of patients were reviewed for the
clinical characteristic and compare with DUE criteria.
The establishing approved criterion of this study was
referred from DUE of Letrozole in the TNF guideline
version 2010 (National List of Essential Medicine
Development Subcommittee, 2010). The DUE criteria
included:
1) Indication: Letrozole should be prescribed for
breast cancer
   - Advance breast cancer
   - Adjuvant therapy as switching therapy in early stage
   breast cancer in two choices
   a. Start with Tamoxifen for 2 – 3 years and follow by
   Letrozole until 5 years total of hormone therapy
   b. Start with Letrozole for 2 years and follow by
   Tamoxifen for 3 years until 5 years of hormone therapy
2) Hormone receptor status: Letrozole should be
prescribed in Estrogen receptor positive (ER) and/or
Progesterone receptor positive (PR).
3) Menopausal status: Letrozole should be prescribed
only in post-menopausal defined as
   - Age more than 60 years old
   - Ovarian ablation
   - Post-menopausal occurred 1 year before breast cancer
diagnosed and confirm by follicle stimulating hormone
(FSH) and luteinizin hormone (LH)
4) Physical status: Letrozole should not be prescribed
in terminal illness patients
5) Dose: Appropriate dose of Letrozole was 2.5 mg.
tablet oral once daily after meal
6) Duration: Depend on stage on breast cancer
   - Advance breast cancer: Letrozole should be
   prescribed until disease progress or poorly respond
   - Early stage breast cancer: Letrozole should be
   prescribed continuity not more than 2 years

The information obtained from the medical record
included indication of use, duration of use, ER/PR receptor
status, menstrual status, physical status and adverse drug
reactions. Those data were recorded in DUE criteria check
list by trained pharmacists. The SPSS/Win version 17.0
was used to analyze the data. The descriptive statistic
was used to describe demographic characteristic of
prescriptions of Letrozole, clinical data of patients and
result in appropriate use. Chi square test of independence
was used to analyze the relation between appropriate use
and health benefit schemes.

Results

Demographic data of the prescription of Letrozole has
been shown in Table 1. There were 681 prescriptions of
Letrozole for 254 patients. The average age of patients was
58.6 ± 10.0 years old. Patients were in Universal Coverage
Scheme (UCS) (77.7%), Civil Servant of Medication
Benefit Scheme (CMBS) (18.5%) and Social Security
Scheme (SSS) (8.7%). 10.6% were prescribed of Letrozole
for the first time. Letrozole were prescribed by oncologists
(82.8%), radiologists (13.7%) and surgeons (3.5%). The
average amount of tablets per prescription was 58 ±
10 tablets. 100.0% of prescriptions were appropriately
dose prescribed. 19.4% of Letrozole prescriptions were
prescribed with calcium supplement.

The clinical data of breast cancer patients obtained
from medical record has been shown in Table 2. The
clinical criteria for evaluate appropriate use of Letrozole composed of diagnosis, hormone receptor, menstrual status, physical status, recommend dose and adverse reaction. 177 prescriptions (25.9%) were prescribed in advance stage breast cancer and 284 prescriptions (41.7%) in early stage. 654 prescriptions (96.0%) were prescribed in ER and/or PR positive. Menopausal status was defined as post-menopause and pre-menopause, 620 prescriptions (91.0%) were prescribed in post-menopause. All prescriptions of Letrozole were not prescribed for patients in terminal illness. Common adverse drug reactions were reported in 11 prescriptions (1.60%) including bone pain, flushing and edema.

45 from 681 prescriptions were excluded from this study because lack of clinical data such as hormone receptor status and/or menstrual status. 636 prescriptions of Letrozole were analyzed with 1 - 5 DUE criteria respectively.

Criteria 1: Letrozole must be rationally prescribed in ER (+) and/or PR (+) (ER(+)/PR(+), ER(+)/PR(-) and ER(-)/PR(+)). Mechanism of Letrozole is inhibiting of breast tumor growth by inhibiting biosynthesis of hormone, so high density of hormone receptor show better efficacy. 6 from 636 prescriptions (0.9%) were not appropriately prescribed for ER and/or PR positive. 630 appropriated prescriptions were continually evaluated in next criteria.

Criteria 2: Letrozole must be rationally prescribed in post-menopausal breast cancer patients. Post-menopausal can be identified by 3 criteria: 1) Age more than 60 years old, 2) under ovarian ablation 3) Post-menopausal occurred for 1 year before breast cancer diagnosed and confirm by FSH and LH. Pre-menopausal patients show estrogen effect that stimulates tumor cell growth. There were 31 prescriptions (4.9%) of Letrozole prescribed in pre-menopausal. Those were evaluated as inappropriate use. 599 prescriptions were continually evaluated in next criteria.

Criteria 3: Approve indication of Letrozole was in advance breast cancer and adjuvant therapy in early stage breast cancer. All 599 prescriptions were appropriated indication.

Criteria 4: The appropriate dose of Letrozole was fixed as 2.5 mg tablet orally once a day. All 599 prescriptions were prescribed in appropriate dose.

Criteria 5: The appropriate duration of letrozole were defined in line with the indication as follow

-Advance breast cancer: Letrozole can be prescribed continually until the disease progress.

<table>
<thead>
<tr>
<th>Table 1. Demographic Characteristic of the Prescriptions of Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Data</td>
</tr>
<tr>
<td>Number of prescriptions</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Age of patients (years)</td>
</tr>
<tr>
<td>Health benefit schemes</td>
</tr>
<tr>
<td>Civil Servant of Medication Benefit Scheme (CSMBS) (%)</td>
</tr>
<tr>
<td>Universal Coverage Scheme (UCS) (%)</td>
</tr>
<tr>
<td>Social Security Scheme (SSS) (%)</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>First prescribed</td>
</tr>
<tr>
<td>Yes (%)</td>
</tr>
<tr>
<td>No (%)</td>
</tr>
<tr>
<td>Prescriber</td>
</tr>
<tr>
<td>Oncologist (%)</td>
</tr>
<tr>
<td>Radiologist (%)</td>
</tr>
<tr>
<td>Surgeon (%)</td>
</tr>
<tr>
<td>Average amount of tablet per prescription</td>
</tr>
<tr>
<td>Mean ± SD (Tablet)</td>
</tr>
<tr>
<td>Recommended dose (2.5 mg Tablet oral daily)</td>
</tr>
<tr>
<td>Prescribed Calcium Supplement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. The Clinical Data of Breast Cancer Patients Obtained from Medical Record Charges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data requirement</td>
</tr>
<tr>
<td>Number of prescriptions (%)</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Advanced breast cancer</td>
</tr>
<tr>
<td>Early breast cancer: Adjuvant therapy (Start with Tamoxifen)</td>
</tr>
<tr>
<td>Early breast cancer: Adjuvant therapy (Start with Letrozole)</td>
</tr>
<tr>
<td>Hormone receptor: Estrogen (ER), Progesterone (PR)</td>
</tr>
<tr>
<td>ER (+)/PR (+)</td>
</tr>
<tr>
<td>ER (+)/PR (-)</td>
</tr>
<tr>
<td>ER (-)/PR (+)</td>
</tr>
<tr>
<td>ER (-)/PR (-)</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Menopausal status</td>
</tr>
<tr>
<td>Post-menopause</td>
</tr>
<tr>
<td>Pre-menopause</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Terminal illness</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Adverse event occurred</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Drug Use Evaluation Result of Letrozole Referred to the Guideline by TNF Version 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug use evaluation criteria</td>
</tr>
<tr>
<td>Number of prescriptions (-)</td>
</tr>
<tr>
<td>Total analyzed of 636 prescription of Letrozole (n = 636)</td>
</tr>
<tr>
<td>1 Hormone receptor status: ER and/or PR positive</td>
</tr>
<tr>
<td>2 Menopausal status: Post-menopause</td>
</tr>
<tr>
<td>3 Indication:</td>
</tr>
<tr>
<td>Advance breast cancer</td>
</tr>
<tr>
<td>Early breast cancer (Start with Tamoxifen)</td>
</tr>
<tr>
<td>Early breast cancer (Start with Letrozole)</td>
</tr>
<tr>
<td>4 Dose: 2.5 mg, tablet oral once daily</td>
</tr>
<tr>
<td>5 Duration: not more than 2 years</td>
</tr>
<tr>
<td>Summary of appropriate prescriptions</td>
</tr>
</tbody>
</table>
null