

Treatment Pattern and Safety Results of Docetaxel- (Taxotere®)-Based Chemotherapy in Early Breast Cancer Patients in Indonesia: Part of Asia-Pacific Breast Initiative II

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ABSTRACT

Background: Breast cancer is the most diagnosed cancer among Indonesian women. Adjuvant chemotherapy plays a crucial role in the management of early breast cancer patients, with docetaxel-based regimens as a cornerstone therapy. The Asia-Pacific breast initiative II registry was established to evaluate safety parameters of docetaxel-based regimens in the Asia-Pacific region within 2009–2013 period. The result from Indonesia population is presented in this study.

Methods: This study was a part of International, longitudinal, multicenter, and observational research which included a group of consecutive early breast cancer patients with an intermediate-to-high risk of recurrence that was being treated with various docetaxel-based (anthracycline and non-anthracycline) adjuvant chemotherapy regimens during 2009–2013 in real-world clinical settings.

Results: The analysis included 49 subjects (2.8% of total study population). Majority of subjects received non-anthracycline-containing regimen (79.6%). Docetaxel was mainly prescribed in combination (63.27%). Chemotherapy-related adverse events were reported in all subjects. Mean number of cycles received by subjects was 5.5 cycles with dose intensity of 23.78 mg/m²/week.

Conclusions: The Indonesian result, as part of the Asia-Pacific Breast Initiative II Registry, identified some important factors that are relevant to clinical practice, including patient's characteristics and treatment pattern of docetaxel use as adjuvant chemotherapy regimens.

INTRODUCTION

The prevalence of cancer in Indonesia is 1.4% with breast cancer being the most diagnosed cancer among Indonesian women with an estimated proportion of 30.5% of all types of cancer (1,2). In Asia Pacific region, breast cancer is the most common type of cancer among females, contributing up to 18% of all cases in 2012, and was the fourth most common cause of cancer-related deaths (9%) (3). Results from 2 studies showed that Indonesian women with breast cancer seem to present at a younger age with peak age of 47 – 49 years old and were diagnosed at late stages (4).

In the last two decades, adjuvant chemotherapy played a crucial role in the management of early breast cancer patients which significantly improved patients'

survival (5). Docetaxel is a cornerstone of adjuvant chemotherapy because of its consistent positive results among subgroup of patients (age, node, hormone receptor status, human epidermal receptor-2 status) (6).

The understanding of disease epidemiology, safety, and efficacy of current therapeutic adjuvant regimens in a real-world clinical setting is important to support treatment choice among these patients. The Asia-Pacific breast initiative II (APBI-II), an observational registry conducted in 9 countries, was established to evaluate the safety parameters of docetaxel-based anthracycline and non-anthracycline-containing regimens in the Asia-Pacific region within 2009–2013 period. Prospective data regarding major safety parameters were collected and analyzed to better understand treatment patterns and safety outcomes for these patients.

METHODS

The APBI-II registry is a longitudinal, multicenter, multinational, prospective study that collects safety and efficacy data from operable, early breast cancer patients with intermediate to high recurrence risk, which was treated with docetaxel- (Taxotere®; Sanofi-Aventis, Bridgewater, USA) based adjuvant chemotherapy. More detail on the study methods is available on the study publication (7). This study presented results from Indonesian population.

RESULTS

Patient population and baseline data

The total study population of the registry was 1,712 subjects, while the number of subjects that were recruited in Indonesia was 49 (2.8% of total study population). Overall characteristics of the subjects are summarized in **Table 1** and **Figure 1**. All patients underwent mastectomy with lymph node excision and total mastectomy was performed for the majority of subjects (73.5%) (**Table 2**).

Table 1. Demographic data

Patient's characteristics (n=49)	N (%)
Age (mean, SD)	48.9 (10.65)
Co-morbidity	
Yes	10 (20.4)
No	39 (79.6)
Predominant Histological Type	
Ductal carcinoma	43 (87.8)
Lobular carcinoma	3 (6.1)
Others	3 (6.1)
Differentiation of cancer cell	
Well-differentiated	18 (41.9)
Moderately differentiated	18 (41.9)
Poorly differentiated	7 (16.3)
Hormone receptor status	
ER+/PR+	14 (28.6)
ER+/PR-	3 (6.1)
ER-/PR+	3 (6.1)
ER-/PR-	29 (59.2)
HER-2 status	
Positive	21 (42.9)
Negative	28 (57.1)
Risk stratification*	
High risk	28 (57.1)
Intermediate risk	21 (42.9)
Menopausal status at baseline	
Pre-menopause	22 (44.9)
Peri-menopause	3 (6.1)
Post-menopause	24 (49.0)

ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2

*recurrence risk was determined by the investigator as well as by St.Gallen consensus guideline

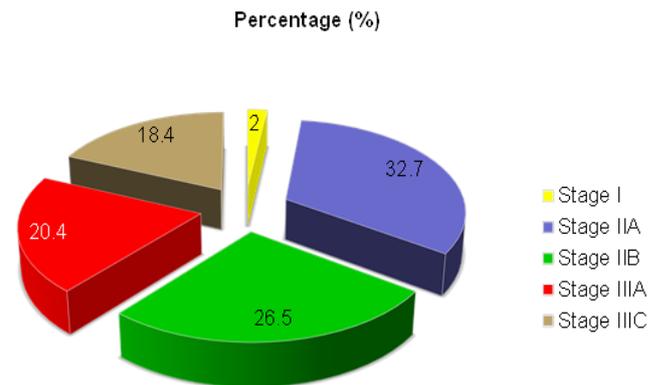


Figure 1. Distribution of cancer stage in Indonesian population according to the classification of the American Joint Committee on Cancer (AJCC) Stage

Table 2. Summary of breast cancer surgery

Parameter	N (%)
Mastectomy with lymph node excision	49 (100)
Breast-Conserving Surgery	13 (26.5)
Unilateral	13 (100)
Bilateral	0 (0)
Total Mastectomy	36 (73.5)
Unilateral	36 (100)
Bilateral	0 (0)
With reconstruction	1 (2.8)
Without reconstruction	35 (97.2)
Lymph node excision	49 (100)
No axillary dissection	0 (0)
SLN biopsy only	1 (2.0)
Axillary dissection with/without SLN biopsy	48 (98.0)

SLN: sentinel lymph nodes

Chemotherapy regimens and docetaxel exposure

Subjects were divided based on docetaxel-based chemotherapeutic regimens, including docetaxel monotherapy, docetaxel sequential regimens, and docetaxel combination regimens. Majority of subjects received non-anthracycline-containing regimen (39/49; 79.6%). Docetaxel was mainly prescribed in combination (31/49; 63.27%), either with other chemotherapeutic agents and/or trastuzumab, in patients with HER2(+). No subjects received docetaxel monotherapy. The distribution of different docetaxel-based regimens used was described in the following **Table 3**.

Mean number of cycles received by subjects was 5.5 cycles with dose intensity of 23.78 mg/m²/week and actual dose of 117.99 mg/cycle. Mean overall duration of chemotherapy was 127.8 days. Around ninety-one percent of subjects (91.3%) completed prescribed dosing.

Table 3. Distribution of docetaxel-based regimen

Regimens	(%)
Combination	
docetaxel/doxorubicin	10.2
docetaxel/doxorubicin/cyclophosphamide	2.0
docetaxel/cyclophosphamide	40.8
docetaxel/cyclophosphamide/trastuzumab	6.1
docetaxel/carboplatin/trastuzumab	16.3
other	12.2
Sequential	
doxorubicin/cyclophosphamide - docetaxel	2.0
docetaxel/cisplatin - docetaxel/carboplatin	2.0
docetaxel/cyclophosphamide/trastuzumab – docetaxel/carboplatin/trastuzumab	2.0
doxorubicin/cyclophosphamide – docetaxel/trastuzumab	6.1

Safety Assessment

Three subjects (6.1%) died within 1.5 years of follow up and 11 subjects (22.4%) lost to follow up. Among subjects who were still alive (35; 71.4%), only 1 subjects (2.9%) experienced relapse and no subjects had second primary malignancy.

Leukopenia was the most common hematological adverse events observed while alopecia and nausea were the major non-hematological adverse events. Adverse events were summarized in the following **Table 4**. Seven subjects (14.29%) received granulocyte-colony stimulating factors as primary prophylaxis to prevent complications, especially for subjects who received docetaxel combination regimens (5 subjects). There was only 1 subject who completed assessment for left ventricular ejection fraction (LVEF) assessment during 1.5 years of follow up. The change from baseline was - 2.00 (from 77.00 to 75.00).

Table 4. Summary of adverse events (all grades)

Adverse Events (%)	Anthracycline-Containing Regimen (I-10)	Non-Anthracycline Containing Regimen (I-39)	All Patients (I-19)
Leukopenia	100	92.3	93.9
Alopecia	90	94.9	93.9
Nausea	70	71.8	71.4
Diarrhea	70	59	61.2
Vomiting	60	30.8	36.7
Stomatitis	60	5.1	8.2
Peripheral sensory neuropathy	20	15.4	16.3
Fatigue	20	33.3	30.6

DISCUSSION

The APBI-II result of Indonesian population might reflect actual practice among physicians in Indonesia as well as the difference in patients' characteristics from other participating countries.

Mean age of subjects in this study is considered younger than in Western countries. This is similar to the finding that the peak age for breast cancer is between 40 and 50 years in Asian countries, whereas the peak age in the Western countries is between 60 and 70 years (8). This finding suggests the importance of routine screening methods in the younger population compared to Western populations, and the need for treatment improvement to reduce morbidity and mortality. Interestingly, the distribution of hormonal status is markedly different from the overall population in APBI-II registry. Majority of Indonesian subjects had negative estrogen and progesterone receptor (ER (-), PR (-)), where most patients in this registry had ER (+) and PR (+). This finding might be explained by the cut-off point for hormonal receptor status determination that, during the study period, was 10% while now the cut-off point is 1%. If the hormonal status is examined now, there is a high possibility that the result might be different. However, there is a limitation of the small sample size from Indonesian population that might also contribute to this finding. Another interesting finding is despite younger patients more frequently have HER2+ breast cancer, as also seen in the overall population of this registry, but this is not the case in Indonesian population, where more patients had HER2(-) (9).

Surgery method that was being used in the Indonesian population was similar to other population, which was mastectomy along with lymphadenectomy. While most of the APBI-II population received anthracycline-containing regimens (79.0%), the majority of Indonesian population received non-anthracycline containing regimens due to concern that combination of taxane and anthracycline will increase the risk of cardiotoxicity, especially TAC (docetaxel, doxorubicin, cyclophosphamide) regimen. The most commonly prescribed regimen was docetaxel in combination with cyclophosphamide. The docetaxel-based regimens were considered well tolerated as reflected in the high mean number of cycles that the subjects received.

Several adverse events (AEs) were reported and were generally manageable. As expected, leukopenia, which is strongly correlated with neutropenia, was the most commonly observed adverse events. This well-known docetaxel-related adverse event warrants careful review on the need of granulocyte-colony stimulating factor (G-CSF) as primary prophylaxis as well as secondary prophylaxis to prevent complications of neutropenia. The recent recommendation from American Society of Clinical Oncology (ASCO) suggested prophylactic use of G-CSFs to reduce the risk of febrile neutropenia when the risk of febrile neutropenia is equal to 20% or higher (10). TAC regimen is an example of docetaxel-based regimens with a high incidence of febrile neutropenia (23.8%) (11). This regimen was prescribed to 12.2% of patients population. There was no observed significant safety issue that was different

from the overall study population or clinical trials of other populations (12).

The number of relapse cases in Indonesian population is similar to the overall study population, which was 2.9% and 3%, consecutively. The significant number of patients who lost to follow up at 1.5 years (22.4%) warrants further investigation. In daily practice, it is important that cancer patients should have regular follow-up to check for recurrence or metastases, the presence of other types of cancer, and to address the problems due to cancer or the treatment. This important finding suggested that better patient education will help to improve the follow-up visit.

The results of this registry underline the importance of recognizing the great diversity in patients' demographics as well as the treatment strategies in a real-world setting among Indonesian population.

CONCLUSION

Various docetaxel-based anthracycline- and nonanthracycline-containing regimens were not found to cause significant issues in safety outcomes. The result of this study suggested that docetaxel-based chemotherapy is considered to have a good safety profile and a relatively safe choice as adjuvant treatment for breast cancer patients in the Asia-Pacific region as well as among Indonesian population.

DECLARATIONS

Competing of Interest

The authors declare that they have no competing interests.

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