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ORIGINAL ARTICLE

Safety Results of Docetaxel-(Taxotere®)-Based Chemotherapy in Early Breast Cancer Patients of Asia-Pacific Region: Asia-Pacific Breast Initiative II

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Purpose: The goal of this registry was to collect patient characteristics and safety data from patients from the Asia-Pacific region with early breast cancer receiving adjuvant chemotherapy containing docetaxel (Taxotere®). **Methods:** This registry was open-label, international, longitudinal, multicenter, and observational in design and included a prospective group of consecutive early breast cancer patients with an intermediate-to-high risk of recurrence 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 1,712 patients, 79% of whom received docetaxel-based, anthracycline-containing regimens, while 21% received non-anthracycline-containing regimens. Patients receiving adjuvant docetaxel-based chemotherapy were followed for 1.5 years. Chemotherapy-related adverse events (AEs) were reported by 76.2% of patients (anthracycline-containing vs. non-anthracycline-containing regimens: 76.8% vs. 74.1%). Serious AEs were reported in 12% of patients (12.3% vs. 10%). National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 or higher neutropenia was reported in 20% of patients (21.6% vs. 13.9%), leukopenia in 7.4% of patients (5.4% vs. 14.8%), and vomiting in 1.6% of patients (1.8% vs. 0.6%). Treatment-related death was reported in 27 patients (1.6%), while only 3% of patients had a relapse. Low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (HDL-C) and total cholesterol/HDL-C ratios increased after chemotherapy. A clinically insignificant reduction of 1.9% in left ventricular ejection fraction, from 66.43 to 64.53, was observed 1.5 years after therapy was completed. **Conclusion:** The Asia-Pacific Breast initiative II registry identified a variety of important facts regarding patient population characteristics, disease epidemiology and treatment response for early breast cancer patients of the Asia-Pacific region receiving docetaxel-based chemotherapy. Docetaxel-based chemotherapy did not show any significant safety concerns for early breast cancer patients of the Asia-Pacific region, and thus may represent a safe adjuvant chemotherapy regimen for these patients.

Key Words: *Breast neoplasms, Docetaxel, Registries, Safety*

INTRODUCTION

In last two decades, adjuvant chemotherapy has played a crucial role in the management of early breast cancer (EBC), significantly improving patient survival [1]. Despite strong antitumor activity, the role of anthracyclines in adjuvant chemotherapy of EBC has been under constant evaluation [2]. Although short-term toxicities, such as transient arrhythmias, pericarditis, or acute left ventricular failure, can be managed, irreversible long-term cardiotoxicity, such as late onset ventricular dysfunction and arrhythmias, as well as secondary leukemia, can pose significant threats to patient health [3]. Recently, docetaxel has emerged as a prime chemotherapeutic agent in adjuvant chemotherapy worldwide [4]. It is preferred in adjuvant chemotherapy because of its pharmacokinetic profile, consistent positive results, and convenient, intermittent, brief infusion schedule [5]. It is not subject to cross-resistance with anthracyclines and is more active than commonly used anthracyclines [5]. Moreover, unlike paclitaxel, the pharmacokinetic action of docetaxel is independent of commonly used doxorubicin, suggesting that it can be used in combination with doxorubicin without aggravating doxorubicin-associated cardiotoxicity [4]. Nonetheless, docetaxel can produce

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adverse events (AEs), including nausea, alopecia, neutropenia, febrile neutropenia, and leukopenia [6]. Neutropenia, febrile neutropenia, and gastrointestinal complications are the most frequent National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or higher AEs arising from docetaxel therapy. Two of the most common long-term adverse effects of docetaxel chemotherapy are sensory and motor peripheral neuropathy [7]. Grade 3 or higher neuropathy is observed in < 10% of patients receiving docetaxel therapy [7]. Various supportive therapies, such as growth factors, can be administered to ameliorate AEs [7]. As the incidence of breast cancer is increasing in young people of the Asia-Pacific region, it is necessary to study these long-term toxicities in real-world patients from the region.

Breast cancer exhibits significant differences in pathology, progression, and epidemiology between Western and Asian countries [8,9]. Disease onset at younger ages and in urban areas, detection at later stages, and higher frequency of estrogen receptor (ER)-negative and progesterone receptor (PR)-negative breast tumors are some of the main differences in breast cancer between Western and Eastern countries [9]. Moreover, an unexpected surge in breast cancer incidence in the Asia-Pacific region has been observed recently. Taken together, these observations point to an unmet need for an in-depth analysis of disease epidemiology, safety, and efficacy of current therapeutic regimens in real-world clinical settings of the Asia-Pacific region.

Therefore, the Asia-Pacific breast initiative II (APBI-II), an observational registry, has been established to evaluate safety parameters of docetaxel-based anthracycline and non-anthracycline-containing regimens for the treatment of EBC patients in the Asia-Pacific region. Prospective data regarding major safety parameters, including cardiac function, have been collected and analyzed to better understand treatment patterns and safety outcomes for these patients.

METHODS

Study design and patient population

The APBI-II registry is an open-label, longitudinal, multicenter, multicountry, prospective study to collect safety and efficacy data from operable EBC patients with intermediate-to-high risk of recurrence treated with docetaxel (Taxotere®; Sanofi-Aventis, Bridgewater, USA) based adjuvant chemotherapy.

The study was conducted in nine countries in the Asia-Pacific region (China, Hong Kong, Indonesia, Korea, Pakistan, Russia, Taiwan, Thailand, and Vietnam) from 2009 to 2013. Physicians (oncologists/surgeons) enrolled existing or newly diagnosed patients with operable breast cancer with an intermediate-to-high risk of recurrence who were treated with docetaxel-based regimens in the adjuvant setting. Patients were enrolled consecutively. The treatment was determined solely by the patient's physician. Thus, data acquired and reported in the registry reflect a real-world approach to the treatment of patients with early stage breast cancer. Similarly, there was no blinding, as the study aimed to track the real-life prescribing patterns and patient management in Asian-Pacific countries.

The APBI-II registry was planned under the guidance of a steering committee of academic members experienced in the treatment of breast cancer. Patient data were collected using a no-carbon-required copy of a data collection form. The study was performed according to the International Conference on Harmonization guidelines for Good Clinical Practice and Good Epidemiology Practice. The study protocol and the written data release consent forms were approved by Institutional Review Boards/Ethics Committees, and local regulatory authorities. The consent form for data release included a statement by which the patient allowed the sponsor's duly authorized personnel, ethic committees, and the regulatory authorities to have direct access to original medical records, e.g., the patient's medical file, appointment books, original laboratory records, and so forth. Data for each patient were collected only after obtaining that patient's signed written data release forms.

Treatment

Consulting physicians prescribed docetaxel-based adjuvant chemotherapy to the patients at their discretion. The physicians were guided by the prescribing information outlined in the summary of product characteristics/product information. Docetaxel monotherapy was administered by intravenous infusion with dexamethasone premedication and proper antiemetic prophylaxis. The prevention/treatment of febrile neutropenia and other chemotherapy-related AEs was managed according to the physician's treatment strategy. Patients were followed up for 1.5 years to assess safety parameters.

Safety parameters

Efficacy variables and safety outcomes were measured during the course of treatment in this registry. In this study, all AEs/serious adverse events (SAEs) regardless of relationship to chemotherapy were recorded from the first day of chemotherapy through 30 days after the final chemotherapy dose. Investigators identified the worst AEs (by grade according to NCI CTCAE), and seriousness criteria for these AEs. Data regarding action taken with chemotherapy, corrective treat-

ment/therapy for the AE, and whether the AE had resolved by the next chemotherapy were carefully monitored and recorded. Thereafter, through the termination of the study, only related SAEs were reported. Serum cholesterol (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and total cholesterol) were determined using the site's local laboratory before chemotherapy and at the 1.5 years follow-up visit. Echocardiogram or Multi Gated Acquisition (MUGA) scan (within ±2 months of study entrance and within ±1 month of the 1.5 years follow-up visit) was performed for the patients who received anthracycline as an adjuvant therapy. Left ventricular ejection fraction (LVEF) was obtained using the site's local method.

Only AEs having an overall incidence of ≥10% across all patients based on the preferred term from the Medical Dictionary for Regulatory Activities (MedDRA) were summarized both overall and for each country and also for each chemotherapy category. Multiple reports of the same event from a patient were counted only once within each preferred term for MedDRA.

AEs of special interest were defined as neutropenia, febrile neutropenia, neutropenic infection, asthenia, and peripheral sensory neuropathy. AEs of special interest were summarized by the MedDRA preferred term by country and chemotherapy categories for the following: worst toxicity grade for each cycle, number of cycles in which the AE occurred, cycle of first occurrence, and most frequent cycle during which the AE occurred.

Data collection

Data entry, verification, and validation were carried out using standard computer software; data were stored in an Oracle database on a digital Virtual Memory System computer. A double-entry method was used to ensure that the data (except comments) were transferred accurately from the case report forms to the database. Moreover, every modification in the database could be traced using an audit trail. A data checking plan was established to define all automatic validation checks, as well as supplemental manual checks, to ensure data quality. All discrepancies were researched until resolved.

Statistical analyses

All data recorded were analyzed in an exploratory and descriptive manner. Statistical analysis used SAS® version 9.13 (SAS Institute, Cary, USA) All statistical tests were conducted against a two-sided alternative hypothesis at the 0.05 level of significance, unless otherwise specified. Data were summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables.

Table 1. Baseline demographic details of the study population (intent-to-treat) (n=1,712)

Characteristic	No. (%)
Age (yr)*	50.26±9.73
<50	823 (48.1)
≥50	889 (51.9)
Height (cm)*	157.41±6.1
Weight (kg)*	59.99±9.7
Body mass index (kg/m^2)*	24.22±3.77
Proliferative breast disease or hyperplasia history	171 (10.0)
History of other types of cancer (excluding nonmelanoma skin cancer)	40 (2.3)
Menopausal status	
Premenopausal	779 (45.5)
Perimenopausal	137 (8.0)
Postmenopausal	796 (46.5)

*Mean±SD.

RESULTS

Patient population

A total of 1,786 patients were enrolled in the study from the Asia-Pacific region. The intention-to-treat (ITT) and safety populations comprised 1,712 patients. Patients from nine countries participated in the registry: Korea (24.6%), Taiwan (22.4%), China (16.0%), Thailand (11.5%), Russia (7.5%), Hong Kong (7.0%), Pakistan (4.3%), Vietnam (3.9%), and Indonesia (2.8%). The mean (±SD) age of patients was 50.26 (±9.736) years. Patient demographic data are summarized in Table 1.

Clinical assessment and comorbidity

As described in Table 1, 171 patients (10%) had a history of proliferative breast disease/hyperplasia and 40 patients (2.3%) had a history of another type of cancer. In 104 patients (6.1%), proliferative breast disease was confirmed by biopsy. At the inclusion visit, 373 patients (21.8%) had comorbidities, which included diabetes mellitus (n=99, 5.8%), cardiovascular disease (n=359, 21%), osteoporosis (n=27, 1.6%), and thromboembolic events (n=3, 0.2%). Of the 1,712 patients, 779 patients (45.5%) were premenopausal, 796 patients (46.5%) were postmenopausal while 137 patients (8.0%) were perimenopausal women.

Tumor classification and characterization

Tumor classification and characterization data are depicted in Table 2. Ductal carcinoma was present by histology in 1,484

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Table 2. Tumor characteristic (n = 1,712)

Tumor characteristic	No. (%)
Ductal carcinoma	1,484 (86.7)
Differentiation	
Poor	108 (7.3)
Moderate	723 (48.7)
Well	546 (36.8)
Unknown	107 (7.2)
Lobular carcinoma	89 (5.2)
Mixed carcinoma	34 (2.0)
Medullary carcinoma	9 (0.5)
Mucinous carcinoma	13 (0.8)
Tubular carcinoma	35 (2.0)
Other	48 (2.8)
Hormone receptors	
ER+ and PR+	894 (52.2)
ER- and PR-	553 (32.3)
ER+ and PR-	52 (3.0)
ER- and PR+	200 (11.7)
Unknown	13 (0.8)
HER2	
Negative	1,111 (64.9)
Positive	574 (33.5)
Unknown	27 (1.6)
AJCC stage	
I	156 (9.1)
IIA	559 (32.7)
IIB	450 (26.3)
IIIA	347 (20.3)
IIIB	17 (1.0)
IIIC	175 (10.2)
IV	1 (0.1)
Not determined	7 (0.4)

ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; AJCC = American Joint Committee on Cancer.

(86.7%) patients and lobular carcinoma in 89 (5.2%), while all other types were reported in < 3% of patients. More than half of patients were ER+ and PR+. Tumor biopsies were analyzed for molecular subtype by determining the human epidermal growth factor receptor 2 (HER2) status. The majority of patients detected the breast mass themselves. However, the diagnosis for each patient was made from biopsy material obtained using fine needle aspiration, excisional biopsy, or core biopsy in the clinic.

Recurrence risk assessment

Recurrence risk was determined by the investigator as well as by St. Gallen Consensus guidelines. Approximately half of the patients (50.1%) had a high recurrence risk, while the remainder (49.9%) had intermediate recurrence risk according to the investigators' assessments. St. Gallen Consensus Guidelines provided similar estimates of recurrence risk.

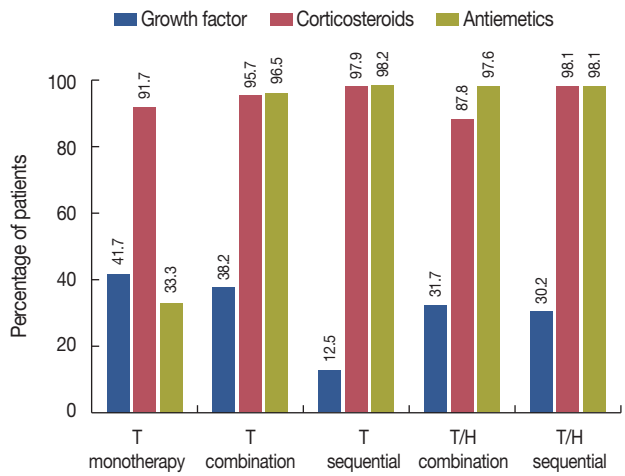

Figure 1. Patients receiving supportive medications (n = 1,712). T = docetaxel; H = trastuzumab.

Radiotherapy and hormonal therapy

More than half of the patients (51.2%) had received radiation therapy by the 1.5 year follow-up visit, 59.2% of whom had nonconserving breast surgery and 40.8% of whom had breast-conserving surgery. Sites treated by radiotherapy included the right or left breast, chest wall, axillary, internal mammary, and supraclavicular regions. Hormonal therapy (anastrozole, exemestane, letrozole, oophorectomy, tamoxifen, and so forth) was administered during the 1.5 years of follow-up in 56.7% of patients.

Supportive medications

All patients received concomitant supportive medication. The main supportive medications were antiemetics, corticosteroids, and growth factors. The details are described in Figure 1. In HER2+ patients, concomitant trastuzumab, along with tamoxifen and aromatase inhibitors, was administered.

Breast cancer surgery

Mastectomy (total or partial) without axillary lymph node surgery was performed for 0.1% of patients. Mastectomy along with lymphadenectomy was performed for 99.2% of patients. Lymphadenectomy alone was performed for 0.7% of patients. Other surgeries were performed for 0.4% of patients.

Chemotherapy regimens and docetaxel exposure

Patients were divided into five groups based on docetaxel-containing chemotherapeutic regimens as described in Table 3. The regimens were docetaxel monotherapy, docetaxel sequential regimens, docetaxel combination regimens, docetaxel-trastuzumab sequential regimens, and docetaxel and trastuzumab in combination. Anthracycline-containing regimens

were administered to 1,353 patients (79.0%), while 359 patients (21.0%) received non-anthracycline-containing regimens. Among the patients who received anthracycline-containing regimens, most received docetaxel sequential (54.1%) or docetaxel combination regimens (36.6%), while for non-anthracycline-containing regimens, most patients received docetaxel combination regimens (83.0%) or docetaxel-trastuzumab combination regimens (11.4%). The actual chemotherapy as chosen by the investigators and the five most frequently selected specific regimens are summarized in Table 4.

Safety assessment

Overall, treatment emergent AEs (TEAE), including those related to surgery, were reported in 77.5% of patients (anthracycline-containing regimen vs. non-anthracycline-containing regimen: 77.9% vs. 75.8%). A total 13,247 AEs were reported. Chemotherapy related AEs were reported in 76.2% of patients (anthracycline-containing regimen vs. non-anthracycline-containing regimen: 76.8% vs. 74.1%). The most commonly reported AEs were alopecia, nausea, neutropenia, vomiting, myalgia, stomatitis, anorexia, diarrhea, and fatigue. In general, the frequency of various types of AEs (including deaths) was broadly comparable across all chemotherapy strategies, with lower rates of AEs for docetaxel monotherapy and combination therapy (66.7% and 65.7%) compared with 84.4% for patients receiving docetaxel sequential chemotherapy, 80.5% for patients receiving docetaxel-trastuzumab combination chemotherapy and 86.8% for patients receiving docetaxel-trastuzumab sequential chemotherapy (Figure 2).

NCI CTCAE ≥grade 3 adverse events

NCI CTCAE ≥ grade 3 AEs were recorded in 35.2% of patients (anthracycline-containing regimen vs. non-anthracycline-containing regimen: 35.6% vs. 33.7%). Chemotherapy-related AEs were observed in 34.8% patients (35.2% vs. 33.4%), the details of which are summarized in Table 5.

Deaths

Twenty-seven patients (1.6%) had died by 1.5 years of follow-up (anthracycline-containing regimen vs. non-anthracycline-containing regimen: 1.6% vs. 1.4%). None of the docetaxel monotherapy patients had died, while 11 (1.8%) of docetaxel combination regimen patients, 14 (1.4%) of docetaxel sequential patients, 1 (2.4%) of docetaxel-trastuzumab combination patients, and 1 (1.0%) of docetaxel-trastuzumab sequential patients had died.

Serious adverse events

Serious AEs were reported by 12.0% of patients (anthracy-

Table 3. Chemotherapy regimen administered in the safety population (n=1,712)

Chemotherapy regimen	Overall No. (%)	Anthracycline No. (%)	Non-anthracycline No. (%)	Mean dose intensity of docetaxel (mg/m²/wk)
T monotherapy	12 (0.7)	-	12 (0.7)	24.1
T combination	626 (36.6)	328 (19.2)	298 (17.4)	22.7
T sequential	927 (54.1)	922 (53.9)	5 (0.3)	25.1
T/H combination	41 (2.4)	-	41 (2.4)	23.8
T/H sequential	106 (6.2)	103 (6.0)	3 (0.2)	25.5
Total	1,712 (100.0)	1,353 (79.0)	359 (21.0)	-

T=docetaxel; H=trastuzumab.

Table 4. Actual chemotherapy (safety population) and five most frequently prescribed regimens in the anthracycline and non-anthracycline groups

Actual chemotherapy	No. (%) of patients				
	T monotherapy (n=12)	T combination (n=626)	T sequential (n=927)	T/H combination (n=41)	T/H sequential (n=106)
Overall	12 (0.7)	626 (36.6)	927 (54.1)	41 (2.4)	106 (6.2)
Anthracycline	-	328 (19.2)	922 (53.9)	0	103 (6.0)
Five most frequent specific regimens		TEC: 136 (7.9)	AC-T: 500 (29.2)	-	FEC-TH: 54 (3.2)
		TAC: 127 (7.4)	FEC-T: 250 (14.6)		AC-TH: 22 (1.3)
		TE: 21 (1.2)	EC-T: 84 (4.9)		EC-TH: 14 (0.8)
		TA: 44 (2.6)	FAC-T: 33 (1.9)		TH-FEC: 6 (0.4)
		TC+THP: 9 (0.5)	T-FEC: 11 (0.6)		FAC-TH: 3 (0.2)
Non-anthracycline	-	298 (17.4)	5 (0.3)	41 (2.4)	3 (0.2)
Five most frequent specific regimens		TC: 269 (15.7)	T+DDP-TCb: 2 (0.1)	TCbH: 30 (1.8)	Each other agent (TC-TCH, TCH-TCbH, and TCbH-TH) selected for single patients only
		TX: 11 (0.6)	NC-T: 1 (0.1)	TH: 7 (0.4)	
		T+DDP: 3 (0.2)	T-TC: 1 (0.1)	TCH: 4 (0.2)	
		TCb: 5 (0.3)	TC-TFC: 1 (0.1)		
		TFCM: 6 (0.4)			

T=docetaxel/Taxotere®; H=Herceptin (trastuzumab); E=epirubucin; C=cyclophosphamide; A=adriamycin; THP=pirarubicin; F=5-fluorouracil; X=capecitabine; DDP=cisplatin; Cb=carboplatin; M=methotrexate.

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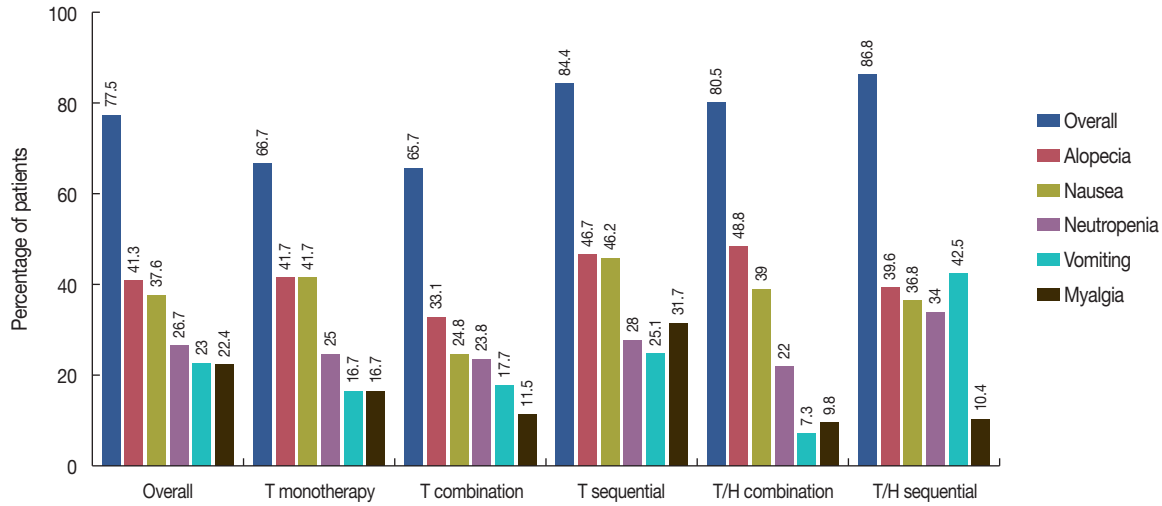

Figure 2. Summary of adverse events by regimen.
T = docetaxel; H = trastuzumab.

Table 5. Summary of adverse events and NCI CTCAE severity grade 3 or higher related to chemotherapy

	Overall (n = 1,712) No. (%)	Anthracycline (n = 1,353) No. (%)	Non-anthracycline (n = 359) No. (%)
Any related AEs	1,326 (77.5)	1,054 (77.9)	272 (75.8)
Most common AEs			
Alopecia	707 (41.3)	554 (40.9)	153 (42.6)
Nausea	643 (37.6)	552 (40.8)	91 (25.3)
Neutropenia	457 (26.7)	394 (29.1)	63 (17.5)
Vomiting	394 (23)	352 (26)	42 (11.7)
Peripheral sensory neuropathy	219 (12.8)	186 (13.7)	33 (9.2)
NCI CTCAE severity grade 3 or higher	603 (35.2)	482 (35.6)	121 (33.7)
Neutropenia	342 (20)	292 (21.6)	50 (13.9)
Vomiting	27 (1.6)	25 (1.8)	2 (0.6)

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; AEs = adverse events.

cline-containing regimen vs. non-anthracycline-containing regimen: 12.3% vs. 10.9%). Chemotherapy-related serious AEs were reported in 11.1% of patients (11.5% vs. 10.0%). The number of cycles in which SAEs occurred is shown in Table 6. The most frequent SAEs were neutropenia, febrile neutropenia, asthenia, and peripheral sensory neuropathy. Neutropenia was reported most frequently in the docetaxel sequential regimens, with a mean of 2.6 cycles per patient (95% confidence interval, 2.37–2.83). Febrile neutropenia occurred most frequently with docetaxel-trastuzumab sequential regimens, with a mean of 1.4 cycles per patient (0.72–2.08). Few patients had neutropenic infections, with only one cycle reported per patient experiencing neutropenic infection. Asthenia occurred most frequently with docetaxel sequential regimens,

Table 6. Number of cycles with serious adverse events

Serious adverse event	Overall (95% CI)	Anthracycline (95% CI)	Non-anthracycline (95% CI)
Neutropenia	2.3 (2.16–2.47)	2.4 (2.22–2.55)	1.9 (1.56–2.25)
Febrile neutropenia	1.3 (1.16–1.35)	1.13 (1.15–1.38)	1.2 (1.01–1.41)
Asthenia	1.4 (1.26–1.51)	1.4 (1.27–1.54)	1.1 (0.79–1.49)
Peripheral sensory neuropathy	1.2 (1.17–1.31)	1.2 (1.16–1.30)	1.3 (1.00–1.54)

CI = confidence interval.

with a mean of 1.4 cycles per patient (1.28–1.58). Peripheral sensory neuropathy occurred most frequently with docetaxel-trastuzumab combination regimens, with a mean of 1.4 cycles per patient (0.49–2.26).

Lipid profile

At the end of chemotherapy, the mean LDL-C and total cholesterol increased while the mean HDL-C decreased from baseline in all menstrual status groups, which resulted in increased LDL-C/HDL-C and total cholesterol/HDL-C ratios. LDL-C, HDL-C, and total cholesterol levels in different menopausal stages are summarized in Table 7.

Cardiac function

To assess cardiac function, the LVEF was measured in 916 of the patients who received anthracycline-containing regimens. The mean (±SD) of LVEF at baseline was 66.4% (±7.389) and 64.5% (±7.165) at 1.5-year follow-up with a mean change of -1.9% (±7.062), which was not clinically relevant. Risk factors for reduced LVEF, such as age, history of hypertension or diabetes, presence of cardiovascular events, total cholesterol, LDL-C, and HDL-C, also did not significant-

Table 7. Lipid profiles in different menopausal stages

	No.	Baseline (mean±SD)	End of chemotherapy (mean±SD)	Change (mean±SD)	*p*-value
LDL-C (mg/dL)					
Premenopausal	177	109.66±34.95	115.54±41.57	5.88±30.21	<0.0001
Perimenopausal	432	110.77±32.71	128.31±35.38	17.55±31.56	<0.0001
Postmenopausal	586	131.51±138.39	139.70±124.45	8.19±40.99	<0.0001
HDL-C (mg/dL)					
Premenopausal	179	59.80±22.94	55.71±23.219	-4.09±16.01	0.0005
Perimenopausal	434	54.65±18.23	52.26±16.22	-2.38±14.7	0.0019
Postmenopausal	595	54.23±17.46	49.41±16.12	-4.82±15.95	<0.0001
Total cholesterol (mg/dL)					
Premenopausal	196	192.11±48.12	205.70±51.7	13.59±35.8	<0.0001
Perimenopausal	470	187.27±36.42	208.60±40.89	21.33±39.82	<0.0001
Postmenopausal	655	206.19±49.62	213.22±41.89	7.03±50.63	<0.0001

LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol.

ly influence LVEF change from baseline.

Treatment discontinuation

Overall, 35 patients had a total of 41 AEs leading to withdrawal from therapy, with 33 TEAEs in 27 patients (2.0%) receiving anthracycline-containing regimens and eight TEAEs in eight patients (2.2%) receiving non-anthracycline-containing regimens. The most frequently reported TEAEs leading to discontinuation were neutropenia in five patients (0.3%), leukopenia in four patients (0.2%), fatigue in three patients (0.2%), and myalgia in one patient (0.1%).

Follow-up

There were 202 patients (11.8%) who were not seen for the 1.5-year follow-up visit. One hundred seventy-five patients (10.2%) were lost to follow-up, and chemotherapy-related death was reported in 27 patients (1.6%). The remaining 1,510 patients (88.2%) were alive; 1,454 patients (96.3%) had no relapse, 45 patients (3.0%) had one relapse, and 11 patients (0.7%) had a secondary malignancy.

Relapse

The number of patients alive was similar between patient groups receiving anthracycline regimens (87.9%) and non-anthracycline regimens (89.4%). Relapse was observed in 45 (3%) patients. In 12 patients, the first relapse was locoregional, while it was distant in 32 patients. Relapse occurred in 22 patients receiving docetaxel combination regimens and 19 patients receiving docetaxel sequential regimens. The relapse rate was similar between anthracycline- and non-anthracycline-receiving patient groups.

With respect to actual chemotherapy regimens, the relapse rate was <2% for each regimen. Most patients who reported relapse were the American Joint Committee on Cancer stage IIIC. The most frequent breast cancer subtype to relapse was the HER2-enriched subtype, which was reported in 15 patients, while the subtype was not determined for 10 patients.

DISCUSSION

The APBI-II was an observational study conducted to examine the safety parameters of the most commonly used chemotherapeutic agent, docetaxel, in anthracycline- and non-anthracycline-containing regimens in EBC patients treated in real-world clinics of the Asia-Pacific region. Significant differences in the epidemiology of breast cancer between Eastern and Western countries and AEs related to docetaxel led to the establishment of this registry.

Consecutive patients were enrolled representing a real-world clinical setting. Patients were at different stages of menopause and different ages at inclusion. In contrast to Western countries, where most patients are older than 65 years of age, two-thirds of the patients in this registry were younger than 55 years, confirming earlier reports that in Asia-Pacific region, a younger population is prone to breast cancer [8,9]. The increased number of younger patients in this area demands better screening methods and treatment availability to reduce morbidity. Interestingly, most patients in this registry had ER+ and PR+ disease, similar to Western countries. Compared with Western patient populations, more patients were found to be positive for HER2 (33% vs. 20%) in the APBI registry [10]. Younger women more frequently have HER2+ breast cancer, as was seen in this patient population, which included more young patients [10]. Since HER2+ status is correlated with poor prognosis, an appropriate treatment at the right time is necessary to ensure good patient sur-

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vival. As in any real-world clinical setting, a variety of surgeries and chemotherapy regimens were applied, based on each patient's condition and disease status. Chemotherapeutic regimens most commonly used docetaxel. More than 10 different regimens were used to treat patients, along with various supportive medications, such as growth factors, antibiotics, and antiemetics. Altogether, the patients' demographics and treatment strategies were highly diverse. Hence, this registry represents real-world clinical settings in which to test the effect of chemotherapeutic agents in patients with EBC.

Several AEs were reported in the APBI-II registry, consistent with other published studies. However, the majority of AEs in all regimens were manageable. AEs, such as neutropenia and vomiting, were recorded more frequently in patients receiving anthracycline-containing regimens than in patients receiving non-anthracycline-containing regimens. Leukopenia occurred significantly more often in patients receiving non-anthracycline-containing regimens. The most common AEs were alopecia, nausea, neutropenia, and leucopenia. The most frequent NCI CTCAE grade 3 or higher AEs were neutropenia and leucopenia. Neutropenia was recorded significantly more frequently in patients receiving anthracycline-containing regimens, while leukopenia was more frequent in patients receiving non-anthracycline-containing regimens. Neutropenia was also reported more frequently in the docetaxel-sequential arm as compared with the docetaxel-combination arm. In a phase III (n = 1,491) trial of lymph node-positive breast cancer patients, Martin et al. [5] reported grade 3 or higher neutropenia in 65% of patients, compared with 20% of patients in the APBI-II registry. Similarly, in another phase III clinical trial, Jones et al. [11] reported grade 3 or higher neutropenia in more than 61% of patients (n = 1,016). In the BCIRG005 trial (n = 1,649), neutropenia was reported in docetaxel-sequential and -combination arms, at 57.8% and 59.9%, respectively [12]. Hence, compared with that in other published reports, the incidence of grade 3 or higher neutropenia was lower in the APBI-II registry.

In the APBI-II registry, relapse was observed in 3% of patients. In the BCIRG005 trial, relapse was observed in 21%, and in a study by Jones et al. the relapse rate was 14% [11,12]. However, the BCIRG005 trial followed patients for 2.5 years and Jones et al. for 5.5 years, compared with the APBI-II registry that had a follow-up of 1.5 years [11,12]. If patients were followed for a longer time in the APBI-II registry, an increase in relapse rates may have been observed. Patients death was observed in < 1% of patients in the BCIRG005 trial and 11% by Jones et al. [11,12]. In the ABPI-II registry, death was reported in 1.6% of patients. The longer follow-up period of 5.5 years may be the main reason for the higher incidence of deaths in the phase III clinical trial by Jones et al. [11]. AEs, NCI CTCAE ≥ grade 3 events, SAEs, death, relapse rates, treatment discontinuation rate, and number of patients alive at 1.5 years of follow-up was approximately equal in both categories of docetaxel-based anthracycline-containing and non-anthracycline-containing regimens. In the APBI-II registry, no significant safety issue was observed in any patient or treatment group of the Asia-Pacific region that differed from those published in clinical trials of other populations [4].

Breast cancer patients are at increased risk for cardiac disease after anthracycline chemotherapy [2]. Hence, cardiac function was evaluated at baseline and at 1.5 years of follow-up in anthracycline-receiving patients (n = 916). LVEF has been used to assess cardiac function [13]. A reduction in LVEF of more than 15%, to an absolute LVEF of 30% to 45%, reflects impairment in cardiac function [13]. LVEF levels were within the normal range at both time points, with a mean reduction of 1.9% from baseline at the 1.5 years follow-up visit. These results indicate that docetaxel-based, anthracycline-containing chemotherapeutic regimens do not cause significant impairment in cardiac function 1.5 years after the completion of chemotherapy in an Asia-Pacific patient population. Moreover, the reduction in LVEF was not correlated with other risk factors for cardiac disease, such as history of hypertension, diabetes, cardiovascular disease and/or total cholesterol, LDL-C, and HDL-C levels. Taken together, these results suggest that administration of docetaxel-based, anthracycline-containing chemotherapy did not cause significant cardiotoxicity in breast cancer patients of the Asia-Pacific region. Nonetheless, a longer follow-up is required to determine the cardiotoxicity related to docetaxel- and anthracycline-based chemotherapy in EBC patients of Asia-Pacific region.

Serum cholesterol levels increase due to chemotherapy [14]. Consistent with previous reports, the APBI-II registry also observed a small but significant increase in LDL-C and total cholesterol levels and a small but significant decrease in HDL-C levels at the end of chemotherapy in pre-, peri-, and post-menopausal women. However, perimenopausal patients had a larger change in lipid levels at the end of chemotherapy, indicative of their unstable hormonal status due to menopause. At the end of chemotherapy, both LDL-C and total cholesterol showed increasing trend in all menstrual status groups. However, mean values were within normal range. Measurement of lipid levels after 3 to 5 years is required to provide better insight regarding the effect of docetaxel-based chemotherapy on cholesterol levels in EBC patients of the Asia-Pacific region.

Long-term cardiac toxicity has been observed in EBC patients treated with anthracyclines. However, in this registry, the lipid profile and LVEF of patients were followed only for

1.5 years after chemotherapy treatment. It is necessary to follow these patients for a longer duration to evaluate the effect of docetaxel on cardiac safety.

This registry underscores the importance of recognizing the great diversity in patients' demographics as well as treatment strategies in real-world patients of the Asia-Pacific region. In this registry, various docetaxel-based anthracycline- and non-anthracycline-containing regimens were not found to cause significant issues in safety outcomes such as AEs, NCI CTCAE ≥grade 3 events, SAEs, death, relapse rates, treatment discontinuation rates, number of patients alive, LVEF, and lipid profile at 1.5 years after treatment. However, a longer follow-up evaluation may be performed to assess long-term safety outcomes. This study's results suggest that docetaxel-based chemotherapy is a safe choice for EBC patients of the Asia-Pacific region.

CONFLICT OF INTEREST

The authors declare that they have no conflict interests.

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