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A Post-Marketing Surveillance Study to Evaluate the Safety Profile of Alvotere[®] (Docetaxel) in Iranian Patients Diagnosed with Different Types of Cancers Receiving Chemotherapy

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ABSTRACT

Background: Docetaxel is a clinically well established antimitotic chemotherapy medication. Labeled docetaxel indications are breast cancer, gastric cancer, head and neck cancer, non-small cell lung cancer, and prostate cancer.

Objective: This is a Phase IV study to evaluate the safety profile of docetaxel (Alvotere; NanoAlvand, Iran) in Iranian patients diagnosed with different types of cancers receiving chemotherapy regimens with docetaxel.

Methods: Patients who received Alvotere as a part of their chemotherapy regimen were enrolled in this Phase IV, observational, multicenter, open-label study. Alvotere was administered as a single agent or in combination with other chemotherapy agents. Safety parameters in each cycle were assessed, and the related data were recorded in booklets.

Findings: A total of 411 patients with different types of cancers were enrolled from 25 centers in Iran. The most common malignancies among participants were breast cancer (49.88%), followed by gastric cancer (22.63%). Participants' mean age was 53.33 years, and the mean total dose used in each cycle was 132 mg. According to the results, 341 patients experienced at least 1 adverse event, that the most common was alopecia (41.12%). In total, 92 (22.38%) patients had at least 1 adverse event of grade 3

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or 4, and 25 (6.08%) patients showed 54 serious adverse events, which the causality assessment for all was possibly related to Alvotele. There was a significant difference between men and women in the incidence of skin and subcutaneous tissue disorders (55.63% in women vs 41.73% in men; $P=0.009$). Also, the incidence of gastrointestinal disorders, nervous system disorders, skin and subcutaneous tissue disorders, hepatic enzymes increase, and fluid retention was significantly higher ($P < 0.05$) in patients receiving anthracyclines in their chemotherapy regimens.

Conclusions: The findings of this open-label, observational, multicenter, postmarketing surveillance showed that Alvotele appears to have an acceptable safety profile in Iranian cancer patients receiving chemotherapeutic regimens. (*Curr Ther Res Clin Exp.* 2022; 82:XXX–XXX) © 2022 Elsevier HS Journals, Inc.

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Introduction

Docetaxel, derived from extracts of the leaves of the European yew tree (*Taxus baccata*), was discovered in the 1980s and has become among the most important chemotherapeutic agents for the treatment of cancers since 1996.¹ The Food and Drug Administration has approved this medication for breast cancer, non-small cell lung cancer (NSCLC), gastric cancer, head and neck cancer, and prostate cancer.²

Docetaxel is a clinically well established antimitotic chemotherapy medication. It promotes the assembly of microtubules from tubulin dimers and inhibits tubulin depolymerization, which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle. Labeled indications for docetaxel are breast cancer (BC), gastric cancer, head and neck cancer, NSCLC, and prostate cancer.²

BC and NSCLC are the most common cancers in the world. The incidence and mortality rates vary across the globe. Globally, both BC and Lung Cancer (LC) have 2.09 million new cases in the world. According to the World Health Organization database, almost 627,000 deaths for BC and 1,761,000 deaths for NSCLC were reported in 2018.³ In Iran, 16,160 and 7,224 new cases with BC and lung cancer were reported in 2017.⁴ Based on 2018 reports, another common cancer is prostate cancer with approximately 1.28 million new cases, of which 60% are metastatic.^{3,5,6} Almost 350,000 deaths were reported in 2018 due to prostate cancer.³ Stomach cancer is another commonly diagnosed cancer with 1.03 million new cases and 783,000 deaths reported in 2018.³

In routine clinical practice, there are some other clinical uses for docetaxel, such as metastatic bladder cancer, esophageal cancer, Ewing sarcoma, ovarian cancer, soft tissue sarcoma, and unknown-primary adenocarcinoma.² Docetaxel is not yet approved by the Food and Drug Administration for these indications. However, it seems to have an acceptable safety profile in these situations because they are included as the off-label indications of the medication in the monograph.² The most common adverse events (AEs) reported for docetaxel are neutropenia, asthenia, leukopenia, nausea, and diarrhea.^{7–9} and the most common serious AEs (SAEs) are neutropenia, febrile neutropenia, and neutropenic infections.¹⁰

Phase III clinical trials are conducted with rigid inclusion/exclusion criteria and have limitations on evaluating all possible safety concerns. Phase IV studies were introduced to assess drugs' safety in a real-world setting. Observational studies are necessary to evaluate the safety of medications in patients being treated in routine clinical practice to assess safety signals and provide additional safety information. In case of acceptable safety profile, the medication may also be marketed in other countries. In the current study, we evaluated a brand-name product of docetaxel

(Alvotele; NanAlvand, Simin dasht, Iran) for its safety profile in patients receiving chemotherapeutic regimens in Iran.

Materials and Methods

Design and treatment

The present study was an observational, multicenter, single-arm, open-label, and postmarketing surveillance (PMS) that evaluated the safety profile of Alvotele in Iran. All data were recorded by the designated physicians in 2 booklets, each containing information on 3 cycles of chemotherapy. Patients' demographic data, cancer type, and habitual and medical history were provided at the baseline visit. Moreover, the setting of therapies (including first line, second line, relapsed/refractory, and unknown), information regarding the other administered medications, adverse drug events, and clinical actions due to the AEs were recorded for all participants during each visit. Designated physicians decided on the administered dose and the duration of therapies.

Ethics approval was obtained from the institutional research ethics committee of the principal investigator's affiliated university (Tehran University of Medical Sciences). All participants voluntarily signed a written informed consent before participation in the study.

Patients

All eligible cancer patients in different centers who received Alvotele based on the physicians' routine practice, were enrolled in this study.

Objectives

The objective of the current study was assessment of safety profile, including the incidence of AEs. The intensity of AEs was determined based on the Common Terminology Criteria for Adverse Events version 5.0, and terminology for AEs was chosen using by MSSO (Maintenance and Support Services Organization), 12975 Worldgate Drive Herndon, VA 20170-6008, USA) system organ class (SOC) and preferred term (PT). The seriousness of AEs was also recorded.

Statistical Analysis

In this PMS study, the calculated sample size was determined to be 418 patients to evaluate the development of hand and foot syndrome with a predicted incidence of 0.006 with 90% power and 15% dropout. In the patient recruitment process, 411 patients were enrolled in the study. Baseline characteristics of the patients and

Table 1
Baseline characteristics of patients.

Variable	Result
Age, y	53.33 (12.81)*
Weight, kg	66.97 (11.82)*
Height, cm	163.62 (7.83)*
BSA, m ²	1.74 (0.17)*
Habitual history	
Smoking	46 (11.19) [†]
Alcohol consumption	12 (2.92) [†]
Medical history	
Liver impairment	25 (6.08) [†]
Cardiac disorders	20 (4.87) [†]
Renal impairment	14 (3.41) [†]
Radiotherapy history	31 (7.54) [†]
Allergy history	6 (1.46) [†]
Laboratory tests	
SCr, mg/dL	1.00 (0.70)*
Bilirubin total, mg/dL	1.00 (0.57)*
ALP, U/L	237.87 (143.14)*
AST, U/L	24.71 (13.18)*
ALT, U/L	25.70 (12.22)*
Platelet, cells/ μ L	265620.10 (104598.30)*
WBC, cells/ μ L	8033.219 (7784.37)*
Neutrophil, cells/ μ L	5201.37 (4066.11)*
Lymphocyte, cells/ μ L	2027.44 (1447.80)*

BSA = body surface area; SCr = serum creatinine; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine transaminase; WBC = white blood cell.

* Values are presented as mean (SD).

[†] Values are presented as n (%).

cancer type were summarized using mean (SD) or frequency (percentage) according to the type of variables. Furthermore, the incidence of AEs categorized by SOC and PT was described. Based on the definition of incidence, the number of patients with at least 1 new AE was counted. The frequency (percentage) of causality assessment and the incidence of at least possibly related AEs were also assessed. The Pearson χ^2 test was performed to assess the incidence of AEs. All data cleaning procedures and analyses were performed using Stata version 14 (Stata Corp LP, College Station, Texas).

Results

Patients

A total of 411 patients with different types of cancers were enrolled in this multicenter PMS study from August of 2015 to March 2019. The study was conducted in 25 centers in 16 different cities of Iran. All patients received chemotherapy regimens containing docetaxel with doses of 60 mg/m² to 100 mg/m². Patients' baseline characteristics and demographic data are presented in Table 1. The mean age of the patients was 53.33 years. BC was the most common cancer among the patients (54.67%) followed by gastric cancer (24.80%). Frequency of cancer types are shown in Table 2.

The mean total dose used in each cycle for the patients were 132.60 (\pm 26.12) mg. According to Table 3, which shows the setting of chemotherapies, 235 (57.18%) patients used Alvotere as first-line therapy.

Safety analysis

Among the individuals treated with Alvotere, the most common reported AE was alopecia (41.12%) followed by leukopenia (38.44%) and asthenia (34.31%). The incidence of all AEs and the incidence of grade 3 and 4 AEs are presented in Table 4 based on SOC and PT. In a total of 411 patients, 341 (82.97%) patients experienced at least 1 AE of any grade, and 92 (22.38%) patients experienced at

Table 2
Frequency of cancer types.

Cancer type	Result*
Breast cancer	205 (49.88)
Prostate cancer	25 (6.08)
Gastric adenocarcinoma	93 (22.63)
Non-small cell lung cancer	14 (3.41)
Head and neck cancer	13 (3.16)
Other cancer type	25 (6.08)
Cervical cancer	1 (4.00)
Esophageal cancer	3 (12.00)
Hepatobiliary cancer	1 (4.00)
Lymphoma	1 (4.00)
Ovarian cancer	8 (32.00)
Sarcoma	7 (28.00)
Small cell lung cancer	3 (12.00)
Unknown-primary of adenocarcinoma	1 (4.00)
Unknown	36 (8.76)

* Values are presented as n (%).

Table 3
Summary statistics for patients' setting of treatment.

Variable	Result*
First line	235 (81.88)
Second line	38 (13.24)
Relapsed/refractory	14 (4.88)

* Values are presented as n (%).

least 1 grade 3 or grade 4 AE. No grade 5 AE was reported in this study.

The analysis also showed that the incidence of skin and subcutaneous tissue disorders was significantly higher in women than men (55.63% vs 41.73%; $P=0.009$). Furthermore, in patients who received anthracyclines as a part of their chemotherapy regimen, the incidence of gastrointestinal disorders (53.93% vs 40.37%; $P=0.02$), nervous system disorders (42.70% vs 24.22%; $P < 0.001$), skin and subcutaneous tissue disorders (61.80% vs 48.45%; $P=0.03$), increase in hepatic enzymes, including alanine aminotransferase and aspartate aminotransferase abnormalities and physician-reported hepatic enzyme increases (58.43% vs 26.71%; $P < 0.001$), and fluid retention (24.72% vs 9.32%; $P < 0.001$) was significantly higher.

The causality of AEs among 411 patients is shown in Table 5. The causality assessment was done based on the World Health Organization causality assessment scale. There were 323 at least possibly related AEs (78.59%) and "Possible" was the most common causality (67.34%).

The number of patients who experienced at least 1 possibly related SAE is demonstrated in Table 6. In the current study, among 411 patients, 25 patients (16 men and 9 women) experienced at least 1 SAE and a total of 54 SAEs were reported, which the most common ones belonged to blood and lymphatic system and gastrointestinal disorders with an incidence of 3.90% and 2.19%, respectively.

Also, there was a trend toward higher incidence of serious blood and lymphatic system disorders in patients older than age 65 years compared with patients younger than age 65 years (3.63% vs 2.66%); however, the difference was not statistically significant. The SAEs categorized by SOCs are presented in Table 6. Furthermore, there were no cases of interstitial lung disease reported among the patients.

Discussion

Real-world studies are of significant importance in the clarification of the medicines' safety profile during the postauthorization

Table 4
Summary statistics for system organ class and preferred term.

System organ class	Result*	Preferred term	All grades*	Grade 3 and 4*
Blood and lymphatic system disorders	218 (53.04)	Leukopenia	158 (38.44)	21 (5.11)
		Thrombocytopenia	70 (17.03)	15 (3.65)
		Neutropenia	68 (16.55)	20 (4.87)
Skin and subcutaneous tissue disorders	211 (51.34)	Anaemia	59 (14.36)	11 (2.68)
		Alopecia	169 (41.12)	38 (9.25)
		Nail disorder	94 (22.87)	13 (3.16)
General disorders and administration site conditions	190 (46.23)	Rash	63 (15.33)	4 (0.97)
		Asthenia	141 (34.31)	10 (2.43)
		injection site erythema	78 (18.98)	2 (0.49)
Investigations	178 (43.31)	Injection site discoloration	40 (9.73)	0 (0)
		Pyrexia	24 (5.84)	2 (0.49)
		Injection site phlebitis	4 (0.97)	0 (0)
		Blood bilirubin increased	115 (27.98)	3 (0.73)
		Alanine aminotransferase increased	98 (23.84)	3 (0.73)
		Aspartate aminotransferase increased	78 (18.98)	1 (0.24)
		Blood alkaline phosphatase increased	74 (18)	3 (0.73)
		Blood creatinine increased	22 (5.35)	4 (0.97)
		Hepatic enzyme increased	8 (1.95)	0 (0)
		Ejection fraction decreased	2 (0.49)	0 (0)
Gastrointestinal disorders	178 (43.31)	Nausea	101 (24.57)	5 (1.22)
		Stomatitis	74 (18)	4 (0.97)
		Diarrhoea	60 (14.6)	4 (0.97)
Nervous system disorders	116 (28.22)	Vomiting	46 (11.19)	3 (0.73)
		Peripheral sensory neuropathy	108 (26.28)	4 (0.97)
Musculoskeletal and connective tissue disorders	82 (19.95)	Peripheral motor neuropathy	18 (4.38)	0 (0)
		Myalgia	82 (19.95)	5 (1.22)
Metabolism and nutrition disorders	52 (12.65)	Fluid retention	52 (12.65)	0 (0)
Vascular disorders	30 (7.3)	Hypotension	30 (7.3)	0 (0)
Immune system disorders	22 (5.35)	Bronchospasm	22 (5.35)	0 (0)
Infections and infestations	4 (0.97)	Bronchitis	4 (0.97)	2 (0.49)
No. of patients with at least 1 adverse event			341 (82.97)	92 (22.38)

* Values are presented as n (%).

Table 5
Summary statistics for causality assessment.

Category	Result*
Possible	2454 (67.34)
Probable	152 (4.17)
Unlikely	1036 (28.43)
Unassessable/unclassifiable	2 (0.05)
Total	3644 (100)

* Values are presented as n (%).

period. The current PMS was designed to evaluate the safety profile of Alvotere in a real-world clinical setting in different cities around Iran.

In 2006, Jones et al¹¹ suggested that a combination of docetaxel with cyclophosphamide had better disease-free survival compared with doxorubicin and cyclophosphamide in patients with BC. At 5 years, the disease-free survival rate was significantly superior for docetaxel with cyclophosphamide compared with doxorubicin and cyclophosphamide.¹¹ In another Phase III study, Fossella et al¹² showed that patients with NSCLC who received docetaxel with the

doses of 100 mg/m² or 75 mg/m², had a better overall response, and longer time-to-progression in comparison with the control group (vinorelbine or ifosfamide).

Tannock et al¹³ demonstrated that patients with prostate cancer who used docetaxel and prednisone had a better outcome than patients taking mitoxantrone and prednisone. Moreover, it is reported that gastric cancer patients using docetaxel in combination with cisplatin and fluorouracil have a longer time to progression versus patients treated with cisplatin and fluorouracil.¹⁴ Additionally, Vermorken et al¹⁵ maintained that patients with stage III or stage IV head and neck cancer (no distant metastases) who received docetaxel, cisplatin, and fluorouracil had better overall survival and PFS compared with the control group (cisplatin and fluorouracil). The most studied dosage of docetaxel is 75 mg/m² every 3 weeks. This administration schedule is often accompanied by the incidence of grade 3 or 4 neutropenia.^{8,12}

The incidence of severe neutropenia in our study was 2.43%, which is comparable with the rate that Kim et al¹⁰ reported (3.57%). The incidence of neutropenia with any grade was 16.55% in our study, which is in the range of 14.60% to 26% reported in the other studies.^{11–14} There are some other reports that showed

Table 6
Incidence of serious adverse events (SAEs).

System organ class	No. of patients (n = 411)	Incidence (n = 411)
SAE	25	6.08
Blood and lymphatic system disorders	16	3.90
Gastrointestinal disorders	9	2.19
General disorders and administration site conditions	5	1.22
Musculoskeletal and connective tissue disorders	1	0.24
Nervous system disorders	3	0.73
Skin and subcutaneous tissue disorders	3	0.73
At least possibly related SAEs	24	5.84

even higher incidences of 62% and 95%.^{7,9} The incidence of grade 3 or 4 anemia in our study (2.68%) was in line with other studies that reported a wide range of 0.5% to 18% for the incidence of anemia.^{1,7-9,11-13} The incidence of thrombocytopenia in the current study was 17.03%, which is consistent with the incidence of 25% reported in a Phase III study of docetaxel, cisplatin, and fluorouracil compared with cisplatin and fluorouracil. Although in a Phase III trial comparing doxorubicin/cyclophosphamide with docetaxel/cyclophosphamide and another study on the safety and efficacy of single-agent docetaxel, rates of 2% and 3.28% were reported for thrombocytopenia.^{7,11,14}

The results demonstrated a 12.65% incidence of fluid retention in the study, whereas a variable range of 5.11% to 34% was reported in other studies.^{7,8,11,13} Furthermore, there was an incidence of 22.87% for nail disorders in our study compared with the incidence of 6.93% to 33.5% in other studies.^{7,9,13}

Peripheral sensory neuropathy incidence was 26.23% in this study, which complies with the range of incidence 23.1% to 38% in other studies.^{8,13,14} Besides, the incidence of diarrhea was 14.6% among participants, which is consistent (9.49%, 19%, 33%, 33.64%, and 75%) with other reports.^{7-9,13,14}

We believe that the reason for differences between the current and the other studies is our study's heterogeneity. The differences in cancer types and chemotherapeutic regimens led to this heterogeneity. On the other hand, there was no other PMS with the same methodology.

This study had some limitations. This was an observational, single-arm survey that did not have a control group. Another main limitation is that the patients' information and AEs were recorded in booklets, which increases the potential risk of incorrect data.

Conclusions

The results of this open-label, observational, multicenter, PMS showed that Alvotere has an acceptable safety profile in cancer patients in Iran receiving chemotherapeutic regimens.

Author contribution

F.Sh. conducted the study according to the accepted protocol and drafted the manuscript. F.V., N.A., A.A., A.S., A.gh., H.V., M.R, Sh.S., M.F., A.M., M.R., H.R., M.S., M.R., A.P. and D.B participated in the design and coordination of the study and revised the manuscript. N.A. was Head of medical department of Orchid Pharmed Company and supervised the clinical trial conduction, helped to draft the manuscript and performed statistical analysis. F.Sh. conducted the study according to the accepted protocol and drafted the manuscript and decided to submit the manuscript for publication. All authors read and approved the final manuscript and are accountable for all aspects of the work.

Conflicts of Interest

N. Anjidani is head of the medical department of Orchid-Pharmed company, which is in collaboration with NanoAlvand in respect to conducting clinical trials. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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