Current Therapeutic Research 96 (2022) 100657

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Post-Marketing Surveillance of a generic Oxaliplatin (Alvoxal®) in Iranian Patients with Cancer

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ARTICLE INFO

Article history:
Received 8 February 2021
Accepted 23 November 2021

Key words:
Alvoxal®
colorectal cancer
gastric cancer
observational
Phase IV
safety

ABSTRACT

Background: CRC is the second and third most common cancer in women and men, respectively. The national comprehensive cancer network guidelines recommend oxaliplatin-based chemotherapy as a preferred regimen for patients with advanced or metastatic colon cancer. Oxaliplatin is also used in the off-label treatment of gastric cancer. FDA uses post-marketing study commitments to gather additional information about a product's safety, efficacy, or optimal use. It is necessary to perform safety monitoring after marketing authorization is received; such monitoring can be done by means of characterizing the safety of drugs in patients being treated in real-world clinical practice settings.

Objectives: This Phase IV study aimed to evaluate the safety profile of a brand-name formulation of the generic drug oxaliplatin (Alvoxal®, NanoAlvand, Tehran, Iran) in Iranian patients diagnosed with either colorectal or other, different types of cancer.

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https://doi.org/10.1016/j.curtheres.2021.100657

Methods: Patients with colorectal cancer, gastric cancer, or other malignancies receiving oxaliplatin as a part of their treatment were included in this open-label, multicenter, observational Phase IV study. This study aimed to assess the safety profile of oxaliplatin in patients diagnosed with different cancers.
Findings: A total of 483 patients from 16 cities in Iran were enrolled. The most common malignancy was colorectal cancer (55.49%), followed by gastric cancer (28.16%). Based on the results, 405 patients experienced at least 1 adverse event. Most of these adverse events were grade 1 or 2, and the most commonly reported adverse event was anemia (60.66%). During the study, 26 serious adverse events occurred in 15 (3.11%) patients, which were perhaps related to oxaliplatin. There were no remarkable differences in the incidences of adverse events in the system organ classes of blood and lymphatic system disorders, gastrointestinal disorders, or nervous system disorders among patients with different malignancies (ie, colorectal cancer, gastric cancer, and other malignancies) or between genders. The results of this open-label, multicenter, observational, postmarketing surveillance study demonstrated no unexpected safety findings from the use of this oxaliplatin product (Alvoxal®) in Iranian patients diagnosed with different types of cancer.
Conclusions: This Phase IV study provides data on the safety profile of a number of chemotherapy regimens containing an oxaliplatin product given to Iranian patients diagnosed with different types of cancer.

Introduction

Oxaliplatin-based regimens are commonly used in the treatment of many cancers. Oxaliplatin acts by binding to tumor cell DNA strands and thereby interfering with DNA replication. Oxaliplatin was approved by the Food and Drug Administration for the initial treatment of advanced colorectal cancer (CRC) on January 2004.[1] In vitro studies demonstrated that oxaliplatin has synergistic antitumor activity with 5-fluorouracil (5-FU).[2–5] Based on clinical trials, the combination regimen of 5-FU, leucovorin, and oxaliplatin was accepted as a fundamental standard first-line therapy in advanced CRC.[6,7]

CRC is the second and third most common cancer in women and men, respectively.[8] Although it is among the most commonly diagnosed cancers worldwide, its incidence and mortality rates differ considerably among countries. In the United States, nearly 147,950 new colon and rectum cancer cases are diagnosed annually, of which 70.7% are colon cancer and 29.3% are rectal cancer.[9] According to the Institute for Health Metrics and Evaluation, during 2017, the incidence of colon and rectum cancer in Iran was approximately 9800 patients.[10]

The National Comprehensive Cancer Network guidelines recommend oxaliplatin-based chemotherapy as a preferred regimen for patients with advanced or metastatic colon cancer.[11] This recommendation is based on the results of several clinical studies, including a multicenter international Phase III study that evaluated the addition of oxaliplatin to 5-FU and leucovorin as adjuvant therapy in patients with stage II or III colon cancer. The results demonstrated significant improvements in 5-year disease-free survival and 6-year overall survival among the patients. This study's 10-year follow-up supported an overall survival and disease-free survival benefit of oxaliplatin as adjuvant therapy for stage III colon cancer. These studies confirmed that chemotherapy with oxaliplatin has a considerable role in palliating symptoms and improving survival.[12–14] Further studies have confirmed the efficacy and acceptable safety profile of oxaliplatin-based regimens.[15–17]

Oxaliplatin is also used in the off-label treatment of gastric cancer.[18] Gastric cancer has the fifth highest incidence among malignancies, and it is the third leading cause of cancer deaths worldwide.[19] In the United States, nearly 26,600 new cases of stomach cancer and 11,010 related deaths are reported annually.[9] According to the Institute for Health Metrics and Evaluation, during 2017, the incidence rate of stomach cancer in Iran was 11.96 new cases per 100,000 people (approximately 9900 patients).[10] Systemic chemotherapy provides survival benefits for patients with advanced gastric cancer.[20] Studies showed that oxaliplatin-based regimens are effective and tolerable first-line chemotherapy strategies for patients with advanced gastric cancer.[21–23]

The Food and Drug Administration uses postmarketing study commitments to gather additional information about a product's safety, efficacy, or optimal use. It is necessary to perform safety monitoring after marketing authorization is received; such monitoring can be done by means of characterizing the safety of drugs in patients being treated in real-world clinical practice settings.[24]

Alvoxal® (NanoAlvand, Tehran, Iran) has been available as a concentrate for solution for injection in the Iranian pharmaceutical market since 2015 and is considered a therapeutic agent for patients with cancer.[25] Alvoxal®, as a brand-name formulation of the generic drug oxaliplatin, is among several oxaliplatin products available in the country. The manufacturer of the product (NanoAlvand) willingly conducts trials to confirm the safety of the product in real-world settings. With this confirmation, the company can promote the product in other countries. Besides, it would help Iranian patients trust the safety profile of the medication.

Other formulations of oxaliplatin in the country include Oxitan (Concentrate for solution, Manufactured by Fresenius Kabi, Germany), Eloxatin (concentrate for solution, Manufactured by Sanofi, France), Riboxatin (lyophilized powder), manufactured by PLIVA, Czech Republic), Xoplat (concentrate for solution, Manufactured by Sobhan, Iran), Oxalan (lyophilized powder, Manufactured by Guerbet,India, and other formulations manufactured by Aqvida (concentrate for solution), Mylan (lyophilized powder), Stragen (lyophilized powder), Cipla (lyophilized powder), and Ebewe (concentrate for solution). This Phase IV study aimed to evaluate the safety profile of oxaliplatin used to treat Iranian patients diagnosed with different types of cancer.

Methods

Design and treatment

The present study was an observational, multicenter, uncontrolled, single-arm, prospective, open-label post-marketing study that aimed to evaluate the safety profile of an oxaliplatin product (Alvoxal®) in a population of Iranian cancer patients given this product as part of their standard care. Ethical approval was obtained from the Institutional Research Ethics Committee of Tehran University of Medical Sciences. Patients were recruited from 24 medical centers across 16 cities in Iran. Each center had a head

physician as the principal investigator and 1 or more physicians as coinvestigators. The principal investigator was required to be Good Clinical Practice certified, and the coinvestigators worked directly under the supervision of that principal investigator. Designated physicians were the principal investigators and coinvestigators at the study centers.

Before the study began, written informed consent was obtained from those who volunteered to participate in the study. The data collected during this study, including safety data, were gathered through patient booklets. Data collection forms were provided through 2 booklets, each containing a list of questions for 3 different periods (each period covers 2–3 weeks). The patients' data were assessed after each injection (every 2–3 weeks). The duration of this study was 4.5 months per patient. These booklets were completed by a designated physician during each visit. Therefore, assessments and reports of adverse events were performed during visits.

The adverse event (AE) reporting form provided in the booklets is a validated and standard form that covers all the required information for AE reporting. At baseline (before starting treatment with Alvoxal®) and at the beginning of each cycle, a complete blood test was performed. During each visit, patients' medications, type and stage of cancers, information of administered medications, AEs, and actions taken in response to AEs were recorded. The duration of treatment and the dose of oxaliplatin were determined according to the physicians' decisions regarding the patient's condition.

At least once a week, the company of the product was obligated to check the availability of the product in pharmacies located in the medical centers of the physicians (study investigators) who enrolled the participants during the recruitment phase. Because the decision for Alvoxal® administration was based on the physician's routine practice, treating physicians were not compensated for the patients' enrollment. The participants were not compensated either.

The product was not free of charge. Data collection forms were designed and provided by the investigators, and the company compensated only for print expenses. This study was conducted to confirm the safety profile of this medication. Based on this confirmation, the manufacturer will be able to market this product in other countries, and the consumers would not need to be Iranian patients only. The study was not done to allow marketing because there is no obligation to conduct trials for generic manufacturers before marketing products[26]. The principal investigators were heads of the medical departments of the collaborating hospitals; all coinvestigators were selected among other physicians of these departments who were eager to volunteer to help with the study. All investigators participated in study design, patient enrollment, and further publication of the work. Principal investigators were made authors even if they did not enroll patients because they had a major role in study design, conduction, and publication.

Patients

All patients who received oxaliplatin as a part of their cancer treatment were included as long as they consented to participate in the study. For all patients enrolled, all chemotherapy cycles (from the first cycle to the last) were recorded. The responsible physician determined the termination of chemotherapy (the last cycle of therapy). Physicians prescribed the product to all patients who needed it as a part of their on- or off-label treatment. However, only the data of those who voluntarily agreed to have their data used in the study were included. Patients were asked if we could use the data in the booklets.

Both label and off-label indications of oxaliplatin are included in the medication monograph of UpToDate[18]. Hence, physicians were allowed to prescribe the medication based on their routine practice and experiences with other patients. The patients were aware that they were receiving an off-label treatment. However, they willingly received the medication because they were told that other patients had experienced beneficial effects after consuming oxaliplatin for the specific off-label indication.

Objectives

The objective of this study was to assess the safety profile of a brand-name formulation of oxaliplatin, including the incidence of AEs. The severity of AEs was graded according to the Common Terminology Criteria for Adverse Events version 5.0, and the terminology for AEs was chosen according to the Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term (PT) (MedDRA Desktop Browser 4.0 Beta).

Statistical Analysis

Continuous variables such as laboratory data results and total dose were analyzed using mean and standard deviation. Categorical variables, including the medical and habitual histories of the patients, frequency and percentage of cancer types, chemotherapy drugs, and premedication medicines, were reported in terms of their frequency and percentage.

Safety end points were analyzed based on the incidence of AEs. Patients with 1 or more episodes of a specific AE were counted only once in the incidence calculation. Data were illustrated according to the SOCs and PTs of the AEs. Also, the incidence of grade 3 and 4 AEs and at least possibly related AEs and serious AEs (SAEs) were tabulated. Moreover, causality assessments were recorded, and these were tabulated by frequency and percentage. In addition, the incidences of AEs were compared according to the type of malignancy (colorectal cancer, gastric cancer, or other malignancies) and gender (male or female) using the Pearson χ^2 test. All analyses were conducted using Stata 14 (Stata Corp LP, College Station, Texas).

Sample size calculation

In this study, the occurrence of anaphylactic shock was considered a rare AE, and the sample size was calculated based on this issue. An anticipated incidence rate of 0.004 for anaphylactic shock was determined based on the literature. Considering 80% power and a 5% dropout rate, the total sample size required was 485. The calculations were performed using PASS 1.[27]

Results

From August 2015 to March 2019, 483 patients from 16 cities in Iran were enrolled in this study. Oxaliplatin was administrated for 268 patients in the approved indication (colorectal cancer) and 215 patients in an off-label indication (eg, gastric cancer). The Figure 1 shows the Consolidated Standards of Reporting Trials diagram for the study. Oxaliplatin was prescribed in combination with other drugs, such as 5-FU (49.07%), leucovorin (38.51%), and capecitabine (25.88%). The baseline characteristics of patients who were enrolled in this study are summarized in Table 1.

Overall, 55.49% of patients had colorectal cancer, 28.16% had gastric cancer, and the rest (16.36%) had other malignancies, including pancreatic cancer (3.11%), hepatocellular cancer (1.45%), and cholangiocarcinoma (1.45%). The majority of patients were in stage 3 of cancer. See Table 2.

The most frequent chemotherapy regimen for colorectal cancer was adjuvant therapy, which was used in 100 (37.31%) patients. The most frequent chemotherapy regimen for gastric cancer and

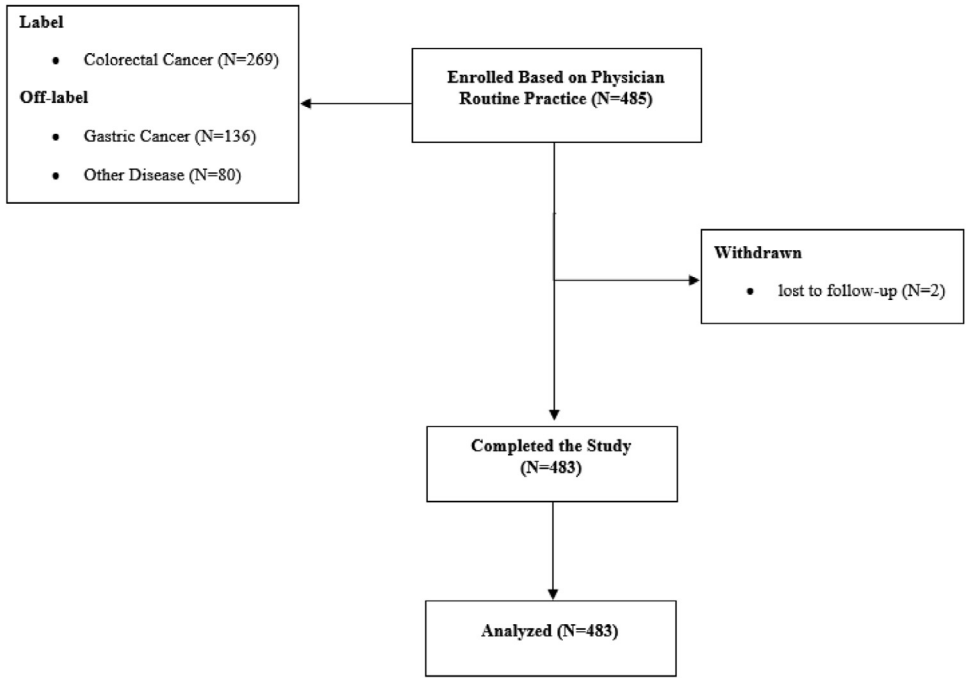

Figure 1. Consolidated Standards of Reporting Trials diagram for the study.

Table 1
Baseline characteristics of the patients.

Characteristic	Result
Population*	483
Age, y†	58.77 (12.39)
BMI†	23.82 (4.22)
BSA, m^2†	1.73 (0.19)
Sex; female‡	218 (45.13)
Smoking‡	76 (15.73)
Alcohol consumption‡	16 (3.31)
Medical history‡	
Liver disease‡	37 (7.66)
Renal disease‡	12 (2.48)
Allergy history‡	7 (1.45)
Cancer type‡	
Colorectal cancer	268 (55.49)
Gastric cancer	136 (28.16)
Other malignancies	79 (16.36)

BMI = body mass index; BSA = body surface area.
* Values are presented as total number.
† Values are presented as mean (SD).
‡ Values are presented as n (%).

Table 2
Patients' cancer type by therapy and stage.

Variable		Colorectal cancer*	Gastric cancer*	Other malignancies*
Therapy	Adjuvant	100 (37.31)	27 (19.85)	15 (18.99)
	Metastatic	68 (25.37)	40 (29.41)	28 (35.44)
	Neoadjuvant	15 (5.60)	21 (15.44)	4 (5.06)
	Missing	85 (31.72)	48 (35.29)	32 (40.51)
	Total	268 (100)	136 (100)	79 (100)
Stage	Stage 1	21 (7.84)	16 (11.76)	4 (5.06)
	Stage 2	50 (18.66)	21 (15.44)	20 (25.32)
	Stage 3	69 (25.75)	29 (21.32)	22 (27.85)
	Stage 4	57 (21.27)	26 (19.12)	19 (24.05)
	Missing	71 (26.49)	44 (32.35)	14 (17.72)
	Total	268 (100)	136 (100)	79 (100)

* Values are presented as n (%).

other malignancies was metastatic situation, which was used in 40 (29.41%) and 28 (35.44%) patients, respectively.

Among all patients, regardless of the type of cancer, the most common dose administered was 80 to 130 mg/m^2 in each cycle. Specifically, 430 (54.99%) patients with colorectal cancer, 247 (64.16%) with gastric cancer, and 112 (48.28%) with other malignancies received oxaliplatin at a dose of 80 to 130 mg/m^2 (Table 3).

Moreover, 320 (66.25%) patients took corticosteroids and 5-hydroxytryptamine 3 (5HT3) receptor antagonists as premedication. Also, 330 (68.32%), 327 (67.70%), 246 (50.93%), and 103 (21.33%) patients received corticosteroids, 5HT3 antagonists, aprepitant, and metoclopramide as premedication, respectively.

Safety analysis

Among 483 patients, 405 (83.85%) patients experienced at least 1 AE during the study. The majority of treatment-related AEs were grade 1 or 2. Table 4 summarizes the incidence of AEs categorized by PTs and SOCs. The incidence of grade 3 or 4 AEs is also shown in Table 4. During the study, 3007 AEs occurred: 763 in patients with stage 1 and 2 cancer and 1825 in patients with stage 3 and 4 cancer.

Most (90.89%) of the AEs were at least possibly drug-related based on the World Health Organization Causality Assessment Scale (Table 5). About 83.85% of patients experienced at least one possibly related AE, and 3.11% experienced at least 1 possibly related SAE. There were no significant differences in the percentage of men and women who experienced at least 1 AE (82.06% and 86.70% in men and women; P = 0.166).

Disorders of the blood and lymphatic system, gastrointestinal system, and nervous system are the most critical reported AEs associated with oxaliplatin administration. A subgroup analysis revealed no significant difference between men and women in terms of the incidence of AEs reported in the SOCs of blood and lymphatic system disorders (70.61% and 75.69% in men and women, respectively; $P = 0.213$, gastrointestinal disorders (25.57% and 31.19% in men and women, respectively; $P = 0.173$) and ner-

Table 3
Summary statistics for dose category in each cycle by cancer type.

Dose category, mg/m^2	Colorectal cancer*	Gastric cancer*	Other malignancies*
40–60	31 (3.96)	21 (5.45)	17 (7.33)
65	10 (1.28)	6 (1.56)	6 (2.59)
70	4 (0.51)	8 (2.08)	12 (5.17)
75	1 (0.13)	3 (0.78)	2 (0.86)
80–130	430 (54.99)	247 (64.16)	112 (48.28)
135–350	306 (39.13)	100 (25.97)	83 (35.78)
Total	782 (100)	385 (100)	232(100)

* Values are presented as n (%).

Table 4
Incidence of adverse event by system organ class (SOC) and preferred term (PT).

SOC	Result*	PT	All grades*	Grade 3 and 4*
Blood and lymphatic system disorders	351 (72.67)	Anaemia	293 (60.66)	24 (4.97)
		Leukopenia	143 (29.61)	4 (0.83)
		Neutropenia	40 (8.28)	12 (2.48)
		Thrombocytopenia	144 (29.81)	24 (4.97)
Investigations	167 (34.58)	ALT increased	107 (22.15)	5 (1.04)
		AST increased	91 (18.84)	2 (0.41)
		Blood bilirubin increased	82 (16.98)	14 (2.90)
		Blood creatinine increased	26 (5.38)	7 (1.45)
		Hepatic enzyme increased	5 (1.04)	-
Nervous system disorders	151 (31.26)	Headache	36 (7.45)	5 (1.04)
		Insomnia	31 (6.42)	2 (0.41)
		Neuropathy peripheral	126 (26.09)	6 (1.24)
General disorders and administration site conditions	147 (30.43)	Decreased appetite	52 (10.77)	2 (0.41)
		Fatigue	103 (21.33)	4 (0.83)
		Hyperhidrosis	9 (1.86)	-
		Injection site erythema	16 (3.31)	2 (0.41)
		Injection site pain	24 (4.97)	-
		Injection site swelling	11 (2.28)	-
Gastrointestinal disorders	135 (27.95)	Diarrhea	37 (7.66)	3 (0.62)
		Nausea	108 (22.36)	8 (1.66)
		Stomatitis	34 (7.04)	1 (0.21)
		Vomiting	52 (10.77)	4 (0.83)
Skin and subcutaneous tissue disorders	103 (21.33)	Alopecia	68 (14.08)	-
		Palmar-plantar erythrodysesthesia syndrome	19 (3.93)	2 (0.41)
		Pruritus	43 (8.9)	2 (0.41)
		Rash	14 (2.9)	-
Immune system disorders	34 (7.04)	Bronchospasm	24 (4.97)	3 (0.62)
		Urticaria	16 (3.31)	1 (0.21)
Respiratory, thoracic, and mediastinal disorders	27 (5.59)	Cough	9 (1.86)	–
		Dyspnea	20 (4.14)	2 (0.41)
Vascular disorders	24 (4.97)	Flushing	18 (3.73)	3 (0.62)
		Hypotension	7 (1.45)	-
Musculoskeletal and connective tissue disorders	17 (3.52)	Back pain	17 (3.52)	1 (0.21)
Infections and infestations	6 (1.24)	Infection	6 (1.24)	6 (1.24)
No. of patients with at least 1 adverse event			405 (83.85)	100 (20.70)

ALT = alanine aminotransferase; AST =aspartate aminotransferase.
* Values are presented as n (%).

Table 5
Frequency of adverse event by causality.

Causality	Result*
Probable/likely	354 (11.77)
Possible	2379 (79.12)
Unlikely	274 (9.11)
Total	3007 (100)

* Values are presented as n (%).

vous system disorders (24.05% and 28.9% in men and women, respectively; $P = 0.229$).

The most common AE reported in this study was anemia (60.66%). Other common hematologic AEs included thrombocytopenia (29.81%) and leukopenia (29.61%). Peripheral neuropathy, a notable AE associated with oxaliplatin use, was reported in 26.09% of patients.

The difference in the incidence of AEs reported in the SOC of blood and lymphatic system disorders among patients with different malignancies (colorectal cancer, 70.52%; gastric cancer, 73.53%; and other malignancies, 78.48%) was not statistically significant ($P = 0.365$). Similarly, there were no substantial differences in the incidence of AEs reported in the SOCs of gastrointestinal disorders among patients with different malignancies (colorectal cancer, 28.73%; gastric cancer, 24.26%; and other malignancies, 31.65%; $P = 0.464$). The incidence of AEs reported in the SOCs of nervous system disorders was not remarkably different among patients with different malignancies (colorectal cancer, 29.48%; gastric cancer, 23.53%; and other malignancies, 18.99%; $P = 0.127$).

Three SAEs were observed in patients with stage 1 or 2 cancer, and 22 were observed in patients with stage 3 or 4 cancer. The causality assessment of these AEs suggested that they were possibly related to Alvoxal®. Among the 15 patients who experienced at least 1 serious event, 9 were given oxaliplatin for a label indication (colorectal cancer). Meanwhile, 6 patients received the medi-

Table 6
The frequency of serious adverse events based on preferred term (PT).

PT	Result*
Infection	6 (23.08)
Anaemia	5 (19.23)
Nausea	3 (11.54)
Vomiting	3 (11.54)
Fatigue	2 (7.69)
Headache	2 (7.69)
Neuropathy peripheral	2 (7.69)
Thrombocytopenia	2 (7.69)
Dyspnea	1 (3.85)
Total	26 (100)

* Values are presented as frequency (%).

cation for an off-label indication. The incidence of SAEs based on PT is shown in Table 6. The most frequently reported SAEs were infection (23.08%), anemia (19.23%), nausea (11.54%), and vomiting (11.54%).

Discussion

Real-world surveillance in patients who use a medicinal product can help provide information about adverse drug events, detect safety signals, and assess drugs' safety profiles in the postmarketing phase. The present postmarketing surveillance protocol was designed to evaluate the safety profile of Alvoxal® in real-world clinical practice settings in different cities in Iran.

According to the literature, the most frequently reported AEs following oxaliplatin therapy were gastrointestinal, hematological, and neurological toxicities.[28] Similarly, the most frequently reported AEs in the present study were related to blood and lymphatic system and nervous system disorders.

In our study, among blood and lymphatic system disorders, the incidence of grade $\geq$ 1 anemia, thrombocytopenia, leukopenia, and neutropenia were 60.66%, 29.81%, 29.61%, and 8.28%, respectively. In other randomized controlled trials of oxaliplatin—consisting of 259 and 209 patients with metastatic CRC[28,29]; 1108 patients with stage 2 or 3 colon cancer[13]; 112 patients with gastroesophageal adenocarcinoma[30]; 338 patients with advanced gastric cancer[31]; and 2 other clinical studies, consisting of 1356 patients with metastatic colorectal cancer[32] and 159 patients with stage 2 or 3 colon cancer[33]—the incidence rates ranged from 43% to 78.4% for thrombocytopenia and from 28.6% to 88% for neutropenia. These were higher than reported in our study results.

The incidence rate of anemia in our study was in line with these previous studies. It is worth mentioning that the incidence rates of anemia, neutropenia, and thrombocytopenia for Alvoxal® are similar to that of oxaliplatin monograph.[18] For nervous system disorders, the incidence of grade $\geq$ 1 peripheral neuropathy was 26.09%. This is lower than the rates reported in other studies, which range from 52% to 92%.[12,13,18,27–33]

In terms of gastrointestinal disorders, oxaliplatin is a moderate emetogenic antineoplastic agent. The incidence rates of nausea (22.36%) and vomiting (10.77%) in our study were lower than other reports because the rates of nausea and vomiting in other studies ranged from 47% to 84% and from 23% to 59%, respectively. This discrepancy might be due to the fact that about two-thirds of patients in the present study used corticosteroids and 5HT3 antagonists.[32,34,35]

Based on the results of this Phase IV study, this oxaliplatin product (Alvoxal®) appears to be a safe and well-tolerated medication with no meaningful differences in terms of the incidences of AEs related to blood and lymphatic system disorders, gastrointestinal disorders, and nervous system disorders between patients with colorectal cancer, gastric cancer, and other malignancies. It was also demonstrated that the incidence of AEs was similar between female and male patients.

Compared with other studies, the incidences of all AEs in the current study were within or below the expected range.[12,13,18,27–33] Most of the reported AEs in this study were grade 1 or 2. This postmarketing surveillance study revealed no unexpected safety findings considering previous studies' results and oxaliplatin monographs.

There are some limitations to this study. This survey is an observational, open-label single-arm study that did not include a control group; these features may have influenced the results. Furthermore, patients' information and AEs were recorded in booklets, which increases the risk of incorrect data collection. Also, the type of cancer was not recorded for all patients.

Conclusions

The results of this open-label, multicenter, observational, postmarketing surveillance study demonstrated no unexpected safety findings from the use of this generic oxaliplatin product (Alvoxal®) in Iranian patients diagnosed with different types of cancer.

Acknowledgments

Study concepts and design were the responsibility of Farhad Shahi, Mojtaba Gorji, Mohammad Vaezi, Reza Khalili Dizaji, Hosein KamranZadeh, Davoud Oulad Dameshghi, and Nassim Anjidani. Data acquisition and quality control of data and algorithms were the responsibility of Farhad Shahi, Mehrdad Payandeh, Sharareh Seifi, Seyed Mehdi Hashemi, Babak Shazad, Mehdi Sarkheil, and Nassim Anjidani. Data analysis and interpretation and statistical analysis were performed by Farhad Shahi, Hamid Rezvani, Alireza Baari, Saeid Salimi, Sina Salari, and Mehrzad Mirzania. Manuscript preparation was undertaken by Farhad Shahi, Mojtaba Gorji, Mehrdad Payandeh, Sharareh Seifi, Reza Khalili Dizaji, Saeid Salimi, Babak Shazad, Mehdi Sarkheil, and Nassim Anjidani. Manuscript editing was performed by Farhad Shahi, Hamid Rezvani, Mohammad Vaezi, Alireza Baari, Seyed Mehdi Hashemi, Hosein KamranZadeh, Sina Salari, Davoud Oulad Dameshghi, Mehrzad Mirzania, and Nassim Anjidani. Manuscript review was performed by Farhad Shahi, Mojtaba Gorji, Mehrdad Payandeh, Hamid Rezvani, Mohammad Vaezi, Sharareh Seifi, Alireza Baari, Reza Khalili Dizaji, Seyed Mehdi Hashemi, Saeid Salimi, Hosein KamranZadeh, Babak Shazad, Sina Salari, Davoud Oulad Dameshghi, Mehdi Sarkheil, Mehrzad Mirzania, and Nassim Anjidani.

Conflicts of Interest

Dr Anjidani is the head of the medical department of Orchid Pharmed Company. This company conducts clinical trials of the medications manufactured by NanoAlvand Company. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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