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Efficacy and Side Effects of Generic (Osloda®) and Brand-Name (Xeloda®) Capecitabine in Metastatic Breast Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: To compare the efficacy and side effects of brand-name capecitabine (Xeloda®) vs. generic (Osloda®) in metastatic breast cancer.
Methods: In this non-randomized clinical trial, 39 patients with metastatic breast cancer were included and divide into Xeloda® (19 patients, mean age of 49.5 years) or Osloda® (20 patients, mean age of 51.7 years) groups. A total of six 3-week cycles (1250 mg/m^2 daily) were administered. Efficacy and side effects were documented in a three-year follow-up period.
Results: The four most common treatment-related adverse events did not differ significantly in Xeloda group vs. Osloda group including hand-foot syndrome (68.4% vs. 65%, P= 0.82), Anorexia (47.4% vs. 50%, P= 0.86), pain (57.9% vs. 40%; P= 0.26), and nausea (52.6% vs. 35%; P= 0.26). Most patients in both groups (25 subjects) showed partial response. Nine patients in each group died (47.4% in Xeloda group and 45% in Osloda group, P= 0.88). Mean overall survival was 20.13 months in Xeloda group and 25.82 months in Osloda group (P= 0.47).

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Conclusion: Xeloda and Osloda had comparable efficacy and side effects in metastatic breast cancer. Considering the lower cost of Osloda, this agent can be used instead of Xeloda.

Keywords: Capecitabine; breast cancer; metastasis; adverse event; side effect; efficacy.

1. INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women with estimated 246,660 new cases in 2016 in the US [1] and globally over 1 million cases annually [2]. Most patients are diagnosed with breast cancer localized to breast tissue and about 5-6% are diagnosed with de novo metastasis upon first presentation [3] and about 30% will develop distant metastasis later in the course of the disease [4]. The most common involved organs in metastasis are bone, liver, and lungs.

Cytotoxic chemotherapy is advised for some women with metastatic breast cancer. The major objectives of treatment in metastatic breast cancer are to prolong survival with minimum side effects as well as improve quality of life. Several chemotherapy agents alone or in combination are used to achieve this goal. One of these agents is capecitabine which is an oral prodrug of anti-metabolite fluorouracil. As oral preparation is available, it is an advantage to many other chemotherapeutic agents used in such patients. This agent has been the focus of attention by many studies [5-8] and currently, as monotherapy, is a favorite option in many patients who require chemotherapy.

Capecitabine has been approved by FDA (Food and Drug Administration) in metastatic breast cancer as monotherapy or in combination with taxanes and anthracyclines [6]. It is also a suitable option in patients pretreated with taxanes and anthracyclines [9]. Median overall survival time with this agent ranges from 10 to 15 months [6]. The major side effects of capecitabine are hand-foot syndrome, fatigue, and gastrointestinal symptoms (nausea, anorexia, diarrhea, etc) [10].

Capecitabine under the trade name of Xeloda® is available in many centers. Some pharmaceutical companies have produced generic form of this drug. One of these generic forms is Osloda® manufactured in Iran. Osloda® currently is available in Iran and as this formulation is less expensive than Xeloda®, many oncologists may desire to prescribe this agent for the patients. So far, no study has been done to compare the efficacy and side effect profile of Osloda®. The objective of this study was to compare the efficacy and side effects of Osloda® vs. Xeloda® in female patients with metastatic breast cancer.

2. MATERIALS AND METHODS

In this non-randomized single-blinded parallel phase IV clinical trial, 40 patients with metastatic breast cancer who were receiving their care at or university oncology center were enrolled. The patients were divided to receive either Osloda® (manufactured by Osvah PharmaceuticalCo., Iran) or Xeloda® (manufactured by Hoffmann-La Roche Inc., Nutley, NJ, US). Inclusion criteria were female patients of any age with documented breast cancer and distant metastasis (stage IV). The patients who had received capecitabine before the study initiation were excluded. The diagnosis of breast cancer and its type (invasive ductal carcinoma, invasive lobular carcinoma, etc) had been made by histopathologic examination of the tumor excised surgically. The metastasis locations were examined by radiologic studies.IHC (immunohistochemistry) staining had been done to examine estrogen receptor and progesterone receptor analysis.

The patients received capecitabine 1250 mg/m^2 twice daily (days 1 to 14) every 3 weeks for a total of six cycles. The chemotherapy was completed for 6 cycles unless severe inhibitory side effects developed or the cancer progressed.

The previous treatments were document that included histopathologic examination, adjuvant therapy, and previous chemotherapies. The patients were visited weekly and side effects were documented. The side effects documented were pain, jaundice, dyspnea, hand-foot syndrome, hypotension, constipation, dermatitis, gastric ulcer, nausea, vomiting, anorexia, fever, leukopenia, leukocytosis, fatigue, oral inflammation, dysentery, rectal bleeding, anemia, and nail inflammation. Any delay required during chemotherapy and capecitabine cessation due to inhibitory side effects was recorded. Response to

chemotherapy was graded as stable, progression, partial response, and complete response according to the revised RECIST guidelines [11].

2.1 Statistical Analyses

The descriptive indices including frequency, percentage, mean and its standard deviation were used to express data. In order to compare nominal variables between the two groups, the Chi-square test or the Fischer's exact test was used. The normal distribution of the continuous variables was determined using the Kolmogorov-Smirnov test and histogram. In order to compare the continuous variables between the two groups, student t test or Mann-Whitney test was applied. Survival time was compared using the Kaplan-Meier analysis. Significance level was set at 0.05.All analyses were performed using SPSS software (ver. 20.0, IBM, US).

3. RESULTS

One patient in Xeloda group was lost in the follow-up. So, 39 patients remained for final analysis. There were 20 cases in Osloda group and 19 in Xeloda group. Mean (±SD) age of the sample was 50.64 (±10.82) years. Mean (±SD) age in Osloda group (51.7± 10.19 years) was comparable to Xeloda group (49.53± 11.61 years); P= 0.35. Right breast involvement was documented in 13 patients (65%) of Osloda group and in 9 patients (47.4%) of Xeloda group; P= 0.26.

Invasive ductal carcinoma was the most common histopathology in both groups (35 cases, 89.7%). Bone was the most common distant location for metastasis (12 patients, 30.7%). In 23 patients, metastasis was found in only one organ. In 16 patients, distant metastasis was detected in more than one location (bone and lung in seven patients and bone and liver in three patients). Adjuvant therapy had been administered in 13 cases (68.4%) of Xeloda group and 15 cases (75%) of Osloda group (P= 0.73). More patients in Osloda group (13 cases, 65%) had received prior chemotherapy than in Xeloda group (six cases, 31.6%): P= 0.03. Table 1 compares histopathologic examinations, distant metastasis location, and adjuvant therapy between the two groups.

The four most common treatment-related adverse events were hand-foot syndrome (26 cases, 66.6%), anorexia and pain (each documented in 19 cases, 48.7%), and nausea (17 cases, 43.6%). Overall, 19 patients (100%) in Xeloda group and 16 patients (80%) in Osloda group experienced one or more adverse events (P= 0.01). Diarrhea was seen in 31.6% of Xeloda and 45% of Osloda groups (P= 0.38). Table 2 presents frequency of the most common side effects in each group. As seen no significant statistical difference existed regarding frequency of the most common side effects. Mean (±SD) pain episodes in Xeloda and Osloda groups were respectively 1.16 (±1.43) and 1.1 (±1.65); P= 0.31. Other less common side effects were dyspnea and gastric ulcer (1 patient in each group), jaundice and constipation (two in Xeloda group and one in Osloda group), dysentery (one in Xeloda and two in Osloda groups), hypotension, skin inflammation, nail inflammation, and lacrimation (each was documented in one patient in Osloda group), and anemia and rectal bleeding (each was documented in one patient in Xeloda group).

Table 3 shows comparison of side effect severity between the two studied groups. As observed, except for fever which was more severe in Xeloda group, the severity of other side effects did not have significant difference between the two groups.

Chemotherapy dose reduction due to side effects was required in seven patients (36.8%) of Xeloda group and among 11 patients (55%) in Osloda group (P= 0.25). Delay in chemotherapy was required in five subjects (26.3%) in Xeloda group and in seven patients (35%) of Osloda group (P= 0.55). No significant difference was noted regarding chemotherapy discontinuation due to inhibitory side effects/disease progression between Xeloda (8 cases, 42.1%) and Osloda group (5 cases, 25%); P= 0.25. In all eight patients in Xeloda group, chemotherapy was stopped due to adverse events. However, in Osloda group, two patients required chemotherapy discontinuation due to side effects and in 3 cases it was done due to disease progression.

Table 4 presents the response to capecitabine. Most patients in both groups (25 subjects) showed partial response. Four patients (21.1%) in Xeloda group had tumor marker rise, while none of Osloda patients had such finding (P= 0.01).

Table 1. Comparison of histopthalogic type, metastasis location, adjuvant therapy, and previous chemotherapy among 39 women with metastatic breast cancer who received Xeloda or Osloda

Variables	Subgroups	Xeloda (N= 19)	Osloda (N= 20)	P value
Histopathology	Invasive ductal carcinoma	18 (94.7%)	17 (85%)	0.06
	Invasive lobular carcinoma	0	3 (15%)	
	Invasive mucinous carcinoma	1 (5.3%)	0	
Hormone receptor	Estrogen receptor	16 (84.2%)	16 (80%)	0.73
	Progesterone receptor	16 (84.2%)	15 (75%)	0.69
	Her2 new	4 (21.1%)	5 (25%)	0.77
Metastasis location	Liver	2 (10.5%)	4 (20%)	0.44
	Bone	5 (26.3%)	7 (35%)	
	Lung	3 (15.8%)	2 (10%)	
	More than one location	9 (47.4%	7 (35%)	
Adjuvant chemotherapy	Anthracycline combination	3 (23.1%)	6 (40%)	0.33
	Anthracycline-Taxane combination	10 (76.9%)	9 (60%)	

Table 2. Comparison of the frequencyside effects of capecitabine among 39 women with metastatic breast cancer who received Xeloda or Osloda

Side effects	Xeloda (N= 19)	Osloda (N= 20)	P value
Hand-foot syndrome	13 (68.4%)	13 (65%)	0.82
Anorexia	9 (47.4%)	10 (50%)	0.86
Pain	11 (57.9%)	8 (40%)	0.26
Nausea	10 (52.6%)	7 (35%)	0.26
Diarrhea	6 (31.6%)	9 (45%)	0.38
Fatigue	9 (47.4%)	6 (30%)	0.26
Vomiting	3 (15.8%)	5 (25%)	0.47
Mucositis	3 (15.8%)	3 (15%)	0.94
Leukopenia	3 (15.8%)	3 (15%)	0.94
Leukocytosis	3 (15.8%)	3 (15%)	0.94
Fever	2 (10.5%)	3 (15%)	0.67
Stomatitis	1 (5.3%)	4 (20%)	0.15

3.1 Mortality and Survival Analysis

Nine patients in each group died (47.4% in Xeloda group and 45% in Osloda group, P= 0.88). Of nine patients who died in Xeloda group, seven died due to disease progression and two died due to side effects of Xeloda. Of nine patients who died in Osloda group, disease progression was recognized as cause of the death in 7 patients, side effects of carboplatin and novelbin in two patients.

Mean overall survival was 20.13 months (95%CI= 14.85 to 25.42 months)in Xeloda group and 25.82 months (95%CI= 19.89 to 31.74 months)in Osloda group (P= 0.47) (Fig. 1).

4. DISCUSSION

Based on the obtained findings, Xeloda and Osloda had nearly comparable efficacy and side effect profiles. Although more patients in Xeloda group (100%) had side effects compared to patients of Osloda group (80%), the severity of side effects did not differ between the two groups.

In pharmaceutical industry, it is of crucial importance to study generic products and compare the efficacy and safety profile of these agents to brand products. Capecitabine with the brand name of Xeloda® is produced for many years and distributed in many countries. Its efficacy as monotherapy in metastatic and advanced breast cancer has been studied widely and approved [6,7,10]. Osloda as a generic form of this agent has been produced recently in Iran. So far, no study has been done to compare these two agents. The administration of generic products instead of brand name products is used widely owing to several factors such as cost-efficiency and broad availability [12,13].

Table 3. Side effect severity among 39 women with metastatic breast cancer who received Xeloda or Osloda

Variables	Subgroups	Xeloda (N= 19)	Osloda (N= 20)	P value
Hand-foot syndrome	Grade 2	3 (23.1%)	0	0.17
	Grade 3	6 (46.2%)	7 (53.8%)	
	Grade 4	4 (30.8%)	6 (46.2%)	
Anorexia	Grade 1	1 (11.1%)	1 (10%)	0.86
	Grade 2	5 (55.6%)	4 (40%)	
	Grade 3	2 (22.2%)	4 (40%)	
	Grade 4	1 (11.1%)	1 (10%)	
Nausea	Grade 1	0	1 (14.3%)	0.39
	Grade 2	7 (70%)	4 (57.1%)	
	Grade 3	3 (30%	2 (28.6%)	
Diarrhea	Grade 1	0	2 (22.2%)	0.49
	Grade 2	1 (16.7%)	1 (11.1%)	
	Grade 3	3 (50%)	3 (33.3%)	
	Grade 4	2 (33.3%)	3 (33.3%)	
Fatigue	Grade 2	4 (44.4%)	1 (16.7%)	0.51
	Grade 3	3 (33.3%)	3 (50%)	
	Grade 4	2 (22.2%)	2 (33.3%)	
Vomiting	Grade 2	0	2 (40%)	0.14
	Grade 3	2 (66.7%)	3 (60%)	
	Grade 4	1 (33.3%)	0	
Mucositis	Grade 2	1 (33.3%)	0	0.2
	Grade 3	2 (66.7%)	3 (100%)	
Fever	Grade 2	0	3 (100%)	0.03
	Grade 3	1 (50%)	0	
	Grade 4	1 (50%)	0	
Oral mucosa inflammation	Grade 2	1 (100%)	1 (25%)	0.13
	Grade 3	0	3 (75%)	

Table 4. Comparison of the response to capecitabine among 39 women with metastatic breast cancer who received Xeloda or Osloda

Response	Xeloda (N= 19)	Osloda (N= 20)	P value
Progression	1	4	0.45
Stable	1	1	
Partial response	12	13	
Complete response	0	1	

Generally, the cost of generic drugs is lower than their original equivalents. Considering the significant effect this factor can impose on healthcare systems, in particular when facing with chronic diseases or cancer patients which require highly costly drugs for long periods, the importance of generic preparations in developing countries becomes more evident. Usually, pharmaceutical companies use bioequivalence as similar systemic bioavailability to demonstrate the efficacy of the corresponding generic preparation. However, there is concern whether bioequivalence per se reflects therapeutic efficacy [12,14].

There are reports however that some generic products may not necessarily have similar therapeutic equivalence meaning lower efficacy and more side effects [15]. This becomes more important when the drug of question is an antineoplastic agent. Capecitabine is an established agent for metastatic breast cancer and we think that any generic drug should be studied thoroughly. In addition, the high burden of breast cancer as the second most common malignant solid tumor in women renders this topic important.

The most common side effects we observed here are in agreement with previous reports. Hand-foot syndrome and GI toxicities such as anorexia and diarrhea were the most common adverse events. In a previous study of capecitabine monotherapy, hand-foot syndrome (palmar-plantar erythrodysesthesia)was reported as the most common side effect in 66.7% of patients [6].

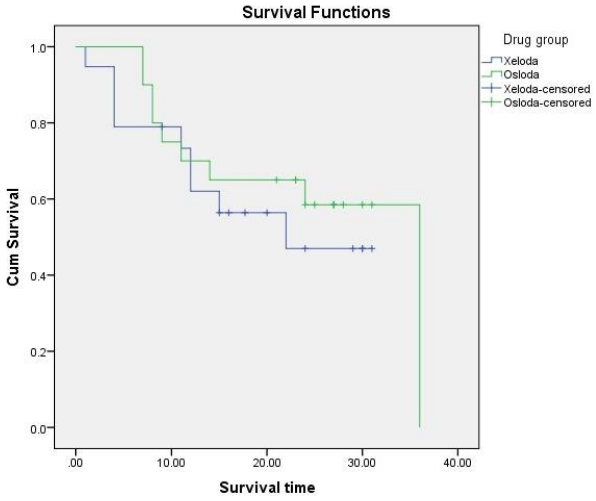

Fig. 1. Overall survival curves for Xeloda® and Osloda® groups among patients with breast cancer

This figure is similar to both Xeloda and Osloda groups, though 14 patients in the mentioned study [6], had received vitamin B6 to avoid hand-foot syndrome. Another trial in older women (> 55 years) reported the prevalence of hand-foot syndrome as 43% [16]. GI toxicities have also been reported to occur with high frequency after capecitabine use. Although some studies have not reported grade 4 toxicities, we observed patients with grade 4 hand-foot syndrome, anorexia, diarrhea, and fatigue. These required chemotherapy dose reduction that managed the condition in some patients, but others required chemotherapy discontinuation. Chemotherapy discontinuation was more common in Xeloda group (42%) than in Osloda group (25%). However, this was not statistically significant. This rate has been reported as 16% [16]. Overall, response to chemotherapy was satisfactory in both groups and partial response was the most common finding.

5. CONCLUSION

The generic preparation of capecitabine studied here (Osloda) was comparable to brand-name Xeloda with regard to side effect profile and efficacy. This agent can be used in cases that Xeloda is not available or due to limited financial resources.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The study protocol and objectives were explained to the patients. Written informed consent was obtained from the participant upon enrollment into the study. The Ethics Committee of our medical university approved the study protocol.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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