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Adverse Effects of Chemotherapy Regimens Used in Colorectal Cancer Patients in a Referral Cancer Center in North of Iran, 2008-2014

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ABSTRACT

Background: Gastrointestinal tract cancers are the most common cancers in Iran, especially in the North of the country. Different chemotherapy regimens have been used in the treatment of colorectal cancers (CRC). Considering lack of data, this study aimed to determine the adverse drug reactions (ADRs) of chemotherapy regimens used in the treatment of patients with CRC.

Methods: This cross-sectional prospective study was carried out in Emam Khomeini Hospital and Tooba Clinic, both affiliated to Mazandaran University of Medical Sciences. ADRs of chemotherapy regimens were documented based on CTCAE Version 4.0 (Common Terminology Criteria for Adverse Events).

Results: Two hundred sixty seven different courses of chemotherapy regimens received by 48 patients were evaluated in terms of adverse events. Three more common chemotherapy regimens were FOLFOX (Folinic acid, Fluorouracil, Oxaliplatin), FOLFIRI (Folinic acid, Fluorouracil, Irinotecan) and XELOX (Capecitabine, Oxaliplatin).FOLFIRI and FOLFOX regimens were associated with more nausea and vomiting compared to XELOX. The rate of vomiting (P=0.06) and neuropathy were marginally different between regimens, but the rate of hair loss and headache were not. The diarrhea was more common with FOLFOX (P=0.027). Neutropenia occurred in14% of FOLFIRI, none of XELOX and almost 5% of FOLFOX regimens. Mucositis happened in 17.8% and of XELOX and FOLFOX regimens, respectively.

Conclusion: The results of our study showed that the GI adverse events including nausea, vomiting and severe diarrhea were more common with FOLFIRI regimen. Mucositis and neuropathy were more common with XELOX. Hair loss was more common with FOLFIRI followed by XELOX and FOLFOX.

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Introduction

Colorectal cancers (CRC) is a the fourth most common cancer with about nearly one-million new cases diagnosed and half a million deaths each-year worldwide (1, 2). In Iran, CRC is the third most common cancer in males and fourth most common cancer in females (3). The incidence of CRC in the past two decades, especially in the Northern regions of Iran, had an increasing trend (4). Several treatment modalities have been used in CRC treatment including surgery, chemotherapy and radiotherapy along with targeted agent therapies. In addition, different

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chemotherapy regimens have been introduced in treatment of CRC with a different adverse drug reactions (ADRs) profile. FOLFOX (Folinic acid, Fluorouracil and Oxaliplatin), short term infusion of fluorouracil and leucovorin (FU/LU), XELOX (Capecitabine and Oxaliplatin) and FOLFIRI (Folinic acid, Fluorouracil and Irinotecan) are common adjuvant chemotherapy regimens used in colorectal cancer (5-7).

Nausea and vomiting are the most commonly observed toxic effects of the FOLFOX regimen. All patients should be premedicated with antiemetic drug (7). The adverse drug reactions profile of XELOX is similar to the FOLFOX regimen, except that myelosuppression is uncommon with XELOX (grade 3 or 4 neutropenia, 7%). Most adverse events are mild to moderate and the most common one is acute sensory neuropathy (85%) (8). FOLFIRI is associated with acceptable toxicity, in heavily pretreated patients, with limited diarrhea, mostly asymptomatic neutropenia and manageable nausea and relatively uncommon alopecia (9). Most common treatment-related grade 3 or grade 4 adverse events of XELIRI regimen are neutropenia, diarrhea, vomiting, dehydration, nausea, abdominal pain, and hand-foot syndrome (10).Considering lack of data, this study aimed to determine ADRs of common chemotherapy regimens used in treatment of patients with CRC.

Methods

This cross-sectional prospective study was carried out sequentially in Emam Khomeini hospital and Tooba Clinic, both affiliated to Mazandaran University of Medical Sciences, 2008-2014. The study was approved by Research Deputy of Mazandaran University of Medical Sciences. Patients were enrolled into the study after giving an informed consent form. All colorectal cancer patients receiving one of chemotherapy regimens were eligible for enrolment. Patients receiving chemotherapy regimens were evaluated every 3 weeks. The staging of the patients were done according to tumor/node/metastasis (TNM) scoring system (11). Patients were entered into study at any time of receiving chemotherapy regimens if they experienced any side effects. The primary aim of this study was to evaluate the adverse effects of chemotherapy regimens. The severity of side effects was determined based on CTCAE Version 4.0 (Common Terminology Criteria for Adverse Events). Based on the severity of toxicities, CTCAE Version 4.0, classifies adverse reactions into five groups from grade 1 to grade 5 (12). Nausea grade 1 has been defined as loss of appetite without changing eating habits. Nausea with loss of appetite as well as reduced oral feeding without significant weight loss, dehydration or malnutrition was categorized as grade 2. Nausea grade 3 was considered for patients required TPN and hospitalization. Regarding vomiting, it was grade 1, if occurred 1-2 times in 24 hours with an interval of at least 5 minutes, and if the frequency of this complication was between 3-5 times in 24 hours with a minimum interval of five minutes from each other, it was called grade 2. If the frequency of vomiting was more than 6 times or the patient required tube feeding or TPN, as well as hospitalization, it was considered grade 3. Life-threatening vomiting was defined as grade 4. Fever and neutropenia was defined as neutrophil count of less than 1000 per mm^2 and recording a body temperature of 38.3 °C at one time or body temperature of above 38 °C for one hour. Fever and neutropenia grade 1 and 2 were not defined by CTCAE, so the minimum severity of febrile neutropenia was grade 3. Diarrhea was defined grade 1 if the frequency was more than 7 times a day. More severe diarrhea (e.g., life-threatening reactions) was recorded as grade 3 and 4 according to CTCAE criteria. In terms of oral mucositis, it was classified as grade 1, if inflammation was in small area and the patient was asymptomatic. If inflammation was associated with low pain but did not affect the oral intake, the mucositis was considered grade 2. If the severity of pain was high with decreased oral intake, it was grade 3 and life-threatening reactions was classified as grade 4. Neuropathy (e.g., disruption in the sensory nerve function accompanied with experiencing cold, warmth, pressure, numbness sensation or a feeling like insects movement on the skin relentlessly in the absence of any stimulant) was classified as grade 1, 2 or 3 according to its' severity based on CTCAE definitions (12). Hair loss was considered grade 1 if less than 50% of normal hair reduction was happened and the patient did not need hair covering. Hair loss with greater than 50%of normal hair reduction and need for using a hair cover were considered grade 2.

Patients received usual supportive care if they were experienced nausea, vomiting and mucositis.

Statistical analysis was performed using SPSS v.16. Descriptive statistics were used to describe the basic and clinical features of the patients. Categorical variables were compared using the chi-square or Fisher exact test. Independent samples T-test was used to compare the mean of quantitative variables in different sexes. P-value of less than 0.05 was considered as a significant difference.

Results

Demographic and basic clinical characteristics of patients have been presented in table 1. Two hundred and sixty seven different courses of chemotherapy regimens administered to 48 patients were evaluated in terms of side effects.

The frequency and severity of different ADRs of chemotherapy regimens have been presented in Table 2. FOLFIRI and FOLFOX regimens were associated with more nausea and vomiting compared to XELOX. The rate of vomiting was marginally different between regimens (P=0.06). Most of nausea and all vomiting

Table 1. Demographic and clinical characteristics of patients.

Sex	
Male	32 (66.7%)
Female	16 (33.3%)
Age (year)	
Mean	52
SD	13.3
Min	27
Max	82
Median	50
Stage (%)	
1	0 (0%)
2	13 (34.2%)
3	12 (31.6%)
4	13 (34.2%)
Site of Tumor	
Colon	37 (77.1%)
Rectum	11 (22.9%)
Chemotherapy Regimens	
FOLFOX	34 (70.8%)
XELOX	8 (16.7%)
FOLFIRI	6 (12.5%)

FOLFIRI: Folinic acid, 5FU, Irinotecan; FOLFOX: Folinic acid, 5FU, Oxaliplatin; XELOX: Xeloda, Oxaliplatin.

were categorized as grade 1 or 2. The diarrhea was more common with FOLFOX (P=0.027); whereas 14% of patients received FOLFIRI experienced neutropenia, none of patients in XELOX and almost 5% of FOLFOX patients experienced neutropenia. Mucositis happened in 16.1 and 17.8% of patients received FOLFOX and XELOX, respectively. The rate of neuropathy was different among regimens, as XELOX and FOLFOX were associated with more neuropathy compared with FOLFIRI (P=0.019). The rate of hair loss and headache were not different between three regimens.

The side effects were classified as acute (within 24 hour after initiation of chemotherapy) or late (after 24 hours of initiation of chemotherapy). Most of the side effects (e.g., nausea, vomiting, neuropathy, and headache) were acute except for XELOX (Table 3). Vomiting and mucositis with XELOX were just happened after 24 hours of initiation of chemotherapy. Headache also happened

Table 2. Severity of side effects of chemotherapy regimens.

Side Effects	FOLFOX (N=186)		XELOX (N=45)		FOLFIRI (N=36)		P-value
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	
Nausea	47.3%	1.1	40%	2.2%	44.5%	0%	0.71
Vomiting	22%	0%	13.3%	0%	38.9%	0%	0.06
Diarrhea	24.2%	0%	8.9%	0%	13.9%	2.8%	0.027
Neutropenia	4.8%	0%	0%	0%	13.9%	0%	0.019
Mucositis	16.1%	0%	17.8%	0%	0%	0%	0.054
Neuropathy	34.9%	0%	42.2%	0%	13.9%	0%	0.019
Hair loss	1.6%	0%	6.7%	0%	8.3%	0%	0.5
Headache	9.1%	0%	4.4%	0%	5.6%	0%	0.5

Table 3. Timing of side effects of different chemotherapy regimens.

Side Effects	FOLFOX (N=186)		XELOX (N=45)		FOLFIRI (N=36)		P-value
	Within 24 hours	After 24 hours	Within 24 hours	After 24 hours	Within 24 hours	After 24 hours	
Nausea	92.2%	7.8%	100%	0%	81.2%	18.8%	0.124
Vomiting	68.3%	31.7%	0%	100%	78.6%	21.4%	0.02
Diarrhea	46.7%	53.3%	100%	0%	33.3%	66.7%	0.088
Mucositis	50%	50%	0%	100%	0%	0%	0.1
Neuropathy	96.9%	3.1%	100%	0%	100%	0%	0.69
Headache	100%	0%	100%	0%	100%	0%	-

only during the initial 24 hours of chemotherapy with all three regimens.

Discussion

This study was designed to evaluate the profile of side effects of different chemotherapy regimens including FOLFOX, XELOX, and FOLFIRI used in the treatment of colorectal cancer. According to result of our study, nausea is still a frequent side effect of chemotherapy in patients with colorectal cancer and the rate of nausea with three regimens was similar. The poor control of nausea and vomiting was previously documented in a survey of patients in the west of province, too (8). FOLFIRI regimen was associated with a higher frequency of vomiting (39%) compared to FOLFOX and XELOX. Both fluorouracil and irinotecan can cause diarrhea, as it was reported that 50 % to 80 % of patients may experience diarrhea, in which in 60% of cases affect the course of chemotherapy (3-5). In our study, we did not have any patients with grade 4 diarrhea and 2.8% of patients, all received FOLFIRI, experienced grade 3 diarrhea. The rate of grade 3 and 4 diarrhea with regimens contain irinotecan has been reported to be less than 30% (13-15). The initiation of diarrhea by irinotecan may be acute (within 24 hours) or late, with different pathophysiological characteristics. The acute-onset diarrhea occurs through the active metabolite of irinotecan, SN-38, with a cholinergic-mediated process and could be managed with anticholinergic such as atropine (10). The late onset diarrhea associated with irinotecan is caused by a secretory mechanism with an exudative component that could be controlled with loperamide (9). In our study, among all 36 FOLFIRI cycles, six cycles of diarrhea were happened, 2 and 4 episodes were acute and late-onset, respectively. The rate of late-onset diarrhea with FOLFIRI regimens was 11% in our study and only one episode of six was grade 3 (2.7% of total). The rate of severe delayed diarrhea in our study was less than the other studies (6),delayed diarrhea was reported in 37% of the patients with grades 3 and 4 in 12 % of courses of FOLFIRI chemotherapy (6). With FOLFOX and XELOX regimens all cases of diarrhea were grades 1 and 2. The rate of diarrhea with FOLFOX in our study (24%) was less than the previous studies of Cassidy et al., (62% and 12% grade 3/4) (16), and similar to the study of De Vita et al., (26%, 3% grade3/4) (17). Adding bevacizumab to FOLFOX regimen causes a significant increase in rate of diarrhea, as presented in study of Meyerhardt et al., while 83% of patients experienced diarrhea (half of the episodes were grade 3/4) (18). In patients received XELOX regimen, the rate of nausea (42.2%, 2.2% grade 3/4) was comparable to the study of Cassidy et al., (57%, 5% grade 3/4) (16) and Hurwitz et al., (51%, 8% grade 3/4) who used XELOX plus bevacizumab as a first line treatment for metastatic colorectal cancer (19), though the rate of grade 3/4 nausea was somewhat less than noted studies. The rate of vomiting in our study (28.6%, 0% grade 3/4) was less than the study of Cassidy et al., (41%, 5% grade 3/4) and Hurwitz et al., studies (37%, 6% grade 3/4), particularly we did not have any severe vomiting in our study (16, 19). Unlike our study, the rate of nausea, vomiting and diarrhea was significantly less in study of Hasegawa et al., who used XELOX combined with bevacizumab for high-risk localized rectal cancer in neoadjuvant setting (20).

Cassidy and colleagues conducted a study to compare the toxicity profile of XELOX and FOLFOX regimens as first line treatment of metastatic colorectal cancer. According to their results, XELOX and FOLFOX regimen were very similar in terms of side effects unlike XELOX regimen was associated with higher rates of diarrhea and FOLFOX regimen was associated with higher rate of neutropenia. Also, the neuropathy of XELOX was 2 times more common compared with FOLFOX (16). In our study, the gastrointestinal toxicity of FOLFOX was more than XELOX and on the other hand, neuropathy and hair loss of XELOX was more common compared to FOLFOX.

Regarding the onset of adverse reactions, most of gastrointestinal adverse reactions happened during 24 hours of initiation of chemotherapy except mucositis of

FOLFOX which has a late presentation in half of courses.

Conclusion

The results of our study showed that the nausea and vomiting of FOLFIRI regimen was more common than FOLFOX and XELOX. Severe diarrhea was occurred only by FOLFIRI regimen. Mucositis was more common with XELOX, also FOLFOX regimen was associated with similar rate of mucositis as XELOX. The rate of neuropathy was more common with XELOX followed by FOLFOX and FOLFIRI. Hair loss was more common with FOLFIRI followed by XELOX and FOLFOX.

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