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Risk Factors of Chemotherapy-Induced Neutropenia associated with FOLFOX, FOLFIRI, and FOLFOXIRI Regimens used in Patients with Advanced and Metastatic Colorectal Cancer

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ABSTRACT

Background: *Since the introduction of oxaliplatin and irinotecan, they have been the mainstay chemotherapies in the fluorouracil-based regimens, FOLFOX, FOLFIRI, and FOLFOXIRI, used in the treatment of advanced and/or metastatic colorectal cancer (CRC). These regimens are effective and usually well-tolerated in patients. However, they have been associated with neutropenia in some patients.* ***Objective:*** *The aim of this study was to assess risk factors of chemotherapy-induced neutropenia associated with the regimens used in CRC patients.* ***Methods:*** *A retrospective analysis was conducted of all CRC patients' records who had been treated with the aforementioned regimens between January 2016 and February 2019 at the oncology clinics in a tertiary referral hospital in Riyadh, Saudi Arabia.* ***Results:*** *A total of 136 patients treated with the standard CRC regimens were identified. The majority of CRC patients (63.2%) had stage IV with extensive metastases. Twenty-two patients (16.2%) had developed neutropenia. However, only 13 of the neutropenic patients (59.1%) had shown symptoms of infections or fever. Most neutropenia occurred between the third and the fourth cycle of the used regimen. A significant increase in neutropenia was found in females (p=0.0273) and in patients with stage IV (p=0.0378). However, 53 CRC patients (39.0%) who received filgrastim had shown a significantly lower incidence of neutropenia (p=0.0027).* ***Conclusion:*** *Despite the effectiveness of the CRC chemotherapy regimens, the risk of neutropenia is still considerably elevated. The use of granulocyte colony-stimulating factors such as filgrastim is an effective intervention to reduce neutropenia, hence infections, in high-risk CRC patients*

Keywords: Colorectal cancer, Neutropenia, Oxaliplatin, Irinotecan, Filgrastim

INTRODUCTION

Colorectal cancer (CRC) describes malignancies that affect either the colon or rectum that are often categorized collectively because they share many features. Most CRCs begin as asymptotic diseases with small benign adenomatous polyps that can become malignant as time passes [1]. CRC is the third most commonly diagnosed cancer in most countries after lung cancer and either prostate cancer for men or breast cancer for women. It affects both genders, all races, and various ethnic backgrounds. There are an estimated 2 million new CRC cases in 2018, which account for

more than 6% of the total cancer cases worldwide [2]. CRC has been reported as the most common type of cancer in males (13.3%) and the third type among females (9.3%) in Saudi Arabia, with the Eastern region and Riyadh province displaying the highest incidence rates [3,4].

Since the commence of 5-fluorouracil (5-FU) in the treatment of CRC in the 1950s, a number of FDA-approved drugs were added to augment the treatment. Oxaliplatin and irinotecan were introduced in the mid-1990s as the additional mainstay chemotherapy drugs for CRC that have led to enhancing therapeutic outcomes and survival rates in metastatic CRC patients [5,6]. Capecitabine (Xeloda®) was developed in the early 2000s as an oral derivative of 5-FU to simplify the chemotherapy delivery [7]. Recently, great advances have been attained by the introduction of biologic agents such as; bevacizumab (Avastin®), Cetuximab (Erbitux®), and panitumumab (Vectibix®). These agents are often used in combination with the former drugs in the treatment of CRC in various different settings [8].

FOLFOX and FOLFIRI are the commonly used standard 5-FU-based chemotherapy in the treatment of metastatic and advanced stages CRC [9]. Both regimens are combination chemotherapies that include FOL=folinic acid; and F=fluorouracil, in addition to either OX=oxaliplatin or IRI=irinotecan. Nevertheless, several modified FOLFOX and FOLFIRI regimens, have been employed in CRC patients that differ in either the given doses or intervals of administered [10]. FOLFOXIRI regimen has also been employed in CRC patients, which includes both oxaliplatin and irinotecan in addition to folinic acid and fluorouracil. All these regimens are effective and usually well-tolerated in CRC patients. However, they have been associated with neutropenia in some patients, as a result of their significant myelosuppression effect [11]. Thus, a substantial increase in the risk of infection was correlated with the severity of neutropenia in cancer patients [12], which is directly associated with the intensity of chemotherapy and the number of treatment cycles received [13,14].

The aim of the present study was to assess risk factors associated with chemotherapy-induced neutropenia in CRC patients due to FOLFOX, FOLFIRI and FOLFOXIRI regimens.

MATERIAL AND METHODS

A retrospective review analysis of electronic medical records was conducted for all CRC patients who had been treated with FOLFOX, FOLFIRI and FOLFOXIRI regimens between January 2016 and February 2019 in the oncology outpatient clinics at King Abdulaziz Medical City (KAMC) and King Abdullah Specialized Children Hospital (KASCH) in Riyadh, Saudi Arabia. Elderly patients with advanced terminal diseases were excluded.

Data were collected using a structured data collection format, which comprised patients' demographic information including gender, age at the start of chemotherapy, weight, height, and health status; in addition to histological cancer staging, and metastasis, site of surgery and detail of chemotherapy therapies received. Neutropenia was defined whenever the absolute neutrophil count (ANC) was less than 1,500 per microliter of blood.

Results were summarized as mean ± SD or range for continuous variables and as proportions for categorical variables. Descriptive and statistical analyses of all variables were performed by Student's t, one-way ANOVA or chi-squared tests. Risk/odds ratios were calculated from the multivariate logistic regression analysis to identify independent factors for drug-induced neutropenia. Statistical significance was considered at p-values <0.05.

RESULTS

A total of 136 patients with stage III and IV CRC who were treated with the standard 5-FU-based chemotherapy regimens were identified. The mean age of patients was 55.6 ± 11.5 years, with a median value of 57 years (range 18-78). Seventy-three (53.7%) patients were males and 63 (46.3%) were females. Almost two-thirds of patients were either overweight or obese (33.1% and 27.2%, respectively). Most of the patients had stage IV CRC with extensive metastases. Table 1 displays the general profile of CRC patients included in the present study.

Table 1 General profile of patients with colorectal cancer, n=136

Variable	Value
Age in years	
Mean ± SD	55.6 ± (11.5)
Median (range)	57 (18-78)

Gender n (%)	
Male	73 (53.7%)
Female	63 (46.3%)
BMI n (%)	
<18.5 (underweight)	15 (11.0%)
18.5-24.9 (healthy weight)	39 (28.7%)
25-29.9 (overweight)	45 (33.1%)
>30 (obesity)	37 (27.2%)
Smoking n (%)	
No	125 (91.9%)
Yes	11 (8.1%)
Allergies n (%)	
No	121 (89.0%)
Yes	15 (11.0%)
Hypertension n (%)	
No	83 (61.0%)
Yes	53 (39.0%)
Hyperlipidemia n (%)	
No	113 (83.1%)
Yes	23 (16.9%)
Diabetes n (%)	
No	84 (61.8%)
Yes	52 (38.2%)
Tumor site n (%)	
Cecum/Ascending/Descending	6 (4.4%)
Sigmoid/Descending	3 (2.2%)
Sigmoid only	28 (20.6%)
Rectal only	25 (18.4%)
Recto-sigmoid	18 (13.2%)
Non-specified	56 (41.2%)
CRC stage n (%)	
III	50 (36.8%)
IV	86 (63.2%)
Metastasis n (%)	
No	38 (27.9%)
Yes	98 (72.1%)
Surgery n (%)	
No	47 (34.6%)
Yes	89 (65.4%)

The majority of CRC patients had received FOLFOX regimen (50.7%); the remaining were treated with either FOLFIRI (27.9%) or FOLFOXIRI (21.3%) regimens. The selection of the chemotherapy regimen was based on the consensus agreement of the surgical and oncology teams after thorough discussions with the patient and his/her family. Table 2 shows the distribution of patients and their characteristic variables according to the used chemotherapy regi-

mens. Most of these variables did not show any significant difference among the three used regimens, except for the largest proportion of patients with stage III CRC had received the FOLFOX regimen.

Table 2 Patient's variables distributed among FOLFOX, FOLFIRI, and FOLFOXIRI chemotherapy regimens used in CRC patients

Variable	FOLFOX	FOLFIRI	FOLFOXIRI	p-value
	n=69 (50.7%)	n=38 (27.9%)	n=29 (21.3%)	
Age in years				
Mean ± SD	55.9 ± 12.5	56.7 ± 9.6	53.2 ± 11.4	0.4411
Median (range)	57 (18-78)	57 (38-74)	55 (30-74)	
Gender n (%)				
Male	38 (55.1%)	21 (55.3%)	14 (48.3%)	0.8054
Female	31 (44.9%)	17 (44.7%)	15 (51.7%)	
BMI n (%)				
Underweight/normal weight	32 (46.4%)	12 (31.6%)	10 (34.5%)	0. 2643
Overweight/obesity	37 (53.6%)	26 (68.4%)	19 (65.5%)	
Hypertension n (%)				
No	37 (53.6%)	24 (63.2%)	22 (75.9%)	0.1138
Yes	32 (46.4%)	14 (36.8%)	7 (24.1%)	
Hyperlipidemia n (%)				
No	55 (79.7%)	30 (78.9%)	28 (96.6%)	0.0923
Yes	14 (20.3%)	8 (21.1%)	1 (3.4%)	
Diabetes n (%)				
No	39 (56.5%)	24 (63.2%)	21 (72.4%)	0.3284
Yes	30 (43.5%)	14 (36.8%)	8 (27.6%)	
CRC stage n (%)				
III	38 (55.1%)	4 (10.5%)	8 (27.6%)	<0.0001
IV	31 (44.9%)	34 (89.5%)	21 (72.4%)	
Metastasis n (%)				
No	33 (47.8%)	2 (5.3%)	3 (10.3%)	<0.0001
Yes	36 (52.2%)	36 (94.7%)	26 (89.7%)	
Surgery n (%)				
No	22 (31.9%)	17 (44.7%)	8 (27.6%)	0.275
Yes	47 (68.1%)	21 (55.3%)	21 (72.4%)	
Neutropenia n (%)				
No	62 (89.9%)	31 (81.6%)	21 (72.4%)	0. 0918
Yes	7 (10.1%)	7 (18.4%)	8 (27.6)	
Fever n (%)				
No	64 (92.8%)	35 (92.1%)	24 (82.8%)	0.2825
Yes	5 (7.2%)	3 (7.9%)	5 (17.2%)	
Filgrastim n (%)				
No	45 (65.2%)	18 (47.4%)	20 (69.0%)	0.1189
Yes	24 (34.8%)	20 (52.6%)	9 (31.0%)	

Most patients (61.8%) had also received one or more of the following biologic targeted cancer therapies alongside with the first-line standard treatments; including bevacizumab (Avastin®), cetuximab (Erbitux®), or panitumumab (Vectibix®) (34.7%, 20.8%, 8.3%, respectively). Additionally, the granulocyte colony-stimulating factor (CSF), filgrastim, was given to 53 (39.0%) patients as supportive cancer care to treat severe neutropenia or as a prophylactic medication in high-risk patients.

A number of side-effects were described by patients received those regimens. Among the most commonly reported ones in the FOLFOX regimen were numbness (27.5%, with 11.6% confirmed neuropathy), followed by abdominal pain, nausea/vomiting, and diarrhea (21.7%, 21.7%, and 20.3%, respectively). Patients who received the FOLFIRI regimen had also reported pronounced abdominal pain (34.2%), followed by skin rash, nausea/vomiting, and diarrhea (31.6%, 31.6%, and 28.9%, respectively). However, only, three patients (7.9%) had reported numbness due to

the FOLFIRI regimen and it was not associated with neuropathy. Similarly, patients who received the FOLFOXIRI regimen complained of abdominal pain as the most common side-effect (44.8%) with substantial severity, followed by fatigue, nausea/vomiting, and constipation (31.0%, 27.6%, and 20.7%, respectively). Four patients (13.8%) treated with the FOLFOXIRI regimen had reported numbness; two of them (6.9%) had confirmed neuropathy symptoms.

On the other hand, 22 patients out of 136 patients (16.2%) developed neutropenia. However, only 13 of the neutropenic patients (59.1%) had shown symptoms of infections or fever. Most neutropenia occurred between the third and fourth cycle of the used chemotherapy regimen. Table 3 shows neutropenia distribution in CRC patients and the multivariate logistic regression analysis of different assessed factors. A significant increase in the neutropenia was found in female patients (OR=4.21; 95% CI: 1.17-15.08; p=0.0273). Patients with stage IV CRC also showed a significantly higher risk of neutropenia (OR=13.41; 95% CI: 1.16-155.37; p=0.0378). However, CRC patients received filgrastim had a significant lower risk for neutropenia (OR=0.03; 95% CI: 0.00-0.30; p=0.0027). No significant difference was found amongst other patients' variables.

Table 3 Multivariate logistic regression analysis among CRC patients

Factors	Neutropenia				OR (95% CI)	p-value
	Positive		Negative			
	n=22		n=114			
	n	%	n	%		
Age in years						
<Mean (55.6)	9	40.9%	52	45.6%	2.89 (0.73-11.44)	0.1303
≥ Mean	13	59.1%	62	54.4%		
Gender n (%)						
Male	8	36.4%	65	57.0%	4.21 (1.17-15.08)	0.0273
Female	14	63.6%	49	43.0%		
BMI n (%)						
Underweight/normal weight	12	54.5%	42	36.8%	0.66 (0.33-1.33)	0.2444
Overweight/obesity	10	45.5%	72	63.2%		
Hypertension n (%)						
No	15	68.2%	68	59.6%	0.38 (0.09-1.69)	0.2033
Yes	7	31.8%	46	40.4%		
Hyperlipidemia n (%)						
No	20	90.9%	93	81.6%	0.34 (0.04-2.70)	0.3048
Yes	2	9.1%	21	18.4%		
Diabetes n (%)						
No	15	68.2%	69	60.5%	3.07 (0.60-15.69)	0.1787
Yes	7	31.8%	45	39.5%		
CRC stage n (%)						
III	2	9.1%	48	42.1%	13.41 (1.16-155.37)	0.0378
IV	20	90.9%	66	57.9%		
Metastasis n (%)						
No	2	9.1%	36	31.6%	0.91 (0.06-13.11)	0.9473
Yes	20	90.9%	78	68.4%		
Surgery n (%)						
No	9	40.9%	38	33.3%	0.71 (0.19-2.59)	0.6019
Yes	13	59.1%	76	66.7%		

Chemotherapy regimens n (%)						
FOLFOX	7	31.8%	62	54.4%	2.03 (0.88-4.71)	0.0988
FOLFIRI	7	31.8%	31	27.2%		
FOLFOXIRI	8	36.4%	21	18.4%		
Filgrastim n (%)						
No	21	95.5%	62	54.4%	0.03 (0.00-0.30)	0.0027
Yes	1	4.5%	52	45.6%		
Targeted therapy n (%)						
Bevacizumab	11	50.0%	39	34.2%	0.78 (0.33-1.84)	0.5683
Cetuximab	4	18.2%	23	20.2%		
Pantimumab	1	4.5%	6	5.3%		
None	6	27.3%	46	40.4%		

DISCUSSION

Chemotherapy-induced neutropenia is a well-documented adverse effect associated with numerous cytotoxic chemotherapies that have been always recognized as the primary cause of infections in cancer patients [15]. A significant reduction in the neutrophil count has been reported in a considerable number of CRC patients treated with various chemotherapy regimens. However, few studies have explored the risk factors associated with chemotherapy-induced neutropenia in CRC patients [13,16,17]. The present study has recognized females and patients with stage IV CRC as noteworthy factors associated with increased risk of neutropenia in patients using oxaliplatin and/or irinotecan-containing chemotherapy as the standard regimens in CRC.

In spite of the fact that less than one-fifth of the CRC patient in the present study had developed neutropenia, almost 60% of those neutropenic patients had shown evident symptoms of infections and fever. Most of the febrile neutropenia occurred after the mid-period of the chemotherapy treatment. Nevertheless, no significant difference was found in the frequency, severity or duration of neutropenia in CRC patients between the three used chemotherapy regimens (FOLFOX, FOLFIRI or FOLFOXIRI).

The dramatic and deleterious effects of neutropenia had sometimes necessitated reforms in the used chemotherapies, such as dose modifications or delays in the treatments (data not shown). Several studies had reported similar observations and interventions due to chemotherapy-induced neutropenia in cancer patients [18-21]. However, these detrimental adjustments in treatment could, unfortunately, increase the risk of cancer progression or adversely impact the therapeutic outcome of chemotherapy treatment [22-24].

On the other hand, more than 98% of patients in the present study who received filgrastim did not show neutropenia, which confirms the pivotal prophylactic effect of filgrastim in the majority of CRC patients. Recent studies have also revealed a tangible benefit of CSFs treatment in reducing the incidence and severity of neutropenia in high-risk patients [25,26]. Moreover, CSFs such as filgrastim or pegfilgrastim were used successfully in the treatment of severe neutropenia in CRC patients [27,28].

Furthermore, oxaliplatin and irinotecan are occasionally combined together, in some patients, with 5-fluorouracil/leucovorin (in FOLFOXIRI regimen) in an attempt to augment treatment of metastatic CRC [29]. Some studies reported high response rates and enhanced survival for this regimen, particularly in patients with liver metastases [5]. Moreover, several studies have proven the efficacy of the FOLFOXIRI regimen with comparable toxicity to FOLFOX and FOLFIRI regimens in most patients [30,31]. On the contrary, few studies reported aggravation of potential adverse effects for FOLFOXIRI [32]. Therefore, the rational use of any of these effective regimens should be based on the judicious decision of the anticipated therapeutic outcome and risk of toxicities.

CONCLUSION

Despite the significant strides made in the treatment of advanced and metastatic CRC, chemotherapy-induced neutropenia is still considerably high. A significant increase in the risk neutropenia was found in female patients and in

patients with stage IV CRC. The present data have undoubtedly revealed a significant decline in febrile neutropenia in CRC patients treated with filgrastim in conjunction with the anticancer regimens.

DECLARATIONS

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Shussman, N., and S. D. Wexner. "Colorectal polyps and polyposis syndromes." *Gastroenterology Report,* Vol. 2, No. 1, 2014, pp. 1-15.

[2] Ferlay, J., et al. "Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods." *International Journal of Cancer,* Vol. 144, No. 8, 2019, pp. 1941-53.

[3] Alsanea, Nasser, et al. "Colorectal cancer in Saudi Arabia: incidence, survival, demographics and implications for national policies." *Annals of Saudi Medicine,* Vol. 35, No. 3, 2015, pp. 196-202.

[4] Bazarbashi, Shouki, Haya Al Eid, and Joan Minguet. "Cancer incidence in Saudi Arabia: 2012 data from the Saudi cancer registry." *Asian Pacific Journal of Cancer Prevention: APJCP,* Vol. 18, No. 9, 2017, pp. 2437-44.

[5] Aparicio, Jorge, et al. "FOLFOX alternated with FOLFIRI as first-line chemotherapy for metastatic colorectal cancer." *Clinical Colorectal Cancer,* Vol. 5, No. 4, 2005, pp. 263-67.

[6] Grivicich, Ivana, et al. "Irinotecan and oxaliplatin: An overview of the novel chemotherapeutic options for the treatment of advanced colorectal cancer." *Brazilian Journal of Medical and Biological Research,* Vol. 34, No. 9, 2001, pp. 1087-103.

[7] Hirsch, Bradford R., and S. Yousuf Zafar. "Capecitabine in the management of colorectal cancer." *Cancer Management and Research,* Vol. 3, 2011, pp. 79-89.

[8] Moriarity, Andrew, et al. "Current targeted therapies in the treatment of advanced colorectal cancer: A review." *Therapeutic Advances in Medical Oncology,* Vol. 8, No. 4, 2016, pp. 276-93.

[9] Goodwin, Rachel A., and Timothy R. Asmis. "Overview of systemic therapy for colorectal cancer." *Clinics in Colon and Rectal Surgery,* Vol. 22, No. 4, 2009, pp. 251-56.

[10] Crawford, Jeffrey, et al. "Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice." *Journal of the National Comprehensive Cancer Network,* Vol. 6, No. 2, 2008, pp. 109-18.

[11] Chen, Menghua, et al. "Oxaliplatin-based chemotherapy combined with traditional medicines for neutropenia in colorectal cancer: A meta-analysis of the contributions of specific plants." *Critical Reviews in Oncology/ Hematology,* Vol. 105, 2016, pp. 18-34.

[12] Hecht, J. Randolph, et al. "5-Fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus sunitinib or bevacizumab as first-line treatment for metastatic colorectal cancer: A randomized phase IIb study." *Cancer Management and Research,* Vol. 7, 2015, pp. 165-73.

[13] Lalami, Yassine, et al. "Can we predict the duration of chemotherapy-induced neutropenia in febrile neutropenic patients, focusing on regimen-specific risk factors? A retrospective analysis." *Annals of Oncology,* Vol. 17, No. 3, 2005, pp. 507-14.

[14] Rasmy, A., M. Mashiakhi Al, and A. Ameen. "Chemotherapy-induced febrile neutropenia in solid tumours." *The Gulf Journal of Oncology,* Vol. 1, No. 25, 2017, pp. 77-84.

[15] Crawford, Jeffrey, David C. Dale, and Gary H. Lyman. "Chemotherapy-induced neutropenia: Risks, consequences, and new directions for its management." *Cancer,* Vol. 100, No. 2, 2004, pp. 228-37.

[16] Kimura, M., et al. "Severe neutropenia: A prognosticator in patients with advanced/recurrent colorectal cancer under oral trifluridine-tipiracil (TAS-102) chemotherapy." *Die Pharmazie-An International Journal of Pharmaceutical Sciences,* Vol. 72, No. 1, 2017, pp. 49-52.

[17] Yasue, F., et al. "Risk factors contributing to the development of neutropenia in patients receiving oral trifluridine-tipiracil (TAS-102) chemotherapy for advanced/recurrent colorectal cancer." *Die Pharmazie-An International Journal of Pharmaceutical Sciences,* Vol. 73, No. 3, 2018, pp. 178-81.

[18] Oppenheim, Beryl. "Management of febrile neutropenia in low risk cancer patients." *Thorax,* Vol. 55, No. 1, 2000, pp. S63-69.

[19] Chang, J. "Chemotherapy dose reduction and delay in clinical practice: Evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer." *European Journal of Cancer,* Vol. 36, 2000, pp. 11-14.

[20] Fortner, Barry V., et al. "Experiencing neutropenia: Quality of life interviews with adult cancer patients." *BMC Nursing,* Vol. 4, No. 1, 2005, p. 4.

[21] Dale, David C. "Advances in the treatment of neutropenia." *Current Opinion in Supportive and Palliative Care,* Vol. 3, No. 3, 2009, pp. 207-12.

[22] Fortner, Barry V., et al. "Impact of chemotherapy-induced neutropenia on quality of life: A prospective pilot investigation." *Supportive Care in Cancer,* Vol. 13, No. 7, 2005, pp. 522-28.

[23] Lai, P., et al. "Palliative chemotherapy in advanced colorectal cancer patients 80 years of age and older." *Current Oncology,* Vol. 23, No. 3, 2016, pp. 144-53.

[24] Nagel, C. I., et al. "Effect of chemotherapy delays and dose reductions on progression free and overall survival in the treatment of epithelial ovarian cancer." *Gynecologic Oncology,* Vol. 124, No. 2, 2012, pp. 221-24.

[25] Weycker, Derek, et al. "Burden of chemotherapy-induced febrile neutropenia hospitalizations in US clinical practice, by use and patterns of prophylaxis with colony-stimulating factor." *Supportive Care in Cancer,* Vol. 25, No. 2, 2017, pp. 439-47.

[26] Bongiovanni, Alberto, et al. "Clinical role of filgrastim in the management of patients at risk of prolonged severe neutropenia: An evidence-based review." *International Journal of Clinical Practice*, Vol. 73, No. 11, 2019, p. e13404.

[27] Hecht, J. Randolph, et al. "A randomized, placebo-controlled phase II study evaluating the reduction of neutropenia and febrile neutropenia in patients with colorectal cancer receiving pegfilgrastim with every-2-week chemotherapy." *Clinical Colorectal Cancer,* Vol. 9, No. 2, 2010, pp. 95-101.

[28] Virizuela, J. A., et al. "Management of infection and febrile neutropenia in patients with solid cancer." *Clinical and Translational Oncology,* Vol. 18, No. 6, 2016, pp. 557-70.

[29] Leal, Frederico, Fernanda Proa Ferreira, and Andre Deeke Sasse. "FOLFOXIRI regimen for metastatic colorectal cancer: A systematic review and meta-analysis." *Clinical Colorectal Cancer,* Vol. 16, No. 4, 2017, pp. 405-09.

[30] Ogata, Takatsugu, et al. "Safety and effectiveness of FOLFOXIRI plus molecular target drug therapy for metastatic colorectal cancer: A multicenter retrospective study." *Oncotarget,* Vol. 10, No. 10, 2019, pp. 1070-84.

[31] Loupakis, Fotios, et al. "Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer." *New England Journal of Medicine,* Vol. 371, No. 17, 2014, pp. 1609-18.

[32] Montagnani, F., et al. "A systematic review of FOLFOXIRI chemotherapy for the first-line treatment of metastatic colorectal cancer: Improved efficacy at the cost of increased toxicity." *Colorectal Disease,* Vol. 13, No. 8, 2011, pp. 846-52.