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Hematologic Toxicities in Colorectal Cancer Patients who Received FOLFOX4

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Abstract

Background: Over the past decade, survival from advanced colorectal cancer is increasing. Therefore patients have more exposure to chemotherapy and related toxicities. This study determines how hematologic toxicity patterns affect therapy and care.

Methods: From April 2010 to March 2013, we enrolled 127 patients with stages IIb to IV colorectal cancer. Patients underwent complete blood count monitoring prior to and during each cycle of FOLFOX4 chemotherapy. Granulocyte colony stimulating factor was injected if their white blood cells were below 3.5×10^9/L.

Results: The most common hematologic toxicities were grades 1-2 for hemoglobin (76.83%) and leukopenia (26.48%). The least common hematologic toxicity was thrombocytopenia (4.69%) for all grades of platelet toxicity. The median granulocyte colony stimulating factor injection was 3.33 per 12 cycles.

Conclusion: Anemia and leukopenia are the most common hematologic abnormalities expected with FOLFOX4 chemotherapy regimens for colorectal cancer. The most important factor for predicting hematologic toxicities in patients who receive chemotherapy for colorectal cancer is the number of chemotherapy cycles.

Keywords: Colorectal cancer, Chemotherapy, FOLFOX4, Granulocyte colony stimulating factor, Hematologic toxicities

Introduction

Currently, cancer is a major problem that affects public health and is approximately the leading cause for one-fourth of deaths.[1] In Iran, colorectal cancer is the third most common cancer and the fifth cause of cancer deaths.[2]

Over the past decade new treatments have significantly improved outcomes for patients with colorectal cancer. The addition of irinotecan or oxaliplatin to fluorouracil and leucovorin has increased median progression-free and overall survival in metastatic colorectal cancer.[3]

Patients with stages III and IV

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colon cancer can benefit from chemotherapy agents, however these agents may be associated with gastrointestinal, blood, and cardiac toxicities that compromise treatment efficacy.[3] Additionally, in metastatic colorectal cancer the main concern is to find the optimal balance between efficacy, toxicity and quality of life.[4]

The most frequently observed toxicities in metastatic colorectal cancer patients managed by the FOLFOX7 regimen as a first-line treatment were grades 3-4 hematologic toxicities.[5]

According to the Multicenter International Study, the addition of oxaliplatin to a regimen of bolus and continuous-infusion fluorouracil (5-FU) combined with leucovorin (FOLFOX4) significantly improved disease-free survival in stages II and III and metastatic colon cancer.[6] A study on the FOLFOX4 regimen showed that tolerance of this chemotherapy in elderly patients did not significantly differ compared to younger patients. This treatment should be considered regardless of patient age however attention should be paid to the capacity of these patients to tolerate adverse events.[7]

Chemotherapy in colorectal cancer has been associated with increased risk of gastrointestinal, hematologic and cardiac toxicities which lead to treatment discontinuation and rehospitalization.[8]

Materials and Methods

This prospective cross-sectional study and chart review was carried out for every patient who received chemotherapy for colorectal cancer at Amir Oncology Hospital in Shiraz, Iran.

All subjects were under the care of an oncologist and received their treatment from April 2010 until March 2013.

We included patients with confirmed stages II to IV colorectal cancer who received either adjuvant or palliative treatment as first line of chemotherapy and patients who received more than half of the 12 chemotherapy cycles. Excluded were all patients who received concurrent or sequential radiation therapy because of the additive toxicity of radiotherapy on the hematopoietic system.

All patients received the FOLFOX4 chemotherapy regimen. A complete blood count (CBC) was taken prior to each chemotherapy cycle. Because of the risk of leukopenia and neutropenia after chemotherapy, this study defined the lower limit of normal thresholds for white blood cells (WBCs) as <3500 and an absolute neutrophil count of <1500 for administration of granulocyte colony stimulating factor (G-CSF) injections. If the patients became leukopenic (WBC $<3.5\times10^3$) or neutropenic (Polymorphonuclear neutrophil (PMN) <1500), G-CSF was injected with no modifications to the chemotherapy dose.

We recorded patient characteristics such as age, gender, tumor site, treatment regimen and dates, CBC, renal function tests, medications and

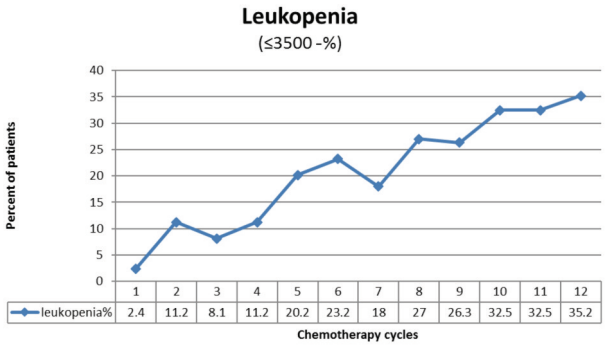

Figure 1. Leukopenia in patients treated by 12 cycles of FOLFOX4 chemotherapy.

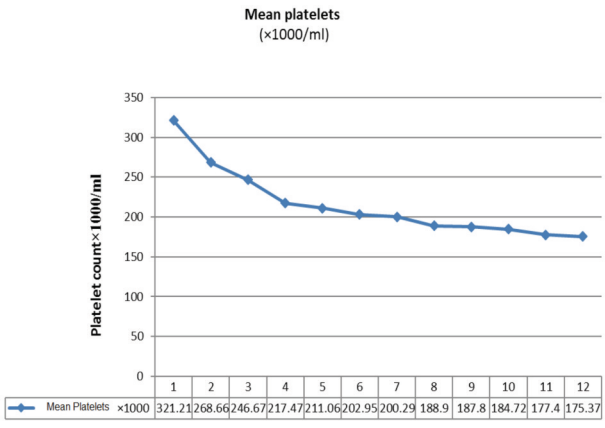

Figure 2. Mean platelet count during 12 cycles of FOLFOX4 chemotherapy.

toxicities. Data regarding chemotherapy delivery, G-CSF use, hematological toxicities, secondary admissions for hematologic toxicities and neutropenic fever were recorded for each patient.

Statistical analysis

Demographic and clinical data were presented descriptively as means, medians for continuous variables, and counts or proportions for categorical variables. Analyses were performed using SPSS version 22.0.

Results

The study sample included 127 patients. Approximately 112 (88.2%) were received FOLFOX4 as first line of treatment and more than half of the 12 chemotherapy cycles. These patients met the protocol-specified inclusion criteria and entered in this study. Their demographic characteristics are summarized in Table 1.

A total of 57 patients completed 12 cycles of chemotherapy (median: 10.43 cycles). The mean age of patients was 51.02±12.26 years. The most common site of cancer involvement was the right side of the colon in 34 (26.8%) patients. Stage IV disease was the most common stage observed in 42 (33.1%) patients.

All patients received the FOLFOX4 chemotherapy regimen. Stage IV patients who received monoclonal antibodies were not included. Hematologic toxicities are summarized in Table 2.

Febrile neutropenia was defined as a single oral temperature ≥38.3°C or a temperature of ≥38.0°C for ≥1 h with a neutrophil count of $<1.0\times10^9$/L.

One neutropenic fever and readmission occurred in a 66-year-old man on cycle five of FOLFOX4. This patient had anemia and neutropenia during previous cycles. He received 15 bags of packed cells for transfusion and frequent G-CSF injections.

Platelet transfusion was needed in 4 (3.14%) patients due to severe thrombocytopenia, bleeding tendency and platelet counts below 20×10^3.

Overall, 24 (18.9%) patients developed significantly lowered hemoglobin (<8 g/dl) and received transfusions during different chemotherapy cycles.

There were 8 patients who received packed cell

Table 1. Demographic features of study patients who underwent FOLFOX4 chemotherapy.

Patient characteristics	Number (%)
Age (years; mean±SD)	51.02 ± 12.26
Range	12-77
Median	52
Age (years)	
<60	95 (74.8)
>60	32 (25.2)
Male	67 (52.8)
Female	60 (47.2)
Neutropenic fever	1 (0.78)
Tumor sites	
Right colon	34 (26.8)
Left colon	9 (7.1)
Sigmoid	30 (23.6)
Rectum	24 (18.9)
Rectosigmoid	10 (7.9)
Transverse colon	1 (0.8)
Unknown	19 (15)
Antibiotic therapy	
Intravenous	37 (29.13)
Oral	40 (31.5)
Total	62 (48.8)
Stage	
IIB	34 (26.8)
IIIA-IIIB	37 (29.1)
IV	42 (33.1)
Unknown	14 (11)

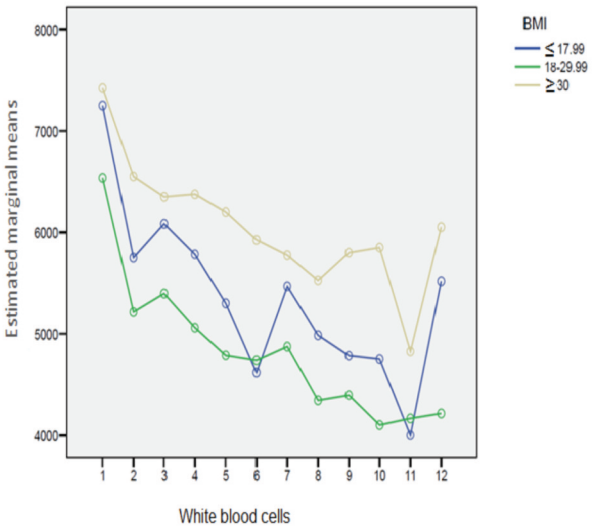

Figure 3. The correlation between white blood cell (WBC) count and body mass index (BMI)

Table 2. Hematologic toxicity, grading and mean hematology index per cycle of FOLFOX4.

Hematologic index		Number/cycle and percent
Number of patients		127
Platelet transfusion		4 (3.1%)
Packed cell transfusion		24 (18.9%)
G-CSF injection		75 (59.1%)
Mean hemoglobin		
	Before chemotherapy	11.57 g/dl
	Mid-cycle	11.73 g/dl
	End cycle	11.61 g/dl
Mean white blood cell count (WBC)		
	Before chemotherapy	6.694×103
	Mid-cycle	5.035×103
	End cycle	4.401×103
Mean platelet count		
	Before chemotherapy	318,000
	Mid-cycle	199,000
	End cycle	169,000
Anemia (mean ± SD)		
	Grade 1	73.41±14.9 (66.4%)
	Grade 2	11.41±2.1 (10.43%)
	Grade 3	0.66±1.15 (0.57%)
	Grade 4	0.25±0.45 (0.24%)
Leukopenia (mean ± SD)		
	Grade 1	18±7 (17.14%)
	Grade 2	9.58±4.7 (9.34%)
	Grade 3	1.6±1.6 (1.62%)
	Grade 4	0.16±0.4 (0.14%)
Thrombocytopenia (mean ± SD)		
	Grade 1	2.91±2.5 (3.05%)
	Grade 2	0.83±1.4 (0.83%)
	Grade 3	0.083±0.3 (0.066%)
	Grade 4	0.16±0.4 (0.15%)

G-CSF: Granulocyte colony stimulating factor

transfusions before FOLFOX4 chemotherapy, thus only 16 (23.38%) had blood transfusions after starting chemotherapy. Fifty five bags were transfused in total with 0.43 bag/patient (median 2.29). Thirty of these fifty five bags were given after start of chemotherapy with median 0.23 and 1.87 means the amount of packed cells given during chemotherapy.

During hospitalization many patients became febrile due to local and systemic infections. In 4 patients fever was due to underlying malignant disease because of a negative workup for infection and all patients became afebrile after starting FOLFOX4 chemotherapy. Thus fever in these four patients not attributed to FOLFOX4 regimen and neutropenia. Overall, 62 (48.8%) patients were treated by oral and intravenous antibiotics, 40.2% received antibacterial agents and 2.4% received antifungal agents.

There were 75 (59.1%) patients who received G-CSF injections during different cycles of chemotherapy due to significant leukopenia ($<3.5\times10^9$/L) and neutropenia ($<1.5\times10^9$/L). With the increasing number of chemotherapy cycles, both leukopenia and neutropenia significantly increased from 2.4% during the first cycle to 36.2% in the last cycle.

Overall, there were 423 G-CSF injections administered (range: 1-31) during twelve cycles of FOLFOX4. The most common cycle for injection was the eighth cycle; the median injection was 3.33 for all cycles and 5.64 for neutropenic patients in this study. In 52 (40.9%) patients, there were no G-CSF injections administered

during the 12 cycles of chemotherapy.

An analysis of WBC, red blood cells, hemoglobin, mean corpuscular volume (MCV)and platelets showed that WBC (P=0.0001) and platelets (P=0.0001) significantly declined after starting chemotherapy (Figures 1 and 2).

There was no correlation between independent variables (age, sex, chemotherapy regimen, body mass index, body surface area, stage of disease) and all hematologic toxicities.

According to National cancer institute toxicity criteria for grading hematologic toxicities, the median toxicity grades 1-2 for all 12 cycles was 76.83% for hemoglobin, 26.48% for WBCs and 3.88% for platelets. Median hematologic toxicity grades 3-4 in all 12 cycles was 0.81% for hemoglobin, 1.76% for WBCs and 0.81% for platelet counts.

Overall, patients under age 60 years had lower WBC counts compared to those over 60 years. The patients with a higher body mass index (>30) had higher WBC counts (Figure 3).

The MCV significantly increased during the eighth to twelfth cycles. Mean corpuscular volume increased with an increase in age (P=0.014).

Platelet counts significantly declined during the chemotherapy cycles but there was no correlation with age, sex, chemotherapy regimen, body mass index, body surface area and stage of disease.

According to the definition of anemia (hemoglobin <14 g/dl in males and <12 g/dl in females), overall anemia was present in 75.32% to 83% of patients.

Although anemia was a common finding, hemoglobin and red cell counts did not show a wide variation during the chemotherapy cycles. Body surface area was effective on hemoglobin (P= 0.001) and red cell count (P= 0.012) changes. These means patients with high body surface area had more anemia.

Discussion

The primary study objective was to describe the incidence and characteristics of hematologic toxicities in patients treated with FOLFOX4 for stages II – IV colorectal cancer and estimate G-CSF needs during FOLFOX4 chemotherapy. The results could guide physicians to predict both hematologic side effects of FOLFOX4 chemotherapy and determine the need for G-CSF according to patient characteristics in order to prevent severe bone marrow suppression and neutropenic fever.

According to this study, about 50%-60% of patients on chemotherapy for colorectal cancer were at risk for grades 2-4 WBC toxicities and needed G-CSF injections for continuation of chemotherapy.

In a study by Nardi et al., severe hematologic toxicity from the FOLFOX-4 regimen as first-line chemotherapy in elderly patients with advanced gastric cancer was uncommon. Grade 3 anemia was 9.09% and grade 3 neutropenia was 18.18%.[9]

Bone marrow suppression, as an important predictor of toxicity, can result in dose modifications, treatment delays and discontinuation of chemotherapy.

In the current study, severe hematologic toxicity was not common. The most frequent abnormalities (76.83%) were grades 1-2 hemoglobin toxicities. Febrile neutropenia was seen in one (0.78%) patient. It should be kept in mind that platelet and WBC counts decreased more during later FOLFOX4 chemotherapy cycles. Patients were at high risk for hematologic toxicity during the last cycles.

It is a question that neutropenia and relative dose intensity on adjuvant FOLFOX4 chemotherapy are associated with increased survival from colorectal cancer. In study by Smoragiewicz et al., toxicity and dose modification were not associated with relapse free and overall survival. The risk of febrile neutropenia was not high.[10]

An important factor predictive of toxicity and clinical outcome in colorectal cancer is germline polymorphisms. Martinez-Balibrea et al. have shown that UDP-glucoronosyltransferase1A germline polymorphisms were predictive of hematologic toxicity, specifically for neutropenia alone.[11]

Nonetheless, the results of this study of routine

clinical practice provide important insights into hematologic toxicity assessment and subsequent neutropenia management. We have observed notable differences in chemotherapy-related anemia, leukopenia, neutropenia and thrombocytopenia among patients as chemotherapy progressed from the first to twelfth cycles. We assessed the correlation of independent variable factors - age, sex, chemotherapy regimen, body mass index, body surface area and stage of disease with hematologic toxicity. We observed no direct correlation with the toxicities.

These findings have suggested that physicians should place greater emphasis on individual risk factors when assessing risk in patients with colorectal cancer.

Although the hematologic toxicity risks are greatest in the last cycles, the risk is present in all cycles. Patients should be supported equally during the cycles where they are at high risk. All patients should be monitored before the next chemotherapy cycle.

The identification of an increase in MCV as a new predictive marker in cancer treatment is very important. In recent studies, the increase in MCV has been suggested as a tumor response marker. Bozkurt et al. reported no significant difference between tumor response and increase in MCV.[12]

Mean corpuscular volume rose with increased age as a physiologic response, however chemotherapy significantly impacted MCV, especially after cycle eight. This MCV increase showed the effect of chemotherapy but the prognostic value of this factor was undetermined.

The most common hematologic toxicity was grades 1-2 anemia, defined as hemoglobin levels of 8 g/dl to normal in all patients on FOLFOX4 chemotherapy. The second most common hematologic toxicity was grades 1-2 leukopenia (26.48%), defined by the national cancer institute as a leukocyte count between 2 - 3.9×10^3. Grades 3-4 WBC and platelet toxicities were not common among all patients.

The above data has confirmed that mild anemia and leukopenia are the most common hematologic abnormities expected in colorectal cancer patients who undergo FOLFOX4 chemotherapy.

In summary, this study has suggested that the most important factor for predicting hematologic toxicities in patients who receive chemotherapy for colorectal cancer is the number of chemotherapy cycles and continuation of chemotherapy.

The safety of our practice, giving full-dose adjuvant chemotherapy to patients with colorectal cancer regardless of the result of the CBCs the day before chemotherapy, is confirmed by the results of this study. Our patients on FOLFOX4 are now offered prophylactic G-CSF (average: 3.33 injections per 12 cycles) when they present with toxicity grades higher than grade 1 leukopenia ($<3.9\times10^3$) when beginning the next chemotherapy cycle. The intent is to prevent neutropenic fever and severe WBC toxicity.

Conflict of Interest

No conflict of interest is declared.

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