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Cetuximab is Associated With Excessive Toxicity When Combined With Bevacizumab Plus mFOLFOX6 in Metastatic Colorectal Carcinoma

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Abstract

Background—The bevacizumab-cetuximab combination has shown promising activity in chemotherapy-refractory metastatic colorectal cancer (mCRC). We sought to determine the safety and efficacy of cetuximab added to bevaci-zumab plus standard mFOLFOX6 (modified 5-fluorouracil [5-FU]/leucovorin/oxaliplatin) as first-line therapy for mCRC.

Patients and Methods—Sixty-six patients received cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 weekly intravenously [I.V.]) plus bevacizumab 5 mg/kg and mFOLFOX6 chemotherapy every 2 weeks. The primary endpoint was toxicity.

Results—The most common grade 3–4 events included diarrhea (14%), fatigue (14%), neuropathy (12%), venous thrombosis (9%), acneiform rash (8%), and desquamation (8%). A protocol-defined prohibitive adverse event occurred in 4 patients (6%), including 2 treatment-associated deaths. Thirty-seven patients (56%) discontinued therapy before disease progression because of either toxicity (n = 19; 29%) or patient withdrawal (n = 18; 27%). Twenty-eight of 37 patients (76%) who discontinued therapy before disease progression did so because of cetuximab-associated toxicity.

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This summary may include the discussion of investigational and/or unlabeled uses of drugs and/or devices that may not be approved by the FDA.

Disclosures

Dr. Ocean is a member of the Speaker's Bureau for Eli Lilly and Company, Genentech, Inc., and sanofi-aventis U.S. Dr. Polite is a member of the Speaker's Bureau for sanofi-aventis U.S. Dr. Polite has received honoraria from sanofi-aventis U.S. Dr. Kindler has received research funding from Genentech, Inc. and served as a consultant for Roche and Genentech, Inc. Dr. Sparano has served as a consultant for Genentech and sanofi-aventis U.S. The remaining authors report no potential conflicts of interest.

Conclusion—Although the addition of cetuximab to bevacizumab plus mFOLFOX6 was not associated with excessive life-threatening toxicity, many patients discontinued therapy because of cetuximab-associated toxicity. Taken together with the results of recently reported phase III trials, cetuximab should not be used concurrently with bevacizumab and infusional 5-FU, leucovorin, and oxaliplatin chemotherapy for the treatment of mCRC.

Keywords

KRAS mutation; Oxaliplatin; Vascular endothelial growth factor

Introduction

For almost 40 years, the only chemotherapeutic option for patients with metastatic colorectal cancer (mCRC) was 5-fluorouracil (5-FU); when used in combination with leucovorin (LV) to enhance its efficacy, median survival was approximately 12 months.[1] Subsequently, the addition of irinotecan to 5-FU/LV (IFL) was found to significantly improve response and survival.[2] Additional studies demonstrated that the combination of infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX) to be superior to IFL when used as first-line therapy, resulting in significantly improved response (48% vs. 32%; $P = .006$), time to progression (9.7 months vs. 5.5 months; $P < .0001$) and overall survival (OS; 19.0 months vs. 16.3 months; $P = .026$). Several modifications have been described in order to reduce oxaliplatin-associated neuropathy and improve overall tolerability, including modified FOLFOX6 (which includes bolus and infusional 5-FU plus LV and a reduced oxaliplatin dose).[3–5]

Another major advance for the treatment of mCRC has been the availability of therapeutic agents targeting vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) pathways. Bevacizumab is a recombinant humanized monoclonal antibody targeting VEGF that was found to significantly improve response (45% vs. 35%; $P = .004$) and OS (20.3 months vs. 15.6 months; hazard ratio [HR], 0.66; $P < .001$) when added to IFL.[6] Subsequently, several other trials in the first- and second-line settings have confirmed the effectiveness of bevacizumab when added to FOLFOX or capecitabine and oxaliplatin-based therapies, although not all have shown improved survival.[7–9] Cetuximab is a human-murine chimeric monoclonal antibody that specifically binds to EGFR with high affinity, thereby preventing ligand-induced receptor activation. It has activity when used alone and in combination with irinotecan in refractory mCRC.[10–12] Moreover, a randomized phase II trial demonstrated encouraging activity for the cetuximab/bevacizumab combination in patients with irinotecan-refractory mCRC; response rates (RRs) and median time to disease progression were 37% and 7.3 months, respectively, for the cetuximab/bevacizumab/irinotecan arm, and 20% and 4.9 months, respectively, for the cetuximab-bevacizumab arm without any cytotoxic therapy.[11] In addition to clinical data supporting combined blockage of the EGFR and VEGF pathways, there was emerging data in preclinical models indicating that combined blockade exhibited additive or synergistic antineoplastic effects.[13,14]

Based upon these considerations, we initiated this phase II trial of cetuximab combined with bevacizumab plus a modified FOLFOX chemotherapy regimen (mFOLFOX6) as first-line therapy for mCRC. Our primary objectives were to determine the safety and toxicity profile of the chemotherapy-biologic combination, and secondary objectives included evaluation of objective response and progression-free survival (PFS).

Patients and Methods

Patient Selection

Eligible patients had histologically or cytologically confirmed, unresectable adenocarcinoma of the colon or rectum with measurable metastatic disease by Response Evaluation Criteria in solid Tumors (RECIST, version 1.0).[15] No previous treatment with chemotherapy for metastatic disease was permitted. Treatment in the adjuvant setting with up to 1 previous chemotherapy regimen that did not include oxaliplatin, bevacizumab, or cetuximab was permitted. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, be 18 years of age or older, and have a life expectancy > 3 months. Other requirements included adequate bone marrow function (leukocyte count at least 3500/μL, neutrophil count at least 1500/μL, and platelets at least 150,000/μL), kidney function (normal serum creatinine and no proteinuria, or < 1000 mg urinary protein/24 hours), and normal hepatic function (normal bilirubin and aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times the upper limit of normal). Patients on full-dose anticoagulants were required to either be on a stable dose of warfarin (with an international normalized ration [INR] of 2–3), or low-molecular-weight heparin, and to be free of any active bleeding or pathologic conditions associated with a high risk of bleeding. Patients were excluded if they had clinically significant cardiovascular disease including arterial thrombotic events (cardiac or cerebral vascular ischemia) within 6 months, or if they had brain metastases.

Chemotherapy and Biologic Therapy

Treatment included: (1) cetuximab 400 mg/m^2 loading dose I.V. over 120 minutes, then 250 mg/m^2 weekly over 60 minutes; (2) bevacizumab 5 mg/kg I.V. over 90 minutes, then every 2 weeks over 60 minutes, then over 30 minutes; and (3) mFOLFOX6 every 2 weeks, which included oxaliplatin 85 mg/m^2 over 120 minutes, 5-FU: 400 mg/m^2 I.V. bolus, then 2400 mg/m^2 I.V. over 46 hours, and leucovorin 400 mg/m^2 IV over 120 minutes with oxaliplatin.[5] Treatment was modified for toxicity as summarized in Table 1. Each mFOLFOX6 treatment was repeated every 2 weeks if the neutrophil count was at least 1500/μL, platelet count at least 100,000/μL, and the patient had satisfactorily recovered from toxicity attributed to the previous FOLFOX treatment. Treatment was continued until progression of disease, unacceptable toxicity, inter-current condition, declining performance status preventing further treatment, or patient withdrawal. Bevacizumab and cetuximab were provided by the National Cancer Institute (NCI) for this trial.

Response and Toxicity Evaluation

Computed tomography or magnetic resonance imaging scans of measurable lesions were obtained at baseline and every 8 weeks (each cycle). Responses were classified according to RECIST criteria. [15] National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) were used to grade toxicity.

Statistical Considerations

The primary objective was to evaluate safety in all treated patients, specifically the rate of prohibitive serious adverse events (PSAE), which were defined as grade 5 events, grade 4 hemorrhage or thrombosis, or bowel perforation. A PSAE rate exceeding 8.5% was defined a priori to be prohibitively toxic (exceeding the rate observed with bevacizumab plus IFL, in which 2.6% had a treatment-associated death, 1.5% had bowel perforation, and approximately 4%–5% had grade 4 hemorrhage or thrombosis).[6] There was a 2-stage safety analysis, with up to 40 patients accrued for the first stage. If 7 or more PSAEs (17%) occurred in the initial 40 patients, it could be concluded with 95% confidence that the true

PSAE rate exceeded 8.5%, and the trial would be terminated. If 4–6 patients had a PSAE, the study would be expanded to the second stage to accrue an additional 27 patients to more accurately estimate toxicity. If 10 or more of the 67 patients (15% or more) had a PSAE, the regimen would be considered excessively toxic. A 95% confidence interval (CI) for the objective RR was estimated via exact binomial proportions. The PFS and OS were estimated using the Kaplan-Meier method. The PFS was defined as the time between registration and either progression of disease or death from any cause. The cutoff dates for the toxicity and efficacy analysis was December 31, 2007, at which time all but 3 patients had discontinued therapy.

Informed Consent and Regulatory Approval

The study was reviewed and approved by the Cancer Evaluation Therapy Program of the NCI (P6490), and by the institutional review board at each participating institution (Clinical Trials.gov identifier NCT00100841). All patients provided written informed consent.

Results

Patient Characteristics

Sixty-seven patients were enrolled and 66 were treated between November 2004 and November 2006 at 8 participating institutions. One patient did not begin therapy as a result of deterioration in performance status before treatment was initiated. The characteristics of the 66 treated patients are shown in Table 2. The median age was 57 years (range, 27–82 years), 53% were male, median ECOG performance status was 0 (range, 0–1), 30% had previous adjuvant chemotherapy, and 65% had 2 or more organs involved by metastases.

Adverse Events

There were 4 protocol-defined prohibitive serious adverse events (PSAEs) among the first 40 patients, including 2 deaths (grade 5 events) and 2 episodes of grade 4 venous thrombosis, leading to expansion of accrual goal above 40 patients for the safety analysis. Causes of death included severe diarrhea associated with neutropenia in 1 patient (number 3), and pulmonary fibrosis in a second patient (number 10). There were no additional PSAEs among all 66 treated patients, yielding an overall PSAE rate of 6.1%, which did not surpass the prespecified rate of 8.5% deemed to be prohibitively toxic. The 60-day mortality rate was 1.5%.

Information regarding adverse events grouped by toxicity category is provided in Table 3, and also illustrated in Figure 1 by showing the frequency of adverse events ranging from the most to the least common. The most common adverse events were rash (83%), neuropathy (77%), diarrhea (70%), fatigue (59%), nausea (50%), vomiting (38%), bleeding (32%), and anorexia (27%). Grade 3–4 adverse events included diarrhea (14%), fatigue (14%), neuropathy (12%), venous thrombosis (9%), acneiform rash (8%), and desquamation (8%).

Treatment Administered and Reasons for Modification of Therapy

The median number of treatment cycles given was 3 (range, 1–12 cycles) and the median duration of therapy was 5.8 months (range, 0.2–23.1 months). The proportion of patients who required a dose reduction was 56.1% for oxaliplatin, 47% for 5-FU, and 28.8% for cetuximab; dose reductions for bevacizumab were not permitted. Reasons for discontinuation of all therapy were protocol-defined prohibitive toxicity in 19 patients (28.8%), patient withdrawal in 18 (27.2%), disease progression in 15 (22.7%), alternative therapy in 5 (7.6%), treatment-associated death in 2 (3%), concurrent illness in 1 (1.5%), and other reasons in 4 patients (6%). The number of cycles of therapy was similar in those who discontinued therapy because of disease progression (median, 3; range, 1–8 cycles) as

in those who discontinued to toxicity or withdrawal (median 3, range 1–6). A total of 15 patients (22.7%) discontinued at least 1 therapeutic agent because of toxicity but continued other agents, including 6 patients who discontinued oxaliplatin (9%), 3 who discontinued bevacizumab (4.5%), and 2 patients each who discontinued FOLFOX, 5-FU, and cetuximab (3% for each).

We also examined the reasons for discontinuation of therapy before disease progression, which are summarized in Table 4. For the 19 patients who discontinued therapy because of adverse events, 13 (68%) had a dose reduction in 1 or more therapeutic agents before treatment discontinuation, 8 of whom discontinued therapy because of cetuximab-associated toxicity. There were 6 patients (32%) who did not require dose modification before discontinuing therapy, 4 of whom discontinued therapy as a result of cetuximab-associated toxicity. For the 18 patients who withdrew consent, 11 (61%) had a dose reduction in 1 or more therapeutic agents before treatment discontinuation, 10 of whom discontinued therapy because of cetuximab-associated toxicity. There were 7 patients (39%) who did not require dose modification before discontinuing therapy, 6 of whom discontinued toxicity as a result of cetuximab-associated toxicity. Therefore, 28 of 37 patients (76%) who discontinued therapy before disease progression did so because of cetuximab-associated mucoenterocutaneous toxicity or hypersensitivity.

Response, Progression-Free Survival, and Overall Survival

Complete response occurred in 3 patients (4.5%) and partial response occurred in 35 patients (53.0%), yielding an overall objective RR of 58% (95% CI, 45%–70%). The median PFS was 9.6 months (95% CI, 9.5–12.2 months). After a median follow-up of 16.5 months, there have been 26 deaths (39%), and the estimated median OS was 27.4 months (95% CI, 17.3 months, upper limit not reached).

Discussion

This phase II study was primarily designed to evaluate the safety of cetuximab combined with bevacizumab plus mFOLFOX6 as first-line treatment of mCRC. A secondary objective was to evaluate its efficacy in a population unselected for *KRAS* mutation status, a standard of care at the time the study was performed. The most common grade 3–4 adverse events included diarrhea (14%), fatigue (14%), neuropathy (12%), venous thrombosis (9%), acneiform rash (8%), and desquamation (8%). There were 4 protocol-defined “prohibitive serious adverse events” (6%) that did not surpass the prespecified rate deemed to be prohibitively toxic. In addition, the 60-day mortality rate of 1.5% was similar to previous studies evaluating oxaliplatin-containing chemotherapy plus bevacizumab.[9] Although the grade 3–5 adverse event rate was similar to previous experience with chemotherapy plus bevacizumab or cetuximab, 56% of patients discontinued protocol therapy before disease progression because of adverse events stipulated by the protocol (28.8%) or because of patient withdrawal (27.2%). In addition, about 75% of those who discontinued therapy before progression did so because of cetuximab-associated toxicity.

Two major developments in the management of mCRC influence the interpretation and application of our trial results. First, the role of *KRAS* mutation status has been clearly established as a predictive biomarker for EGFR-directed therapy. Two separate trials have unequivocally demonstrated that both cetuximab and panitumumab produce clinical benefit only in the 60%–70% of tumors with wild-type *KRAS*.[16,17] Our trial was completed before this was known, and we do not have information regarding *KRAS* mutation status. Second, 2 phase III trials have shown no benefit for the double biologic combination targeting EGFR and VEGF when used with chemotherapy as first-line therapy for mCRC. In the CAIRO-2 (Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer) study, 755 front-

line mCRC patients were randomized to receive capecitabine/oxaliplatin plus bevacizumab with or without cetuximab; the addition of cetuximab was associated with inferior PFS (median, 9.4 months vs. 10.7 months; $P = .01$) and higher rates of grade 3–4 toxicity (82% vs. 73%; $P = .006$).[18] Likewise, in the PACCE trial (Panitumumab Advanced Colorectal Cancer Evaluation), 1053 front-line mCRC patients treated with either oxaliplatin-based or irinotecan-based chemotherapy were randomized to receive either bevacizumab alone or combined with panitumumab (a fully humanized monoclonal EGFR antibody).[19] The panitumumab arm was also associated with inferior PFS (median, 10.0 months vs. 11.4 months; $P < .05$) and more grade 3–4 toxicity (90% vs. 77% in the oxaliplatin stratum). A retrospective evaluation of the CAIRO-2 trial indicated that patients with tumors bearing mutated *KRAS* who received cetuximab exhibited inferior PFS compared with the non-cetuximab arm.[18] For the PACCE trial, a retrospective evaluation demonstrated adverse outcomes for the panitumumab arm in tumors with both wild-type and mutant *KRAS*.[19] The results of these phase III trials suggest that the addition of cetuximab is not likely to enhance the effectiveness of bevacizumab plus chemotherapy when used as first-line therapy for patients with mCRC irrespective of *KRAS* mutation status.

This treatment discontinuation rate before disease progression in our trial (56%) is high compared with the Dutch Colorectal Cancer Group CAIRO-2 trial evaluating oxaliplatin/capecitabine plus bevacizumab given either with or without cetuximab (37.1% vs. 32.0%).[18] The reasons for this are unclear, but suggest that low-grade toxicities including rash, diarrhea, and fatigue, though not severe, rendered the regimen poorly tolerated or accepted. Some evidence suggests that a strategy of planned oxaliplatin treatment holidays produces less neurotoxicity with comparable efficacy.[20] Similar strategies may need to be considered for integrating biologic agents with standard chemotherapy.

An ongoing trial (CALGB-80405 [Cancer and Leukemia Group B]) is comparing FOLFOX or leucovorin, 5-fluorouracil and irinotecan (FOLFIRI) chemotherapy plus bevacizumab, cetuximab, or both as first-line therapy for mCRC (ClinicalTrials.gov identifier: NCT00265850). The trial was amended in December 2008 to include only patients with tumors having wild type *KRAS*. It was amended again in September 2009 to drop the combined bevacizumab/cetuximab arm because of the CAIRO-2 and PACCE trial results. The findings from our trial also support the decision to drop the cetuximab/bevacizumab arm because of the high toxicity rates, which contribute to premature treatment discontinuation.

Conclusion

We therefore conclude that cetuximab plus bevacizumab should not be used concurrently with FOLFOX chemotherapy as front-line therapy for mCRC irrespective *KRAS* mutation status.

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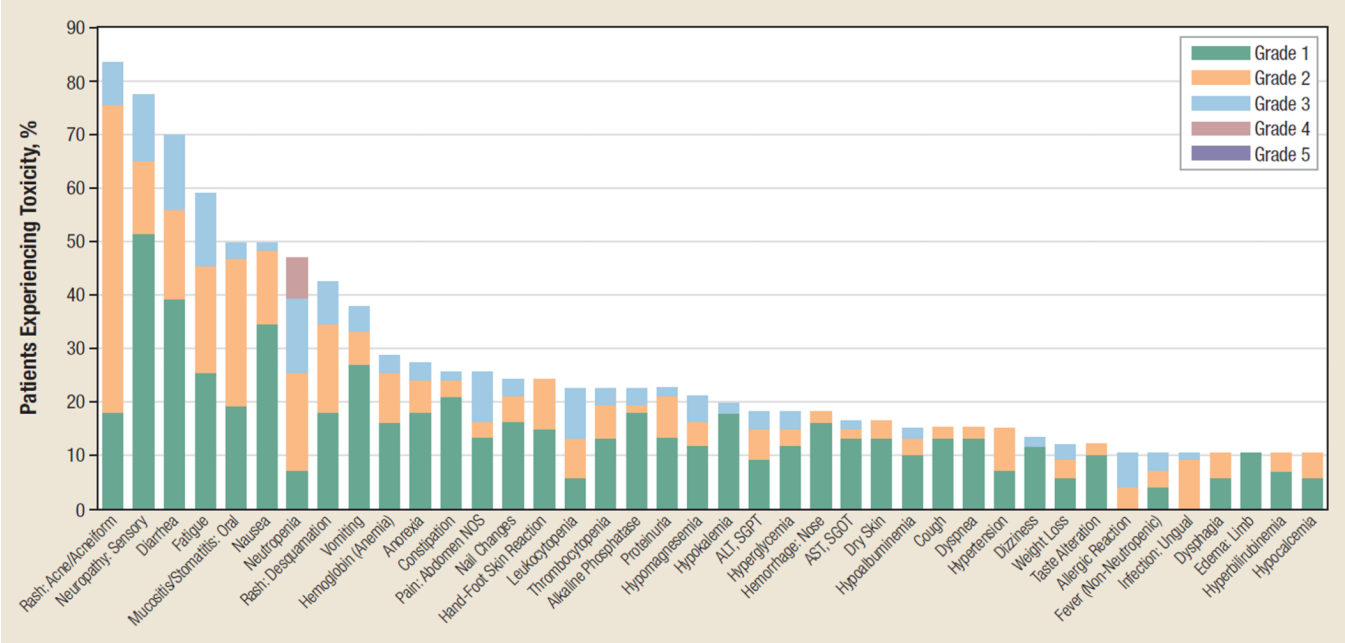

Figure 1. Cumulative Toxicity by CTCAE Grade

This chart shows the frequency of adverse events occurring in at least 10% of patients (or any grade 3–4 event occurring in at least 1 patient).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; NOS = not otherwise specified; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Table 1

Dose Modifications for Adverse Events

Treatment	Starting Dose	Dose Reductions	Criteria for Dose Modification
Biologic Therapy			
Cetuximab	400 mg/m^2 I.V. day 1 (over 120 minutes), then 250 mg/m^2 weekly (over 60 minutes)	Dose level 1: 200 mg/m^2 2: 150 mg/m^2	• Delay 1 – 2 weeks for first, second, or third occurrences of grade 3 rash (or grade 2 if intolerable), resume when grade 2 or less and tolerable • For the first occurrence of rash resulting in delay, resume cetuximab without dose reduction • With improvement following the delay for second or third occurrence of rash, resume cetuximab with dose reduction of 50 mg/m^2 • Discontinue for fourth occurrence of grade 3 rash or any occurrence of grade 4 rash
Bevacizumab	5 mg/kg I.V. day 1 (over 90 minutes), then 5 mg/kg every 2 weeks (over 60 minutes	No dose reduction	• Hold for uncontrolled or symptomatic hypertension, grade ≥ 2 proteinuria, grade 3 hemorrhage, thrombosis, thrombocytopenia, or coagulopathy, or grade 3 nonhematologic, noncutaneous adverse event until resolution to grade < 1 • Permanently discontinue for grade 4 or recurrent grade 3 hemorrhage, grade 4 or recurrent thrombosis, grade 4 hypertension, proteinuria, grade 3 thrombocytopenia lasting > 3 weeks, uncontrolled hypertension lasting > 4 weeks, new grade 2 or worsening of pre-existing arterial thromboembolic event, or any grade 4 nonhematologic, noncutaneous adverse event other than nausea/vomiting (or grade 3 lasting > 3 weeks)
mFOLFOX6 Chemotherapy			
Oxaliplatin	85 mg/m^2 I.V. over 120 minutes every 2 weeks	Dose level 1: 65 mg/m^2 2: 50 mg/m^2 3: 40 mg/m^2	• Repeat every 2 weeks if the neutrophil count at least 1500/μL, platelet count at least 100,000/μL, and had satisfactorily recovered from toxicity attributed to the previous FOLFOX treatment • Reduce 1 dose level for grade 2 neuropathy persisting between cycles of therapy (without resolution during treatment intervals), first/second occurrences of grade 3 neuropathy lasting 1 – 7 days, and for first/second occurrences of grade 3 neuropathy lasting > 7 days • Permanently discontinue if grade 3 neuropathy persisting between cycles, or grade 4 neuropathy resulted in permanent discontinuation of the drug • Extend infusion duration up to 6 hours for pharyngo-laryngo dysesthesias
5-Fluorouracil	400 mg/m^2 I.V. bolus, followed by 2400 mg/m^2 over 46 hours by I.V. infusion every 2 weeks	Dose level 1: 300/1920 mg/m^2[a] 2: 200/1600 mg/m^2 3: 100/1360 mg/m^2	• Repeat every 2 weeks if the neutrophil count is at least 1500/μL, platelet count at least 100,000/μL, and had satisfactorily recovered from toxicity attributed to the previous FOLFOX treatment • Grade 3–4 febrile neutropenia, thrombocytopenia, diarrhea, or mucositis:

Treatment	Starting Dose	Dose Reductions	Criteria for Dose Modification
			decrease 1 dose level when resolved to < grade 1 • Grade 2 neutropenia, thrombocytopenia, diarrhea, or mucositis on planned day of therapy: proceed with therapy with 1 dose level reduction
Leucovorin	400 mg/m^2 administered I.V. over 120 minutes simultaneously with oxaliplatin every 2 weeks	No dose reduction	• Repeat every 2 weeks if the neutrophil count is at least 1500/μL, platelet count at least 100,000/μL, and had satisfactorily recovered from toxicity attributed to the previous FOLFOX treatment • No dose modifications

[a] 5-FU bolus dose/5-FU infusion dose.

Abbreviations: 5-FU = 5-fluorouracil; FOLFOX = infusional 5-fluorouracil/leucovorin/oxaliplatin; I.V. = intravenous

Table 2

Patient Characteristics

Characteristic, n (%)	Value
Age	
Median	57 Years
Mean	56.9 Years
Range	27–82 Years
Sex	
Male	35 (53)
Female	31 (47)
Race/Ethnicity	
White	54 (82)
Black	10 (15)
Asian	2 (3)
Non-Hispanic	63 (96)
Hispanic	3 (5)
ECOG Performance Status	
0	46 (70)
1	18 (27)
Unknown	2 (3)
Primary Cancer Site	
Colon	51 (77)
Rectum	14 (21)
Previous Therapy	
Surgery	51 (77)
Chemotherapy	20 (30)
Radiotherapy	9 (14)
None	8 (12)
Number of Organs With Metastases	
1	23 (35)
2	28 (42)
≥ 3	15 (23)

Abbreviation: ECOG = Eastern Cooperative Oncology Group

Table 3

A Adverse Events

Toxicity	Number of Patients (%)			
	All Grades	Grade 3	Grade 4	Grade 5
Hematologic and Infectious				
Hemoglobin (Anemia)	19 (29)	2 (3)	0	0
Neutropenia	31 (47)	9 (14)	5 (8)	1 (1.5)[a]
Thrombocytopenia	15 (23)	2 (3)	0	0
Catheter-related infection	3 (5)	2 (3)	0	0
Eye infection	6 (9)	0	0	0
Ungual (nails) infection	7 (11)	1 (2)	0	0
Upper airway infection	5 (8)	0	0	0
Urinary tract infection	3 (5)	0	0	0
Nonhematologic				
Cardiovascular				
Cardiopulmonary-restrictive	1 (2)	1 (2)	0	0
Hypertension	10 (15)	0	0	0
Hypotension	2 (3)	2 (3)	0	0
Constitutional				
Anorexia	18 (27)	2 (3)	0	0
Fatigue	39 (59)	9 (14)	0	0
Hemorrhage/Thrombosis				
Cerebrovascular ischemia	2 (3)	1 (2)	0	0
Hemorrhage: nose	12 (18)	0	0	0
Hemorrhage: lower gastrointestinal	7 (11)	0	0	0
Hemorrhage: urine	5 (8)	0	0	0
Venous thrombosis	7 (11)	3 (5)	3 (5)	0

B Adverse Events

Toxicity	Number of Patients (%)			
	All Grades	Grade 3	Grade 4	Grade 5
Nonhematologic				
Hepatic				
Alkaline phosphatase	15 (23)	2 (3)	0	0
Alanine transaminase (ALT/SGPT)	12 (18)	2 (3)	0	0
Aspartate transaminase (AST/SGOT)	11 (17)	1 (2)	0	0
Hypoalbuminemia	10 (15)	1 (2)	0	0
Mucoenterocutaneous				
Constipation	17 (26)	1 (2)	0	0

B Adverse Events

Toxicity	Number of Patients (%)			
	All Grades	Grade 3	Grade 4	Grade 5
Diarrhea	46 (70)	9 (14)	0	1 (1.5)[a]
Dry skin	11 (17)	0	0	0
Hand-foot reaction	16 (24)	0	0	0
Mucositis: oral	33 (50)	2 (3)	0	0
Nausea	33 (50)	1 (2)	0	0
Nail changes	16 (24)	2 (3)	0	0
Rash: acne/acneiform	55 (83)	5 (8)	0	0
Rash: desquamation	28 (42)	5 (8)	0	0
Vomiting	25 (38)	3 (5)	0	0
Neurologic				
Neuropathy: sensory	51 (77)	8 (12)	0	0
Pain			0	
Pain: abdomen	17 (26)	6 (9)	0	0
Pulmonary				
Cough	10 (15)	0	0	0
Dyspnea	10 (15)	0	0	0
Pneumonitis/fibrosis	0	0	0	1 (1.5)
Renal/Metabolic				
Proteinuria	15 (23)	1 (2)	0	0
Hypomagnesemia	14 (21)	3 (5)	0	0
Hypokalemia	13 (20)	1 (2)	0	0
Hyperglycemia	12 (18)	2 (3)	0	0

[a]One patient died with severe diarrhea associated with severe neutropenia with presumed sepsis.

This table includes all adverse events occurring in at least 5% or where there is at least 1 occurrence of a grade 3 or 4 event.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

Table 4

Dose Modifications and Adverse Events in Patients Who Discontinued Therapy Before Disease Progression

Reason for Discontinuation	Adverse Events	Patient Withdrawal
Number	19	18
Drugs With Required Dose Modification Before Discontinuation	13 (68%)	11 (61%)
Oxaliplatin and 5-FU Modification	7 (38%)	8 (44%)
Oxaliplatin Without 5-FU Modification	2 (11%)	3 (16%)
Cetuximab Modification	4 (21%)	7 (39%)
Bevacizumab Discontinued	1 (5%)	2 (11%)
Adverse Events That Occurred in the Last Treatment Cycle		
With Previous Dose Reduction	13 (68%)	11 (61%)
Cetuximab Associated (eg, Rash, Diarrhea, and Stomatitis)	6	8
Cetuximab-Associated Hypersensitivity	2	2
Other Adverse Events	5	1
Without Previous Dose Reduction	6 (32%)	7 (39%)
Cetuximab Associated (eg, Rash, Diarrhea, and Stomatitis)	2	5
Cetuximab-Associated Hypersensitivity	2	1
Other Adverse Events	2	1

Abbreviation: 5-FU = 5-fluorouracil