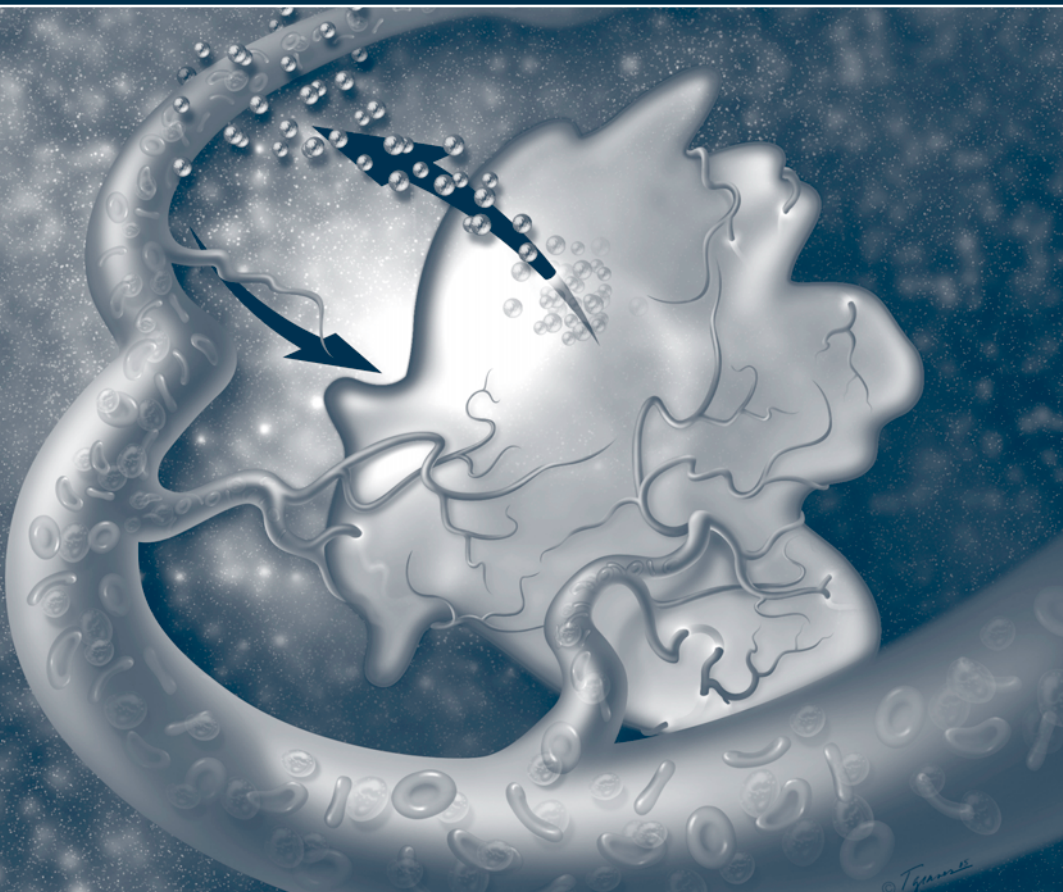


ANTI-ANGIOGENIC THERAPY IN ONCOLOGY



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STATEMENT OF NEED

Every cancer begins as a tiny cluster of abnormal cells. This stage of tumor growth can last from months to years, eventually producing proteins known as angiogenic growth factors. These are released into nearby tissues and stimulate new blood vessels to sprout vigorously from existing healthy blood vessels and into the tumor. Anti-angiogenic therapy is a new form of cancer treatment using drugs called “angiogenesis inhibitors,” which specifically halt new blood vessel growth, stabilize the patient, and in some cases, shrink tumors. Such therapy may be applied to a variety of tumor types, including colorectal, renal, non-small cell lung, prostate, breast, and pancreatic. A better understanding of these novel agents is critical for clinicians to improve the care of patients with cancer.

TARGET AUDIENCE

This activity is designed for oncologists.

ACTIVITY GOAL

The goal of this activity is to provide oncologists with medical information, which should aid them in delivering better care to their patients.

LEARNING OBJECTIVES

After completing this module, the reader should be better able to:

1. Identify many of the dose-limiting toxicities associated with conventional chemotherapies used to treat advanced colorectal cancer
2. Discuss strategies to identify patients who may intrinsically be unable to tolerate such medications
3. Describe recent studies that couple newer targeted therapies with conventional therapies from a safety standpoint

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ISSUE 5: Treatment Toxicity in Colorectal Cancer

INTRODUCTION

More agents than ever before have demonstrated efficacy against colorectal cancer (CRC) [Table 1]. Despite the increasing efficacy of chemotherapeutic regimens used in the treatment of CRC, the adverse reactions associated with some of these agents can render the patient intolerant. CRC is a chronic disease in which the long-term monitoring of side effects of a growing number of agents is crucial. Overall survival and length of therapy are continually increasing. This newsletter will discuss some of the toxicities of the agents used to treat CRC, the potential of targeted agents to minimize these toxicities, and newer treatments that can also either treat or scale down drug-related toxicities experienced by CRC patients.

5-FLUOROURACIL IS A KEY BUT TROUBLESOME CRC DRUG

5-fluorouracil (5-FU) remains, despite its longevity, an important drug in the treatment of advanced CRC.¹ 5-FU, usually coupled with leucovorin, has a variety of toxicities that vary in incidence and severity, including stomatitis (62%), diarrhea (61%), nausea (51%), and fatigue (46%).⁷ Grades 3 and 4 neutropenia are also seen in approximately 1 in 4 CRC patients.⁷ Patterns of toxicity also differ based on the dose, route (bolus vs infusion), and schedule of 5-FU administration.⁸ While a variety of 5-FU regimens are recommended in CRC,¹ the administration of 5-FU as a continuous infusion (CI) for protracted periods, instead of delivery as a bolus, improves the therapeutic index for this agent in patients with advanced CRC with respect to its safety profile, as well as response rate. This regimen is also better tolerated in elderly patients.^{1,9,10} However, a trade-off between the 2 regimens exists: hand-foot syndrome, a painful swelling and erythroderma of the soles, palms, and fingers, occurs in approximately 24% to 40% of patients who receive extended continuous IV 5-FU.¹¹ In one meta-analysis of more than 1200 advanced CRC patients, hand-foot syndrome was more frequent in the 5-FU CI group (34% vs 13%, $P<.001$).¹⁰ However, the same study showed that grade 3 or 4 hematologic toxicities were more frequent in patients assigned to 5-FU bolus (31% vs 4%, $P<.001$). The incidence and severity of stomatitis can be significantly reduced via oral cryoprophylaxis, in which the patient chews and holds ice chips in the mouth during the period between 5 minutes prior to and 30 minutes following bolus injections of 5-FU.¹¹ This protective effect appears to work on the premise that vasoconstriction caused by the ice temporarily reduces blood flow to the oral mucosa, thus decreasing drug exposure to those tissues.

Cryoprophylaxis should not be used when oxaliplatin is being used.

Furthermore, certain individuals are predisposed to 5-FU toxicity. Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in the catabolism of 5-FU. Patients with even a partial deficiency of this enzyme are at risk for developing severe 5-FU-associated toxicity.¹² One study showed that 55% of patients with decreased DPD activity suffered from grade 4 neutropenia, compared with 13% of patients with normal DPD activity ($P=.01$). In addition, the onset of toxicity occurred, on average, 2-fold faster in patients with low DPD activity compared with patients with normal DPD activity (10.0 vs 19.1 days, $P<.05$). Considering the common use of 5-FU in the treatment of CRC patients, the severe 5-FU-related toxicities in patients with a low activity of DPD warrant the analysis of DPD activity in peripheral blood mononuclear (PBM) cells prior to the start of treatment with 5-FU.

GENE VARIATION MAY PINPOINT OXALIPLATIN NEUROTOXICITY

Oxaliplatin is the integral component of the FOLFOX regimen that has emerged as standard therapy in colorectal cancer.¹ Sensory neurotoxicity (sNT) is the dose-limiting toxicity of oxaliplatin. Two forms of sNT exist: an acute reversible type, seen early in therapy, occurs in approximately 95% of patients and is self-resolvable; and a chronic type, which results from an eventual cumulative dose, affects about 15% to 20% as a grade 3 or 4 toxicity that interferes with daily activities. One study provided early evidence that variations in a gene involved in oxaliplatin detoxification, GSTP1, may serve as a predictor of susceptibility to oxaliplatin-mediated sNT.¹³ In this study, germline DNA was extracted from whole blood of 299 patients who received FOLFOX4. Patients with GSTP1 cytosine-cytosine (C/C) polymorphism at position I105V were more likely to discontinue FOLFOX due to sNT (23.7%) than patients with thymine-thymine (T/T; 9.2%) or cytosine-thymine (C/T; 10%) variants ($P<.04$). Patients with GSTP1 I105V C/C also had lower cumulative dose to onset of grade 3 sNT, compared with T/T or C/C patients ($P=.05$). Patients carrying at least one GSTP1 I105V C-allele (C/C or C/T) were more likely to experience rapid onset grade 3 neurotoxicity than T/T patients, who were more likely to tolerate high doses ($P<.03$ for grade 2; $P=.03$ for grade 3). These findings require prospective validation before GSTP1 polymorphisms can be used to identify oxaliplatin patients who might benefit from neurotoxicity prevention strategies.

TABLE 1
Agents That Demonstrate Activity
Against Colorectal Cancer

CONVENTIONAL CHEMOTHERAPY	TARGETED THERAPY
Fluoropyrimidines <ul style="list-style-type: none">• 5-FU (+LV)^{* 1}• Capecitabine^{* 1}• UFT (+LV)²• S1³	VEGF inhibition <ul style="list-style-type: none">• Bevacizumab^{* 1}
Pemetrexed ⁴	EGFR inhibition <ul style="list-style-type: none">• Cetuximab^{* 1}• Panitumumab⁵• Matuzumab⁶
Irinotecan ^{* 1}	
Oxaliplatin ^{* 1}	

^{*}Approved in the United States for treatment of advanced CRC as of September 2006
EGFR = epidermal growth factor receptor;
5-FU = 5-fluorouracil; LV = leucovorin;
S1 = tegafur, 5-chloro-2,4-dihydroxypyridine and oxonic acid;
UFT = tegafur and uracil;
VEGF = vascular endothelial growth factor.

UGT1A1 PROMOTER POLYMORPHISM PREDICTS IRINOTECAN SIDE EFFECTS

Irinotecan is indicated as a component of first-line therapy in combination with 5-FU and leucovorin for patients with metastatic CRC, as well as those whose disease has recurred or progressed following initial fluorouracil-based therapy.¹⁴ Nausea,

vomiting, and diarrhea are common adverse events following treatment with irinotecan and can be severe. Diarrhea occurs in about 84% of patients on irinotecan and is observed in 2 forms: early diarrhea accompanied by cholinergic symptoms of rhinitis, which can be prevented or ameliorated with atropine; and late diarrhea, which can be prolonged and, therefore, life-threatening, and which can be treated with loperamide and fluid replacement.¹⁴ The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in the 10% of North Americans with genetic polymorphisms that lead to reduced enzyme activity. The impact of UGT1A1 on survival and toxicity was analyzed in a group of CRC patients who received one of several chemotherapeutic regimens: IFL (irinotecan/5-FU/leucovorin), FOLFOX (oxaliplatin/5-FU/leucovorin), or IROX (irinotecan/oxaliplatin).¹⁵ While no association was observed between the genotype and diarrhea, tumor responses, time to progression, or overall survival, a strong association was noted for UGT1A1 and grade 4 neutropenia ($P=.004$ for 7/7 genotype) and for grade 3 febrile neutropenia ($P=.006$ for 7/7 genotype) in IROX patients. Patients on IFL or FOLFOX who had UGT1A1 genotypes 6/6, 6/7, or 7/7 also had significantly more grade 4 neutropenia ($P=.007$).

Thus, screening for UGT1A1 promoter polymorphism may be clinically useful for identifying patients at a higher risk of developing a severe or potentially life-threatening neutropenia or febrile neutropenia.

PREDICTIVE FACTORS FOR CAPECITABINE TOXICITY BEING STUDIED

Capecitabine is an oral fluoropyrimidine that is converted to 5-FU primarily in tumor tissue, and has the advantages of ease of administration, acceptable toxicity, and significant antineoplastic activity. However, diarrhea and hand-foot syndrome are the most common dose-limiting adverse events associated with this drug.¹¹ Mucositis, seen typically as stomatitis, also affects many patients. While these side effects are manageable, they could reduce the efficacy of the therapy to the point that the dose

TABLE 2

Selected Adverse Events Associated With the Use of Bevacizumab in the BRiTE Trial¹⁸ vs a Pivotal IFL+bevacizumab Trial¹⁹

ADVERSE EVENT*	BRiTE TRIAL (N=1960)	IFL+BEVACIZUMAB (N=402)
Hypertension requiring medication	16.4%	11.0% [†]
Grade 3 or 4 bleeding event	2.2%	3.1%
Gastrointestinal perforation	1.7%	1.5%
Arterial thromboembolic event	1.5%	4.0%
Postoperative bleeding or wound-healing complications	1.4%	2.1% [‡]

*Patients may have experienced more than 1 type of bevacizumab-associated adverse event.
[†]Grade 3 hypertension
[‡]SAEs in IFL + bevacizumab and 5-FU + bevacizumab arms (n=616)

the gene for methylene tetrahydrofolate reductase (MTHFR) may also determine a patient's risk for capecitabine toxicity. The investigators propose to study the effect of these two polymorphic enzymes on capecitabine's toxicity in adjuvant CRC patients. They anticipate that patients with certain polymorphisms will have higher rates of overall toxicity, diarrhea, neutropenia, and mucositis than those patients who do not. The expected total enrollment is 104 CRC patients.

REGIMENS THAT INCLUDE TARGETED THERAPIES GIVE MORE OPTIONS

CRC regimens that include targeted therapies may have more tolerable safety profiles and boosted efficacy compared with those that include only chemotherapeutic agents, giving clinicians and their patients more options.

BEVACIZUMAB + CHEMO REGIMENS—SAFE AS FIRST-LINE STRATEGY

The interaction of vascular endothelial growth factor (VEGF) with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Bevacizumab binds VEGF and prevents the interaction of VEGF with its receptors on the surface of endothelial cells, resulting in reduction of microvascular growth and inhibition of metastatic disease progression.¹⁷ Administration of bevacizumab can result in the development of gastrointestinal perforation; the incidence of perforation in patients receiving bevacizumab is 2.4%.¹⁷

Bevacizumab prolongs overall survival (OS) and progression-free survival (PFS) when added to standard chemotherapy for patients with metastatic CRC. BRiTE is a large, community-based observational registry of such patients receiving bevacizumab plus first-line chemotherapy. In this registry, 1960 patients were followed for up to 3 years (median 10 months), and safety data, including targeted bevacizumab-associated serious adverse events (SAEs), were updated every 3 months.¹⁸ The most commonly used chemotherapy regimens were FOLFOX (5-FU, leucovorin, and oxaliplatin; 56%); FOLFIRI (5-FU, leucovorin, and irinotecan; 14%); and IFL (irinotecan, bolus 5-FU, and leucovorin; 10%). SAEs were reported in 12% of patients, including

cannot reach its full potential. An ongoing observational prospective study is assessing whether thymidylate synthase polymorphisms can act as a predictor of toxicity to capecitabine chemotherapy in colon cancer treatment.¹⁶ As with 5-FU, capecitabine is prone to cause more severe life-threatening reactions in individuals with DPD deficiency. Also, a polymorphism in

gastrointestinal perforation (GIP), postoperative bleeding/wound healing complications, arterial thromboembolic events (ATE), and grade 3 or 4 bleeding, which were compared with SAEs in a pivotal phase 3 trial that included IFL plus bevacizumab [Table 2].¹⁹

Approximately 3% of patients discontinued bevacizumab due to drug-related toxicity, most commonly bleeding. In such patients, median time to first event was 2.1 months for GIP, 3.5 months for ATE, and 4.0 months for grade 3 or 4 bleeding. In this unselected population of patients with advanced CRC, the safety profile of bevacizumab plus various chemotherapy regimens appears consistent with that observed in the pivotal bevacizumab trial. Overall discontinuation of bevacizumab due to drug-related toxicity was uncommon, and no new bevacizumab-associated safety issues have been identified.

BEVACIZUMAB AS SECOND-LINE THERAPY IN ADVANCED PATIENTS

While bevacizumab is added to first-line chemotherapy for metastatic CRC, few trials have been conducted using the anti-angiogenesis agent as second-line therapy. In a recent study, 16 advanced CRC patients refractory to first-line chemotherapy—oxaliplatin- or irinotecan-based regimens—received the following biweekly regimen: bevacizumab 5 mg/kg infusion, irinotecan 125 mg/m² infusion plus leucovorin 30 mg/m² and 5-FU as bolus infusions.²⁰ These patients had ≥1 metastases at various sites. The results showed that 6 (37.5%) patients had partial responses (PRs), 4 (25%) had stable disease (SD), and the rest (37.5%) progressed. Time to progression (TTP) was 6.4 months (range = 4-8), and the median survival was 9 months (range = 5-12). Grade 2 toxicities included epistaxis in 4 patients (25%), anemia in 5 (31%), leukopenia in 3 (18.7%), granulocytopenia in 2 (12.5%); 1 patient developed jaundice due to bile-duct obstruction. Thus, the biweekly administration of bevacizumab, irinotecan, leucovorin, and 5-FU is acceptable as second-line treatment in patients with metastatic CRC. The study is ongoing, and more patients will be accrued.

CETUXIMAB + FOLFOX OR FOLFIRI—ENHANCING FIRST-LINE CRC TREATMENT?

Cetuximab, an IgG1 monoclonal antibody, which targets the epidermal growth factor receptor (EGFR), is approved for second-line metastatic CRC treatment. In a phase 3 study, treatment-naïve metastatic CRC patients were randomized to FOLFOX or FOLFIRI with or without cetuximab, independent of EGFR status.²¹ Patients received irinotecan 180 mg/m² or oxaliplatin 85 mg/m² infusions combined with leucovorin 400 mg/m² as infusion and 5-FU 400 mg/m² bolus, then a 46- to 48-hour continuous infusion of 5-FU 2400 mg/m² every other week. The cetuximab dose was 400 mg/m² as a loading dose, then 250 mg/m² every week. The accrual goal was 2200 patients with an intended primary endpoint of overall survival; however, the study closed early due to slow accrual

TABLE 3

Significant Toxicities Associated With FOLFOX OR FOLFIRI, With or Without Cetuximab as First-line Therapy in Metastatic CRC²¹

TOXICITY	FOLFIRI	FOLFIRI + C	FOLFOX	FOLFOX + C
Diarrhea grade 3+	9 (15%)	13 (22%)	6 (10%)	8 (14%)
Absolute neutrophil count 3+	16 (27%)	20 (34%)	21 (36%)	21 (38%)

with 238 patients enrolled. The accrual was: FOLFIRI (A), 61 patients; FOLFIRI + cetuximab (B), 59; FOLFOX (C), 60; FOLFOX + cetuximab (D), 58 with an approximate median follow-up of 12 months. The response rate (RR = CR + PR) was: A, 34%; B, 42%; C, 32%; D, 55%. RR was similar in the FOLFIRI and FOLFOX arms (A+B vs C+D; 38% vs 43%, *P*=.44), while cetuximab-containing arms (B+D) vs non-cetuximab (A+C) had a superior RR (49% vs 33%, *P*=.014). It is too early to tell if differences exist in PFS, duration of response, or OS. No significant differences in severe diarrhea or neutropenia were seen, although the FOLFIRI and cetuximab arm resulted in the most diarrhea [Table 3]. These findings imply that FOLFIRI and FOLFOX are similar in efficacy for patients with untreated metastatic CRC, and that adding cetuximab to chemotherapy appears to increase first-line response rates. In fact, further follow-up and analysis of prospective companion correlative studies may identify a true cetuximab-chemotherapy synergism.

CETUXIMAB—PROMISING IN IRINOTECAN-RESISTANT ADVANCED CRC

Cetuximab is a monoclonal antibody that binds specifically to the EGFR on EGFR-expressing tumor cells and inhibits their growth and survival.²² Severe infusion reactions occur in about 3% of patients receiving cetuximab, although rarely with fatal outcome. Cetuximab is active alone and in combination with irinotecan in metastatic CRC patients who failed with irinotecan.²³ The MABEL study investigated cetuximab plus irinotecan in an uncontrolled, multicenter study in patients with EGFR-detectable metastatic CRC whose last treatment regimen contained irinotecan.²⁴ MABEL is to date the largest cetuximab study published in this setting. Primary endpoint was the PFS rate at 12 weeks (expected rate 50% ± 3%). Study treatment was cetuximab, initial dose 400 mg/m², weekly 250 mg/m², plus irinotecan with dose and schedule as prestudy: regimen A, 125 mg/m² weekly for 4 to 6 weeks; B, 180 mg/m² every 2 weeks; or C, 350 mg/m² every 3 weeks.

Week 12 PFS rates were as follows: arm A, 60%; B, 60%; C, 63%; overall, 61%. Week 24 PFS rates were: arm A, 29%; B, 32%; C, 39%; overall, 34%. The current estimate of median survival, based on 717 deaths, is 9.2 months. Treatment was generally well tolerated, with grade 3 or 4 adverse events in more than 5% of patients, including diarrhea (20%), acne-like rash (19%), neutropenia (9%), and asthenia (8%). Grade 3 or 4 immune system disorders included hypersensitivity reactions (1.5%) and hypomagnesemia (0.4%). Thus, the PFS rates observed in this heavily pretreated population fully met the primary endpoint of this study. Estimated survival time is

consistent with previously published results. MABEL visibly confirmed the efficacy and safety of cetuximab plus irinotecan in a wider setting than had been seen in smaller studies.

PANITUMUMAB—WELL TOLERATED IN TREATMENT-EXPERIENCED EGFR+ PATIENTS

Panitumumab is the first fully human monoclonal antibody that targets the EGFR.²⁵ EGFR is activated when ligands such as epidermal growth factor (EGF) bind to it and trigger signals to encourage cell growth, anti-apoptosis, cell migration, and the production of proangiogenic factors. Panitumumab binds to EGFR, thereby preventing ligand-binding to it and interfering with the signals that would otherwise stimulate growth of the cancer cell and allow it to survive.²⁶

In a multicenter, phase 2 study, patients had documentation of progressive disease (PD) during or following adequate doses and 2 to 3 regimens of fluoropyrimidine, irinotecan, and oxaliplatin, as well as EGFR staining in 10% or more of evaluable tumor cells.²⁵ Patients were then administered panitumumab every 2 weeks until PD. Tumor assessments (modified WHO, blinded central review) were taken periodically from weeks 8 to 48 until PD. Study endpoints were objective response rate at week 16, as well as throughout the study, response duration, PFS time, survival time, and safety. In the interim analysis, 91 enrolled patients received at least one dose of panitumumab; 39 were evaluated.

At week 16, 3 (8%) had a PR, 8 (21%) had SD, and 19 (49%) had PD as best overall response (OR) (9 not done/unevaluable). In the safety set of 39 patients, 96% had at least one treatment-related adverse event (24% grade 3, 1% grade 4). Integument and eye toxicities were: 96% skin, 30% nail, 8% eye, 5% hair, and 7% cheilitis. Twenty-five (27%) had diarrhea (3 grade 3); 11 (12%) had hypomagnesemia (3 grade 3 or 4). One patient had a grade 3 hypersensitivity reaction considered related to panitumumab that was treated and resolved with the patient continuing treatment with premedication; no further reactions occurred. In 66 patients with both a baseline and postdose sample, no human antihuman antibodies to panitumumab were detected. Thus, panitumumab has antitumor activity and is well tolerated in patients with EGFR tumor expression levels of at least 10% who failed standard chemotherapy.

CONCLUSIONS

Conventional chemotherapeutic agents remain useful in treating advanced CRC. As research continues, criteria for selecting patients who will better tolerate these agents are being identified. In addition, varied combinations and treatment schedules may also improve tolerability. At the same time, targeted therapies with improved therapeutic index are being combined with traditional therapies to make regimens for advanced CRC more effective and potentially safer. ■

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EVALUATION

1. How well did the activity meet the identified Statement of Need?
2. How would you rate your satisfaction with this activity?
3. How well did this activity help you meet the following objectives?
 - a. Identify many of the dose-limiting toxicities associated with conventional chemotherapies used to treat advanced colorectal cancer
 - b. Discuss strategies to identify patients who may intrinsically be unable to tolerate such medications
 - c. Describe recent studies that couple newer targeted therapies with conventional therapies from a safety standpoint
4. Evaluate whether the activity was free from commercial bias.
5. Assess the degree to which this activity is helpful in your practice.
6. How would you rate the objectivity, balance, and scientific rigor of this activity?
7. How does this activity rate in comparison to other activities that you have participated in?

Send other comments to
CME@montefiore.org

Anti-angiogenic Therapy in Oncology POSTTEST

1. Which of the following agents has not yet been approved in the United States for treatment of advanced CRC?
 - A. Capecitabine
 - B. Panitumumab
 - C. Irinotecan
 - D. Bevacizumab
2. Which of the following statements is true about 5-FU administration?
 - A. More severe hematologic toxicities are seen with bolus administration than continuous infusion (CI)
 - B. More hand-foot syndrome is seen with bolus administration than CI
 - C. Bolus administration improves the therapeutic index for 5-FU in advanced CRC patients
 - D. No clinical differences exist between bolus and CI administration of 5-FU
3. The rationale for using oral cryotherapy to reduce the incidence and severity of 5-FU-induced stomatitis is based on:
 - A. The ability of the ice to numb the nerves in the oral mucosa
 - B. Local vasoconstriction that reduces blood, and therefore, drug flow to the tissues
 - C. The capacity of the ice to give the patient an activity on which to focus during infusion
 - D. All of the above
4. What is the dose-limiting toxicity of oxalipatin?
 - A. Neutropenia
 - B. Nausea
 - C. Neuropathy
 - D. Nephrotic syndrome
5. Which of the following is not true about the early form of diarrhea observed with irinotecan therapy?
 - A. About 84% of patients on irinotecan are affected
 - B. It is accompanied by cholinergic symptoms of rhinitis
 - C. It can be prevented or ameliorated with atropine
 - D. It should be treated with loperamide
6. In a study that assessed the use of bevacizumab as second-line therapy in metastatic CRC, the agent was given:
 - A. Biweekly
 - B. Twice weekly
 - C. Bimonthly
 - D. Weekly
7. In an analysis of the BRIT registry, in which CRC patients on various 5-FU-based regimens were also given bevacizumab, which was the most commonly observed side effect?
 - A. Arterial thromboembolic event
 - B. Gastrointestinal perforation
 - C. Grade 3 or 4 bleeding event
 - D. Hypertension requiring medication
8. In the study that assessed FOLFIRI and FOLFOX, with or without cetuximab, which treatment arm resulted in the most diarrhea?
 - A. FOLFIRI
 - B. FOLFIRI plus cetuximab
 - C. FOLFOX
 - D. FOLFOX plus cetuximab
9. Cetuximab is active alone and in combination with irinotecan in metastatic CRC patients who failed irinotecan.
 - A. True
 - B. False
10. Panitumumab is the first fully human monoclonal antibody that targets:
 - A. VEGFR
 - B. EGFR
 - C. PDGFR
 - D. Raf and Kit signaling

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POSTTEST

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EVALUATION

	<i>Poor</i>	<i>Satisfactory</i>	<i>Good</i>	<i>Very Good</i>	<i>Excellent</i>
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Last Name: _____ First Name: _____
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Degree: MD DO Other Please specify: _____

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Comments: _____

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