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Colorectal Cancer™ UPDATE

Conversations with Oncology Research Leaders
Bridging the Gap between Research and Patient Care

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This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ColorectalCancerUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**.

Colorectal Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Colorectal cancer is among the most common cancers in the United States, and the arena of colorectal cancer treatment continues to evolve. Published results from ongoing clinical trials lead to the emergence of new therapeutic agents and regimens and changes in indications, doses and schedules for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well-informed of these advances.

To bridge the gap between research and patient care, *Colorectal Cancer Update* utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment.
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy.
- Develop and explain a management strategy for patients with metastatic colorectal cancer.
- Describe ongoing clinical trials in colorectal cancer and counsel patients about the availability of ongoing clinical trials.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 3 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Minsky, Kemeny, Giantonio and Smith on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

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Nancy E Kemeny, MD	Grants/Research Support, Consultant and Honorarium: Codman & Shurtleff Inc, Pharmacia & Upjohn SpA, Sanofi-Synthelabo Inc
Bruce J Giantonio, MD	Consultant: Genentech BioOncology Stock Shareholder: Merck and Company Inc
Roy E Smith, MD, MS	No financial interests or affiliations to disclose

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
5-FU (fluorouracil)	Various	Various
bevacizumab	Avastin™	Genentech BioOncology
capecitabine	Xeloda®	Roche Laboratories Inc
erythropoietin	Procrit®	Ortho Biotech Products LP
	Epogen®	Amgen Inc
dexamethasone	Various	Various
floxuridine	FUDR™	Mayne Pharma USA
glutathione	Various	Various
hydrochlorothiazide	Various	Various
irinotecan	Camptosar®	Pfizer Inc
leucovorin calcium	Various	Various
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc

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Editor's Note

One year later

According to Norman Wolmark, colorectal cancer control took its most significant step forward in more than a decade during the 2003 ASCO meeting in Chicago. In an interview for this audio series, the NSABP chairperson noted that for the first time in his memory, more attendees were present at the ASCO GI session than the breast cancer assembly. Whether the audience anticipated the monumental nature of the data or simply had a heightened interest in colorectal cancer, one thing is certain: Two stunning presentations from ASCO have had an immediate and permanent impact on daily patient care and clinical trial design.

First, Aimery de Gramont presented the initial findings of the MOSAIC adjuvant trial, which demonstrated a significant three-year disease-free survival advantage for the oxaliplatin-containing FOLFOX4 regimen compared to 5-FU/leucovorin. While we await more mature analyses of overall survival, many oncologists have immediately embraced the many variations of FOLFOX as off-protocol adjuvant treatment options, and for some, the use of adjuvant regimens containing oxaliplatin has become a new standard of care.

In a recent program, Richard Goldberg previewed an upcoming 2004 ASCO presentation from his group that will document the close historical correlation between three-year disease-free survival and five-year overall survival in adjuvant trials. This will likely provide an even greater incentive for the use of adjuvant FOLFOX in both clinical practice and research trials.

When I interviewed Dr Wolmark during the NSABP meeting just weeks after the 2003 ASCO meeting, he described a new adjuvant study — NSABP protocol C-08 — that had just been presented to the group. Of interest, all three of the control arms for this study contained oxaliplatin. In this issue of *Colorectal Cancer Update*, Dr Roy Smith updates us on the evolution of this trial — which is still being finalized — and several other new trials being launched by the NSABP.

The original adjuvant trial discussed in June 2003 was a three-by-two factorial design attempting to answer two important research questions: What is the optimal oxaliplatin-containing regimen, and what is the adjuvant role of the anti-VEGF factor bevacizumab? The NSABP wished to compare FLOX, the experimental arm of its prior study (C-07), to FOLFOX6 and CAPOX. Although the results of C-07 are not yet available, based on the MOSAIC results, the NSABP trialists were betting that C-07 would show FLOX to be superior to 5-FU/leucovorin.

The NSABP meeting generated a great deal of enthusiasm about CAPOX as adjuvant therapy. This regimen substitutes the oral fluoropyrimidine prodrug capecitabine for continuous infusion 5-FU. The CAPOX regimen not only offers

the possibility of less hassle for patients and doctors, but perhaps an even greater antitumor effect based on the intratumoral activation of this agent.

Dr Smith notes that since this original concept was presented last year, C-08 has been refined and now focuses only on FOLFOX and the bevacizumab question. The rapid evolution of clinical and laboratory research in colorectal cancer has created an imprimatur to complete trials quicker. One of the major reasons that this trial was streamlined was to decrease accrual numbers so it could be completed more expeditiously.

Although the CAPOX arm of the proposed NSABP-C-08 trial was dropped, this patient-friendly regimen is still the basis for another fascinating study that is winding its way through regulatory processes, NSABP-C-09, which compares CAPOX alone to CAPOX plus intrahepatic infusion of floxuridine in patients who have had resection or ablation of hepatic metastases. In this issue, Nancy Kemeny comments on C-09 and her own landmark research on therapy for patients with liver-only disease.

Another NSABP trial discussed last year and still lumbering through the system is R-04, a study combining preoperative radiation therapy with capecitabine or infusional 5-FU. Bruce Minsky provides an update on clinical research in rectal cancer and discusses the possibility that capecitabine might be not only more convenient but perhaps also more effective in this setting.

The other groundbreaking news at the 2003 ASCO meeting was the significant progression-free and overall survival advantage associated with the addition of bevacizumab to IFL in patients with metastatic disease as presented by Herb Hurwitz. This paper, a milestone in colorectal cancer research, spawned a plethora of new trials evaluating this agent in the adjuvant setting, including NSABP-C-08.

Bruce Giantonio updates us on the ongoing clinical research with “bev” and notes that his own ECOG trial will answer perhaps the most pressing current question related to this antiangiogenic agent — whether combining it with oxaliplatin will produce treatment benefits similar to those seen with the combination of bevacizumab and IFL. Those data from ECOG-3200 are not yet available, but the hope is that the synergism between irinotecan and bevacizumab will generalize to other cytotoxic agents. Clearly the NSABP-C-08 adjuvant trial has this as its premise, which is particularly salient in view of the apparent lack of benefit seen with adjuvant IFL.

Personally, I find it somewhat disappointing that some of these trials are not yet up and running. As discussed by Dr Smith, large cooperative studies often take years to activate. I have no doubt there are excellent reasons to explain this, particularly to ensure that participating patients are protected. On the other hand, people with this disease and their doctors want answers now, and frankly, it is troubling that they have to wait so long.

— Neil Love, MD
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German trial of preoperative chemoradiation in rectal cancer

A German trial presented at the 2003 American Society for Therapeutic Radiology Oncology meeting evaluated preoperative versus postoperative chemoradiation in rectal cancer.

This landmark study in patients with ultrasound-confirmed Stage T3-T4 or node-positive rectal cancer was unique in that it was actually completed. Two prior studies — an Intergroup trial and NSABP-R-03 — failed because of lack of accrual. Importantly, all patients underwent a total mesorectal excision, which is now considered the standard of care for surgery. Additionally, all patients were stratified by surgeon, which is important because surgical bias exists in terms of sphincter preservation. In stratifying by surgeon, that bias is essentially removed.

The overall results of the study (Figure 1.1) are positive in that local recurrence significantly decreased from 11 percent to seven percent with preoperative therapy. Second, there was a significant decrease in both short- and long-term toxicity. Third, and most important, preoperative therapy resulted in a doubling of sphincter preservation rate from approximately 20 percent to 40 percent.

As predicted, disease-free and overall survival did not change. Another interesting finding was that there was no difference in the incidence of distant metastatic disease, which suggests that if a patient needs chemoradiation, the ideal time to deliver it is preoperatively. However, we clearly need to develop better systemic therapies to integrate into preoperative chemoradiation, as we have done for patients with advanced disease. The replacement study of the German trial will use the current preoperative arm, which is a continuous infusion of 5-FU plus preoperative radiation therapy, and compare that with capecitabine plus oxaliplatin (CAPOX), with radiation as a somewhat more intensive preoperative regimen.

Dr Minsky is Vice Chairman of the Department of Radiation Oncology at the Memorial Sloan-Kettering Cancer Center and Professor of Radiation Oncology in Medicine at the Weill Medical College of Cornell University in New York, New York.

Figure 1.1

German Rectal Cancer Study of Preoperative versus Postoperative Chemoradiation Therapy (CRT): Efficacy and Side Effects (Median follow-up 43 months)

	Pre-op CRT (n=405)	Post-op CRT (n=392)
5-year pelvic recurrence rate	7%	11%
5-year distant recurrence rate	30%	34%
DFS	59%	55%
OS	78%	73%
Chronic anastomotic stenosis	2.7%	8.5%

"Compared with postop CRT, preop CRT significantly improved local control and in low lying tumors, sphincter preservation. There was a trend to reduced acute toxicity and significantly less chronic toxicity at the anastomotic site…
"In the subgroup of 188 patients with low-lying tumors who were declared by the surgeon prior to randomization to require an abdominoperineal resection, 19% (16/83) underwent a sphincter preserving procedure in the postop CRT arm. This was significantly increased to 39% (41/105) following preop CRT ($p = 0.004$)."

SOURCE: Sauer R. **Adjuvant versus neoadjuvant combined modality treatment for locally advanced rectal cancer: First results of the German Rectal Cancer Study (CAO/ARO/AIO-94).** *Int J Radiat Oncol Biol Phys* 2003;57(Suppl 2):124-5;**Abstract 2**.

Incorporation of capecitabine with preoperative radiation therapy

Emerging data support combining capecitabine and oxaliplatin with radiation therapy. The most interesting data comes from the German group led by Claus Rödel, who published his experience in the August 2003 issue of the *Journal of Clinical Oncology*. He performed a well-designed Phase I/II study evaluating the doses of capecitabine and oxaliplatin appropriate to combine with radiation therapy.

NSABP-R-04 is a new preoperative study in which the experimental arm is capecitabine plus radiation therapy versus the standard arm, which is continuous infusion 5-FU with radiation therapy. Initially, there was going to be a secondary randomization to erythropoietin or no erythropoietin, but that has been dropped. The study is now going forward, although it has been in negotiation with the Cancer Therapy Evaluation Program (CTEP) for approximately two years. There is still some debate because many oncologists have already adopted the experimental arm, capecitabine, as one of their treatment programs.

I want to emphasize that capecitabine is not yet the standard of care. Continuous infusion 5-FU remains the standard of care, and this would be the first study in which capecitabine is directly compared to the continuous infusion. In all of the other randomized studies in both metastatic and adjuvant colon cancer, capecitabine was compared to bolus 5-FU. This would be a valuable study, but I'm not sure if people want to wait five or seven years for the answer.

Adjuvant capecitabine versus continuous infusion 5-FU

I'm not certain capecitabine will be more efficacious than continuous infusion 5-FU, but laboratory data suggest that capecitabine is a radiosensitizer, and radiation therapy increases the activity of capecitabine by upregulating thymidine phosphorylase (TP).

There are many reasons to combine capecitabine and radiation therapy. Many of the new Phase I and II studies in the United States and Europe are using capecitabine in combination with newer agents. For example, a new RTOG study will be opening over the course of the next few months in which patients will be randomly assigned to preoperative capecitabine/oxaliplatin and radiation therapy versus irinotecan/capecitabine and radiation therapy. It is clear where development is going, at least in the investigational approach, and I suspect that's how we will treat colorectal cancer over the next year or two.

The primary motivation for using capecitabine will probably be one of convenience. Many people ask if we are ready to use capecitabine with radiation therapy today, and my answer is "not quite yet." I'm waiting to see the results of the X-ACT study, which is an adjuvant study of colon cancer patients comparing the Mayo Clinic regimen to capecitabine. It is designed to determine whether capecitabine and 5-FU are equivalent. We hope to see results reported at ASCO in 2004. If that study demonstrates equivalence, then I would feel comfortable substituting capecitabine for 5-FU.

Select Publications

Cassidy J et al. **First-line oral capecitabine therapy in metastatic colorectal cancer: A favorable safety profile compared with intravenous 5-fluorouracil/leucovorin.** *Ann Oncol* 2002;13(4):566-75. **Abstract**

Hoff PM et al. **Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study.** *J Clin Oncol* 2001;19(8):2282-92. **Abstract**

Rodel C et al. **Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer.** *J Clin Oncol* 2003;21(16):3098-104. **Abstract**

Sauer R. **Adjuvant versus neoadjuvant combined modality treatment for locally advanced rectal cancer: First results of the German Rectal Cancer Study (CAO/ARO/AIO-94).** *Int J Radiat Oncol Biol Phys* 2003;57(2 Suppl):124-5;**Abstract 2**.

Scheithauer W et al. **Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: Safety results of a randomized, Phase III trial.** *Ann Oncol* 2003;14(12):1735-43. **Abstract**

Twelves C et al. **Capecitabine (Xeloda) improves medical resource use compared with 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma.** *Eur J Cancer* 2001;37(5):597-604. **Abstract 2**

Van Cutsem E et al. **Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: Integrated efficacy data and novel analyses from two large, randomised, phase III trials.** *Br J Cancer Br J Cancer* 2004;90(6):1190-7. **Abstract**

Van Cutsem E et al. **Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study.** *J Clin Oncol* 2001;19(21):4097-106. **Abstract**

Nancy E Kemeny, MD

EDITED COMMENTS

Addition of dexamethasone and leucovorin to hepatic arterial infusion (HAI) FUDR

FUDR is the drug that we used for the hepatic infusion during our initial trials. You don't see diarrhea, vomiting and hair loss with this type of therapy. The major side effect is hepatic toxicity and the most serious toxicity occurs when the bile ducts are damaged.

The hepatic artery feeds the bile ducts just like it does the tumor, therefore profusing the artery and getting rid of the tumor will also affect the ducts.

We thought that this damage was an inflammation so we decided to add dexamethasone. By doing so, we were able decrease the number of patients with elevated bilirubins, but even more interestingly we also increased the response rate and the survival compared to FUDR alone. We couldn't understand why this happened, but when we went back to the laboratory we found out that dexamethasone actually increases the cytotoxicity of FUDR.

We also experimented by adding leucovorin to our regimen because in systemic trials, the addition of leucovorin increased response rates of 5-FU. We observed responses as high as 73 percent in patients with metastatic disease, and those were the days when the response rate with 5-FU/leucovorin was about 20 percent.

Intergroup trial comparing HAI versus systemic therapy

Last year at ASCO we presented the results of a large Intergroup trial comparing 5-FU/leucovorin, which was the best combination at that time, to hepatic arterial infusion (Figure 2.1). The study took years to complete and accrual was very slow for several reasons.

Patients who want hepatic therapy do not want to be randomly assigned to receive systemic therapy, and at the time, some institutions believed in hepatic therapy while others believed in systemic therapy. Another problem with the study was that there was no crossover.

Dr Kemeny is an Attending Physician at the Memorial Sloan-Kettering Cancer Center and Professor of Medicine at the Weill Medical College of Cornell University in New York, New York.

Patients with less than 70 percent liver-only involvement who were not previously treated with systemic therapy — except for adjuvant therapy completed 12 months before entry — were eligible for the study. We accrued 140 patients, of whom 79 percent entered the trial with synchronous disease. Presentation with liver metastases is an adverse prognostic variable, and those patients usually do much worse in terms of survival.

Median survival was 22.7 months for the hepatic group and 19.8 months for the systemic group. The response rate was 51 percent for the hepatic group and 24 percent for the systemic group. In patients with less than 50 percent liver involvement, the median survival was 27 months with hepatic arterial treatment. Patients with more than 50 percent liver involvement based on CAT scan usually have a very poor prognosis.

Figure 2.1

Randomized Study of HAI Floxuridine versus the Mayo Clinic Regimen in Patients with Liver Metastases Only: Efficacy Endpoints

	HAI (n=68)	Mayo Clinic regimen (n=67)	*p*-value
CR + PR	48%	25%	0.009
Median survival	22.7 mo	19.8 mo	0.027
Median survival with less than 50% liver involvement	27.3 mo	21.0 mo	0.017
Median time to progression	5.3 mo	6.8 mo	0.8
Median time to hepatic progression	9.8 mo	7.3 mo	0.017
Median time to extrahepatic progression	7.8 mo	23.3 mo	0.0007

SOURCE: Kemeny NE et al. **Hepatic arterial infusion (HAI) versus systemic therapy for hepatic metastases from colorectal cancer: A CALGB randomized trial of efficacy, quality of life (QOL), cost effectiveness, and molecular markers.** *Proc ASCO* 2003;**Abstract 1010**.

MSKCC trial of HAI plus systemic therapy after hepatic resection

We know that surgical removal of the tumor results in better survival. However, we also know that about 70 percent of patients have a recurrence after surgery, and about half of those recurrences are confined to the liver.

At Memorial, we decided to add hepatic arterial therapy plus systemic therapy after resection to give maximum treatment. We felt if we could treat aggressively, both in the liver and systemically, we could potentially improve survival and decrease the rate of recurrence.

We designed a randomized study comparing hepatic arterial therapy with floxuridine and dexamethasone plus systemic therapy with 5-FU/leucovorin versus systemic 5-FU/leucovorin alone. We chose not to have a complete control

arm because we didn't think we'd get accrual, so one group received combined treatment and one group received systemic therapy alone.

The usual two-year survival for nonresectable metastatic disease is 20 percent; the five-year survival rate for resectable disease without any treatment is 30 percent. In this trial, the two-year survival rate was 86 percent for the combined treatment arm and 62 percent for the systemic therapy alone arm. At five years, the survival rates were 56 percent versus 45 percent, respectively. We now have 10-year data that indicate a survival rate of 40 percent in patients who received combined therapy versus 20 percent in patients who received systemic therapy alone. The *p*-value for the entire curve is still not significant, but we only had 156 patients.

The patients who were alive at 10 years were mostly free of disease. We saw some recurrences in both arms of the study; however, 70 percent of patients in the combined therapy group have not had a liver recurrence compared to only 40 percent in patients who received systemic therapy alone. That is a very significant difference even though the study wasn't powered to evaluate that.

NSABP-C-09: Capecitabine/oxaliplatin (CAPOX) versus CAPOX plus HAI floxuridine

The NSABP has designed a proposed study comparing oxaliplatin/capecitabine and oxaliplatin/capecitabine in combination with the pump. I was somewhat surprised that they initiated this study without even looking at our data. We have found that when you use oxaliplatin with the pump, it's harder to get the pump treatment in. Oxaliplatin must affect the liver more than irinotecan because with oxaliplatin you have to reduce the floxuridine dose a bit and it causes more toxicity. We know that in patients receiving oxaliplatin before surgery, a lot of fatty changes are observed during the procedure. It may be that the drug is affecting the liver more than we think.

I believe pilot studies should be done before adjuvant studies, and you should have more data before you subject a lot of patients to a randomized study. The NSABP went very quickly into the adjuvant arena without a real pilot study.

Select Publications

Kemeny MM et al. **Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy—an intergroup study.** *J Clin Oncol* 2002;20(6):1499-505. **Abstract**

Kemeny N et al. **Phase I/II study of hepatic arterial therapy with floxuridine and dexamethasone in combination with intravenous irinotecan as adjuvant treatment after resection of hepatic metastases from colorectal cancer.** *J Clin Oncol* 2003;21(17):3303-9. **Abstract**

Kemeny NE et al. **Hepatic arterial infusion (HAI) versus systemic therapy for hepatic metastases from colorectal cancer: A CALGB randomized trial of efficacy, quality of life (QOL), cost effectiveness, and molecular markers.** *Proc ASCO* 2003;**Abstract 1010**.

MOSAIC trial

An impressive five-percent improvement in disease-free survival was seen with the addition of oxaliplatin in the MOSAIC trial. We have been using 5-FU/leucovorin for a decade, and I believe this is the first promising data indicating that there's an agent that can improve efficacy without compromise.

The concern with oxaliplatin is neurotoxicity, although in my experience, this toxicity isn't as troubling as anticipated. In the adjuvant setting, the intent is cure, so some degree of neurotoxicity may be acceptable. In advanced disease, patients who perceive a clinical benefit from the drug may be willing to tolerate some side effects. However, not all patients feel this way. It's not clear whether agents that might prevent or ameliorate neurotoxicity, such as glutathione, calcium and magnesium, interfere with the effectiveness of oxaliplatin. These must be used cautiously and further studied.

Capecitabine in the metastatic and adjuvant settings

SWOG-S0303 is a Phase III trial with a two-by-two factional design, comparing FOLFOX versus CAPOX — both regimens with or without bevacizumab — in patients with advanced colorectal cancer (Figure 3.1). Off protocol, in front-line therapy, I currently use FOLFOX4 because the data is strongest for that regimen, or FOLFOX6, which is easier on patients.

The data demonstrate that capecitabine is active, but we don't know how it compares with other regimens, and a myriad of regimens are now available. Capecitabine is an interesting drug with several advantages. Many patients prefer an oral agent. In rural communities, infusional therapies may not be an option. In the nonprotocol setting, I believe capecitabine is a reasonable choice for front-line therapy, and this trial will determine whether it is equivalent to FOLFOX.

I don't believe capecitabine/oxaliplatin in the adjuvant setting is advisable at this time. The data is not conclusive and because the intent is cure, one should be cautious about veering away from proven therapies.

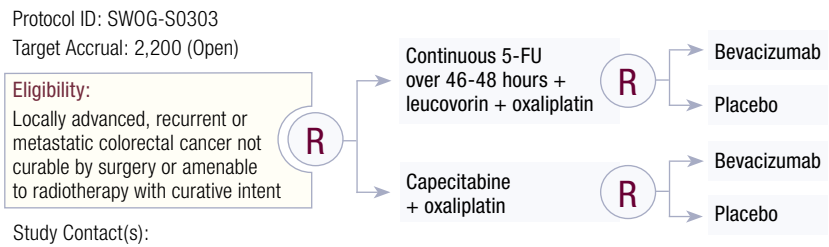
Dr Giantonio is an Assistant Professor of Medicine at the Abramson Cancer Center of the University of Pennsylvania in Philadelphia, Pennsylvania.

Mechanism of action of angiogenesis inhibitors

In a study presented by Herb Hurwitz at ASCO, adding bevacizumab to IFL proved to be clinically beneficial. It also proved that Dr Folkman's angiogenesis hypothesis, at least in this disease, is very likely to be true, although there are several theories as to how angiogenesis inhibitors interface with chemotherapy. One hypothesis is that tumors have a very disorganized vasculature and bevacizumab helps to stabilize that, which enhances the penetration of chemotherapeutic agents into the tumor. Bevacizumab clearly interrupts the signaling with VEGF and its receptor. I believe the long-term effect is disruption of the tumor's ability to develop its own blood supply, but there's probably also some disruption of maintenance or autocrine signaling that has an immediate effect.

Figure 3.1

Phase III Study of Fluorouracil/Leucovorin and Oxaliplatin versus Capecitabine and Oxaliplatin with or without Bevacizumab



SOURCE: NCI Physician Data Query, April 2004.

Bevacizumab-related hypertension and bleeding

Our data shows a relationship between bevacizumab and hypertension and low-grade bleeding, which is mirrored by Dr Hurwitz's data. The small increase in Grade III and IV hypertension may be a result of the drug's impact on the vasculature and the glomerulus in the kidney. Management depends on the patient, the grade and whether they are on an antihypertensive drug. For Grade III or IV, I don't recommend using bevacizumab until it's resolved to at least Grade I. For Grade I hypertension, I add hydrochlorothiazide, assuming there's no contraindication, and if they are already on hydrochlorothiazide or a similar agent, I try adjusting the dose to bring it under control.

In ECOG-2200, the Phase II study of IFL/bevacizumab, approximately 38 percent of the patients had some degree of bleeding, but the vast majority of those events were Grade I and mostly epistaxis. ECOG-3200 excluded patients who required therapeutic anticoagulation, and we did not see much difference between the arms in the rates of Grade III or IV bleeding, which was Dr Hurwitz's experience as well. I believe we still need to monitor these patients, but right now we are not seeing a bleeding rate that suggests it's a significant concern.

Combination of IFL and bevacizumab in Phase II and III trials

When we look at the data from our Phase II study of IFL/bevacizumab, ECOG-2200, with the caveat that it's not legitimate to compare Phase II to Phase III trials, our numbers are comparable to Hurwitz's. In ECOG-2200 the primary endpoint was improvement in progression-free survival. The reported norm for IFL is seven months, but the median progression-free survival in patients who also took bevacizumab is 10 months. Currently, the response rate is approximately 49 percent and although we have not yet reached the survival endpoint, the one-year survival rate is 84 percent.

ECOG-3201: Comparison of three chemotherapy regimens in the treatment of rectal cancer

ECOG-3201 is a Phase III adjuvant study in which patients are randomly assigned to three different chemotherapy regimens — irinotecan/5-FU/leucovorin versus oxaliplatin/5-FU/leucovorin versus 5-FU/leucovorin — for the management of Stage II or III rectal cancer. A unique aspect of this study is that the treating physician (rather than the protocol) decides whether the patient receives chemoradiation before or after surgery, which also affects randomization. This gives the physician greater flexibility, which should improve accrual. We've learned to design studies that are more user-friendly while maintaining scientific integrity.

Select Publications

Benson AB et al. **Bevacizumab (anti-VEGF) plus FOLFOX4 in previously treated advanced colorectal cancer (advCRC): An interim toxicity analysis of the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* 2003;**Abstract 975**.

Giantonio BJ et al. **Bevacizumab (anti-VEGF) plus IFL (irinotecan, fluorouracil, leucovorin) as front-line therapy for advanced colorectal cancer (advCRC): Results from the Eastern Cooperative Oncology Group (ECOG) Study E2200.** *Proc ASCO* 2003;**Abstract 1024**.

Giantonio BJ et al. **Incorporating angiogenesis inhibition with bevacizumab (anti-VEGF) into frontline chemotherapy with irinotecan (CPT-11), fluorouracil and leucovorin (FU/LV) for advanced colorectal cancer (advCRC): A toxicity analysis of ECOG study E2200.** *Proc ASCO* 2002;**Abstract 503**.

Goldberg RM et al. **A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer.** *J Clin Oncol* 2004;22(1):23-30. **Abstract**

Gray R et al. **The safety of adding angiogenesis inhibition into treatment for colorectal, breast, and lung cancer: The Eastern Cooperative Oncology Group's (ECOG) experience with bevacizumab (anti-VEGF).** *Proc ASCO* 2003;**Abstract 825**.

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646**.

Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Roy E Smith, MD, MS

EDITED COMMENTS

MOSAIC adjuvant trial: Implications for clinical practice

The MOSAIC trial certainly had an impact on clinical practice. Ultimately, at least for the short-term, the paradigm of adjuvant therapy will switch to infusional 5-FU therapy. The data has just been published and already members of the Intergroup have decided to largely abandon FOLFOX4, which was used in the MOSAIC trial, in favor of a modified FOLFOX6 or even FOLFOX7 regimen to make it more practical for infusional therapy in the United States.

The implication is that if you had a noninfusional therapy that was equivalent or better, our treatment paradigm would immediately shift to oral therapy. Our future treatment approach may be the use of a CAPOX-type regimen or capecitabine plus another agent.

NSABP-R-04: Preoperative prolonged 5-FU venous infusion versus capecitabine during radiotherapy for resectable rectal cancer

NSABP-R-04 (Figure 4.1) was designed to be a preoperative study for patients with resectable rectal cancer because our R-03 study, which was a comparison of preoperative versus postoperative chemoradiation therapy, failed accrual — as had others in the United States. There was no real equipoise among our membership in how these individuals should be treated. Approximately one-half of our surgeons felt that these patients should be treated with preoperative therapy, and one-half believed it should be postoperative. Therefore, it was unethical to enroll patients in the trial.

We convened a group of 40 to 50 rectal surgeon specialists and members of the Cancer Therapy Evaluation Program (CTEP) to decide on our next trial design. We concluded it would be far better to simply choose a preoperative trial or a postoperative trial. At that time, we were approached by a large group of rectal surgeons who have formed a nonfunded cooperative group in the United States, and they asked us to help design and implement a rectal trial — but they preferred that it be preoperative.

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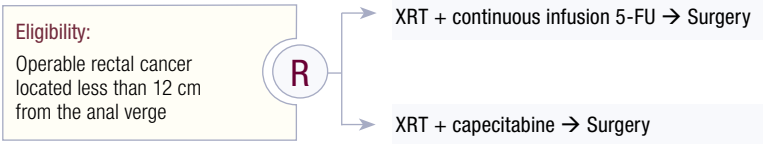
Our rectal surgeon specialists also preferred a design that would guarantee patient compliance as much as possible, so we considered incorporating capecitabine. The evidence that radiation therapy upregulated thymidine phosphorylase levels — the target enzyme for the activation of conversion of capecitabine to 5-FU — suggested a reasonable possibility for synergism between capecitabine and radiation therapy, so we chose to compare capecitabine and radiation therapy versus infusional 5-FU and radiation therapy.

Figure 4.1

Phase III Trial of Preoperative Chemoradiation in Patients with Carcinoma of the Rectum

Protocol ID: NSABP-R-04
Target Accrual: 1,606 (Pending activation)*



*Protocol being revised and resubmitted to the NCI.

All patients are encouraged to receive adjuvant therapy after surgery, which may include enrollment in a clinical trial.

SOURCE: NSABP-R-04 protocol, November 2003.

NSABP-C-09: CAPOX with or without intrahepatic floxuridine infusion after resection or ablation of liver metastases

NSABP-C-09 is designed so that patients with more than six individual hepatic metastases will not be eligible. Eligible patients will be treated by either surgery or ablation or a combination of the two, with quality control parameters to ensure that those procedures adequately remove the tumor burden from the liver.

Patients are randomly assigned to CAPOX or CAPOX plus hepatic arterial infusion floxuridine. During the first four cycles, the floxuridine and the capecitabine are staggered so that the patients do not receive it concurrently. The rationale for using capecitabine is that there is not only increased thymidine phosphorylase activity in the tumor but also in the liver.

Theoretically, the oral delivery of capecitabine may have the same effect as delivering intrahepatic chemotherapy because conversion of capecitabine to 5-FU results in increased concentrations of 5-FU in both tumor tissue and normal liver tissue.

We felt if we administered the floxuridine and the capecitabine simultaneously we might encounter significant toxicity and liver function problems. So, we decided to stagger their administration. After the floxuridine is administered, the two

arms equilibrate in terms of their design and how the capecitabine and oxaliplatin are administered. The purpose of the study is to determine whether intrahepatic infusion is really necessary in that setting.

Select Publications

Corvo R et al. **Radiotherapy and oral capecitabine in the preoperative treatment of patients with rectal cancer: Rationale, preliminary results and perspectives.** *Tumori* 2003;89(4):361-7. **Abstract**

de Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** *Proc ASCO* 2003;**Abstract 1015**.

Dunst J et al. **Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer.** *J Clin Oncol* 2002;20(19):3983-91. **Abstract**

Hyams DM et al. **A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: A progress report of National Surgical Breast and Bowel Project Protocol R-03.** *Dis Colon Rectum* 1997;40(2):131-9. **Abstract**

Lin EH et al. **A phase II study of capecitabine and radiotherapy plus concomitant boost in patients (pts) with locally advanced rectal cancer (LARC): Preliminary safety analysis.** *Proc ASCO* 2003;**Abstract 1152**.

Maung K. **Integrating oxaliplatin and capecitabine in adjuvant therapy of high-risk colorectal cancer.** *Clin Colorectal Cancer* 2003;3(3):150-3. **Abstract**

Pfeiffer P et al. **Short-time infusion of oxaliplatin (Eloxatin) in combination with capecitabine (Xeloda) in patients with advanced colorectal cancer.** *Acta Oncol* 2003;42(8):832-6. **Abstract**

Rodel C et al. **Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer.** *J Clin Oncol* 2003;21(16):3098-104. **Abstract**

Scheithauer W et al. **Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer.** *J Clin Oncol* 2003;21(7):1307-12. **Abstract**

Souglakos J et al. **Multicenter dose-finding study of concurrent capecitabine and radiotherapy as adjuvant treatment for operable rectal cancer.** *Int J Radiat Oncol Biol Phys* 2003;56(5):1284-7. **Abstract**

Twelves C. **Can capecitabine replace 5-FU/leucovorin in combination with oxaliplatin for the treatment of advanced colorectal cancer?** *Oncology* (Huntingt) 2002;16(12 Suppl No 14):23-6. **Abstract**

Van Cutsem E et al. **Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials.** *Br J Cancer.* 2004 Mar 22;90(6):1190-7. **Abstract**

Zeuli M et al. **Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer.** *Ann Oncol* 2003;14(9):1378-82. **Abstract**

Post-test: *Colorectal Cancer Update*, Issue 3, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The German rectal study presented at the 2003 ASTRO meeting demonstrated that compared to postoperative chemoradiation, preoperative chemoradiation resulted in:**
   a. A significant decrease in local recurrence
   b. A significant decrease in acute and long-term toxicity
   c. An improved sphincter preservation rate
   d. All of the above

2. **NSABP-R-04 is a preoperative trial comparing capecitabine plus radiation therapy to:**
   a. Bolus 5-FU/leucovorin plus radiation
   b. Capecitabine/oxaliplatin plus radiation
   c. Continuous infusion 5-FU plus radiation
   d. None of the above

3. **The X-ACT adjuvant study of colon cancer compares the Mayo Clinic regimen to capecitabine.**
   a. True
   b. False

4. **The experimental arm in the MOSAIC adjuvant study was:**
   a. FOLFOX7
   b. FOLFOX6
   c. FOLFOX4
   d. CAPOX
   e. None of the above

5. **NSABP-R-03, comparing preoperative versus postoperative chemoradiation therapy, failed to meet its target accrual.**
   a. True
   b. False

6. **NSABP-C-09 will evaluate _____ with and without hepatic arterial infusion floxuridine after resection or ablation of liver metastases.**
   a. Capecitabine plus irinotecan (CAPIRI)
   b. Capecitabine plus oxaliplatin (CAPOX)
   c. Irinotecan plus oxaliplatin (IROX)
   d. None of the above

7. **In the Memorial Sloan-Kettering Cancer Center's experience, the addition of dexamethasone to HAI floxuridine decreased bilirubin levels but had no effect on response rate and survival.**
   a. True
   b. False

8. **In the Intergroup randomized trial in patients with liver metastases, compared to 5-FU/leucovorin, HAI floxuridine resulted in:**
   a. A higher objective response rate
   b. A longer median survival
   c. A longer time to hepatic progression
   d. All of the above

9. **The Phase III trial presented at the 2003 ASCO meeting of first-line IFL/bevacizumab versus IFL, and the ECOG-2200 Phase II study of IFL/bevacizumab both demonstrated prolonged survival with the addition of bevacizumab in patients with metastatic colorectal cancer.**
   a. True
   b. False

10. **A unique feature of ECOG-3201, a Phase III adjuvant study in which patients with Stage II or III rectal cancer are randomly assigned to one of three different chemotherapy regimens, is that the treating physician (rather than the protocol) decides whether the patient receives chemoradiation before or after surgery.**
    a. True
    b. False

Post-test Answer Key: 1d, 2c, 3a, 4c, 5a, 6b, 7b, 8d, 9a, 10a

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Colorectal Cancer Update — Issue 3, 2004

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5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	NA = not applicable to this issue of *CCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *CCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment. . . . . 5 4 3 2 1 NA
- Counsel patients about the risks and benefits of adjuvant and neoadjuvant chemotherapy. . . . . 5 4 3 2 1 NA
- Develop and explain a management strategy for patients with metastatic colorectal cancer. . . . . 5 4 3 2 1 NA
- Describe ongoing clinical trials in colorectal cancer and counsel patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 NA

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Bruce D Minsky, MD	5 4 3 2 1	5 4 3 2 1
Nancy E Kemeny, MD	5 4 3 2 1	5 4 3 2 1
Bruce J Giantonio, MD	5 4 3 2 1	5 4 3 2 1
Roy E Smith, MD, MS	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
Related to my practice needs. 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

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Colorectal Cancer™ UPDATE

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U P D A T E

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