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HOW TO USE THIS MONOGRAPH

This is a CME activity that 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 on page 18-20 or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program and the website, ColorectalCancerUpdate.com, where you will find 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:

- Describe ongoing clinical trials in colorectal cancer and their potential impact on patient care.
- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment.
- Develop and explain a management strategy for patients with colorectal cancer in the adjuvant and metastatic settings.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 2

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

- Counsel patients regarding the risks and benefits of combination versus single-agent chemotherapy in metastatic colorectal cancer.
- Describe the planned and ongoing trials evaluating capecitabine/oxaliplatin in patients with colorectal cancer.
- Evaluate novel approaches for preventing or ameliorating acute and cumulative oxaliplatin-associated neurotoxicity.

ACCREDITATION STATEMENT

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As a provider accredited by the ACCME, it is the policy of NL Communications Inc to require the disclosure of any significant financial interest or any other relationship the sponsor or faculty members have with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Howard S Hochster, MD	**Grants/Research Support:** Sanofi-Synthelabo Inc, Eli Lilly & Company, Bristol-Myers Squibb Company, ImClone Systems Inc **Consultant:** Sanofi-Synthelabo Inc, ImClone Systems Inc, Bristol-Myers Squibb Company **Honorarium:** Sanofi-Synthelabo Inc, ImClone Systems Inc, Bristol-Myers Squibb Company
James L Abbruzzese, MD	**Grants/Research Support:** Pharmacia Corporation, Novartis Pharmaceuticals Corporation, Eli Lilly & Company, Bristol-Myers Squibb Company, ImClone Systems Inc **Consultant:** Variagenics Inc, Millennium Pharmaceuticals Inc **Honorarium:** Pharmacia Corporation, Novartis Pharmaceuticals Corporation, Eli Lilly & Company, Bristol-Myers Squibb Company, ImClone Systems Inc, Variagenics Inc, Millennium Pharmaceuticals Inc **Other Financial or Material Support:** National Cancer Institute
Al B Benson, III, MD, FACP	**Grants/Research Support:** National Cancer Institute, Frontier Science & Technology Research Foundation, University of Pittsburgh, Cancer Institute of New Jersey, Taiho Pharmaceutical Co Ltd, Bristol-Myers Squibb/Theradex, Matrix Pharmaceutical Inc, Glaxo Wellcome, Merck & Company Inc, Pharmacia & Upjohn, Aventis Pharmaceuticals Inc, Genetics Institute Inc, US Bioscience, Novartis Pharmaceuticals Corporation, Searle Pharmaceutical Company, Genentech Inc, ImClone Systems Inc, Sanofi-Synthelabo Inc, Eli Lilly & Company, AstraZeneca Pharmaceuticals LP **Consultant/Speakers' Bureau:** Matrix Pharmaceuticals Advisory Board, US Bioscience Advisory Board, Glaxo Wellcome Advisory Board, Cell Pathways Advisory Board, AstraZeneca Advisory Board, Novartis Oncologists' Advisory Board, Aventis Advisory Board, ImClone Systems Inc, Vida Healthcare Inc **Speakers' Bureau:** Pharmacia Corporation **Consultant:** Pharmacia & Upjohn, Abbott Laboratories, Searle Pharmaceutical Company, Bristol-Myers Squibb Company, Sugen Inc, Intracel LLC, Genentech BioOncology, Schering Plough
James N Atkins, MD	No financial interests or affiliations to disclose.

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
capecitabine	Xeloda®	Roche Laboratories Inc
fluorouracil, 5-FU	Various	Various
gemcitabine	Gemzar®	Eli Lilly & Company
irinotecan	Camptosar®	Pfizer Inc
leucovorin	Wellcovorin®	Amgen Corporation
loperamide	Imodium®	McNeil-PCC Inc
oxaliplatin	Eloxatin®	Sanofi-Synthelabo Inc
pemetrexed	Alimta®	Eli Lilly & Company

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Editor's Note

Big Fish in a Big Pond

In a small town there's no question that you're a big fish in a small pond, and it's extremely important for us to maintain humility. If patients can't make it in to the office because they're sick and dying, I think it's still important for us to go to their home, even if the only thing you do is hold their hand. That's what doctors did a hundred years ago — hold the patient's hand and allow them to die with peace and dignity. That part of the art of oncology sometimes gets lost, but it's still a critical role.

— James N Atkins, MD

Wandering through this year's ASCO poster sessions, I was fortunate to meet James Atkins, a true champion of clinical research. What initially sparked our conversation was Jim's ASCO poster reporting an encouraging Phase II study of oxaliplatin and pemetrexed in the treatment of metastatic colorectal cancer. The regimen proved to be so well-tolerated, that the next step may be to evaluate it in elderly patients. However, it was what I learned about Jim's background and dedication to clinical research that was intriguing and motivated me to interview him for this series.

Dr Atkins' oncology practice is based in the North Carolina "metropolis" of Goldsboro (population 30,000). Yet each year, he and his partners, Drs M Ernest Marshall and John Inzerillo, enter about 150 patients in clinical research protocols. Jim also travels around the country running seminars on how other community-based physicians can incorporate clinical trials into their practices.

If you were looking for a role model for oncology fellows to emulate, you would not need to look farther than Dr Atkins, as his zeal for patient care is readily apparent. When I asked him what he liked most about being an oncologist, he answered without hesitation, "I love the patients. They are very friendly, kind, warm and extremely appreciative of everything you do."

One of the most important things Jim regularly does is enroll his patients in protocols, and other speakers in this issue address the many recent advances in colorectal cancer that have resulted from clinical research. Dr Howard Hochster comments on the evolving role of oxaliplatin and brings to light some fascinating new research from France on the use of magnesium and calcium infusions to reduce the rates of neurotoxicity.

Dr James Abbruzzese discusses evolving Phase III research evaluating the oral fluoropyrimidine prodrug, capecitabine, in combination with oxaliplatin. These trials are significant in that they may soon provide more patient-friendly treatment alternatives that do not require prolonged intravenous infusion. Dr Al Benson notes that the availability of new combination options correlates with an increase in survival rates for metastatic disease. He also points out that agents such as oxaliplatin are now being tested in other GI tumors including pancreatic cancer, and Dr Abbruzzese notes that capecitabine is being evaluated in both pancreatic cancer and cholangiocarcinoma with encouraging early results.

The global approach to clinical research in these disease states relies on community-based oncologists, like Jim Atkins, for successful and timely accrual. Every time these physicians comfort a dying patient, their hope is that if the pace of clinical research can continue to accelerate, such tragedies can be prevented in the future.

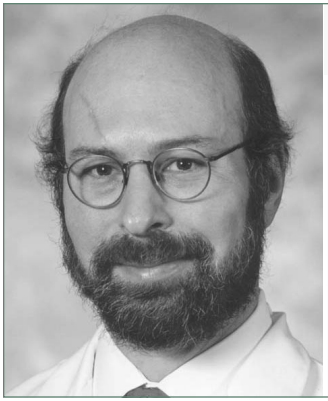
—Neil Love, MD

Active, Pending and Proposed NSABP Clinical Trials in Colorectal Cancer

Protocol ID	Status	Trial design
CI-66 NCCTG-N9945	Active	Multiple metastastectomy combined with HAI of floxuridine + dexamethasone alternating with oxaliplatin + capecitabine for liver metastases
C-09	NCI approved; pending	Oxaliplatin + capecitabine and HAI of floxuridine ***versus*** oxaliplatin + capecitabine in patients with resected/ablated liver metastases
P-03	NCI approved; pending	Celecoxib ***versus*** placebo polyp prevention trial in resected Stage I colon cancer
R-04	NCI approved; pending	Preoperative XRT and capecitabine + epoetin alfa ***versus*** preoperative XRT continuous IV 5-FU + epoetin alfa for operable rectum cancer
C-08	Proposed	Weekly bolus 5-FU + LV + oxaliplatin ± bevacizumab ***versus*** two-weekly infusional 5-FU + LV + oxaliplatin ± bevacizumab ***versus*** capecitabine + oxaliplatin ± bevacizumab for Stage II/III colon cancer

HAI = hepatic arterial infusion; XRT = radiation therapy; LV = leucovorin

SOURCE: NSABP Annual Meeting, June 2003, Orlando, Florida



Howard S Hochster, MD

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Edited comments by Dr Hochster

Use of oxaliplatin-containing regimens as first-line treatment of metastatic disease

I have been very impressed with the responses in my practice to oxaliplatin-based therapy. There does not appear to be a difference in response rates across first-line studies of various combinations — whether FOLFOX, FOLFIRI or IFL — but the studies do not reflect the magnitude of responses I've seen in clinical practice — for example, patients with extensive liver metastases in whom an oxaliplatin-containing regimen reduced the tumor burden to one or two sites. While that's still a partial response, the amount of cytoreduction by oxaliplatin is impressive.

The data suggest you can administer either irinotecan or oxaliplatin as first-line therapy, but there's been a paradigm shift. Intergroup N9741 demonstrated clear superiority of FOLFOX 4 with oxaliplatin and infusonal 5-FU over a bolus IFL regimen, and I'm not sure that the results would have been different if infusional 5-FU had been used with irinotecan. Patients tolerate oxaliplatin better, and the responses are more impressive. Off study, I'm using a modified FOLFOX regimen, with leucovorin on day one followed by a 46-hour 5-FU infusion after a bolus.

Systemic therapy of patients presenting with metastatic disease

I have treated quite a few patients in this situation, without resecting the primary tumor. Many patients could have undergone surgery, but with a large number of liver metastases, our paradigm has shifted. We give chemotherapy first to see if we can reduce the liver metastases to an operable volume, then we remove the residual liver disease and the primary at the same time.

I recall a woman who presented with minimal GI symptoms. Colonoscopy revealed a lesion involving approximately 30 percent of the circumference of the colon, but it was not obstructive. The lesion wasn't friable and bleeding was

minimal, but she had abnormal liver function tests, right upper quadrant discomfort and extensive hepatic metastases.

After six months of FOLFOX, she was restaged for consideration of surgery, and her colon was absolutely clear of tumor by endoscopy and CT scan. The area presumed to have been the primary tumor was biopsied, and she appeared to have a complete pathologic remission of the primary tumor. She also had a partial response of the liver metastases; a small volume of tumor remained, but it was too diffuse for resection.

Local therapy for liver metastases

Local therapy for liver metastases is a real "Pandora's box." We have numerous ways to treat gross liver metastases — resection, freezing, microwaving, embolizing, injecting itrium-labeled glass spheres or ethanol. Unfortunately, none of these extend survival. This is a very difficult concept to communicate to patients.

Most people believe that you're going to live longer if you can resect the metastases. Sometimes that's true, especially if you have another chemotherapy to administer after the resection. Local therapies need to be coupled with effective chemotherapy; otherwise, you're just treating the gross disease. I look forward to any trial demonstrating the role of local therapies. The only one demonstrating any survival benefit is resection of a solitary liver metastasis followed by 5-FU. Hopefully, the cooperative groups will address these questions with appropriate clinical trials.

Management of patients with metastatic disease and poor performance status

I use combination chemotherapy — oxaliplatin/5-FU or irinotecan/5-FU regimens — in otherwise healthy patients with poor performance status that is disease-related. I recall a few patients who presented with severe debilitation, extensive liver involvement and intrahepatic jaundice, whose primary care physicians wanted to refer to hospice.

I treated those patients with combination chemotherapy; they have responded favorably, and have been resurrected with improvement in performance status and reduced jaundice. The key was to treat them with appropriate doses — to use dose reductions if necessary — and to initially proceed very slowly. With older patients, who may have cardiac problems and other comorbidities, I may use single-agent fluoropyrimidines.

Prevention of oxaliplatin-related neuropathy

Erick Gamelin, a neurologist who works with Aimery de Gramont, studied the neurophysiology of oxaliplatin-associated neuropathy. He discovered the oxalato portion of oxaliplatin actually becomes a chelating agent once it's dissolved from the platinum. Oxalato strips off the bivalent cations (calcium and magnesium), opens up sodium channels and causes an intense

depolarization that can damage nerves. He postulated that administration of calcium and magnesium salts before and after oxaliplatin administration could prevent depolarization.

Gamelin presented data from a nonrandomized study comparing patients treated with calcium and magnesium salts before and after oxaliplatin to those who were untreated with the cation salts. The treated patients had much less acute neuropathy and could tolerate greater cumulative doses.

We use this Gamelin approach as our standard of care in patients treated with oxaliplatin. Patients uniformly report much less acute neurotoxicity. Our patients receive much more oxaliplatin because they don't have to discontinue treatment due to cumulative neuropathy. I believe this regimen will reduce Grade II and III neuropathy by one-half. A Phase III trial in Europe is currently evaluating this approach, so we'll soon have confirmation of its effectiveness.

A Retrospective Study Evaluating Ca+ Gluconate and Mg+ Chloride Infusion for the Prevention of Oxaliplatin-associated Peripheral Neuropathy

	Treated Group* (n=63)	Untreated Group (n=38)
Median cumulative oxaliplatin dose	910 mg/m^2	650 mg/m^2
Patients on treatment ≥ 9 months	15%	5%
Treatment withdrawal		
All causes	23%	40%
Due to neurotoxicity	6%	56%
Neuropathy (any grade) at the end of treatment	27%	75%

Both groups were comparable for age, sex, performance status and regimens.

*Treated Group received Ca (1 g) and Mg (1 g) before and after oxaliplatin.

DERIVED FROM: Gamelin E et al. **Prevention of oxaliplatin peripheral sensory neuropathy by Ca+ gluconate/ Mg+ chloride infusions: A retrospective study.** *Proc ASCO* 2002;**Abstract 624.**

Challenges in treatment decision-making

Oncologists are struggling to determine the most appropriate candidates for combination chemotherapy, which agents should be utilized and how 5-FU should be administered. If you treat many patients with colorectal cancer, it's easier to adapt to administering infusional therapy, but in the United States, the use of infusional therapy has many barriers, including insurance-related concerns. Randomized studies will inform us if we need to use infusional 5-FU or if we can substitute an oral agent, such as capecitabine.

Select publications

Publications discussed by Dr Hochster

Gamelin E et al. **Clinical aspects and molecular basis of oxaliplatin neurotoxicity: Current management and development of preventive measures.** *Semin Oncol* 2002;29 (5 Suppl 15):21-33. **Abstract**

Gamelin E et al. **Prevention of oxaliplatin peripheral sensory neuropathy by Ca+ gluconate/Mg+ chloride infusions: A retrospective study.** *Proc ASCO* 2002;**Abstract 624.**

Goldberg RM et al. **N9741: Oxaliplatin (oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Initial toxicity and response data from a GI Intergroup study.** *Proc ASCO* 2002;**Abstract 511.**

Goldberg RM et al. **N9741: Oxaliplatin (Oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Updated efficacy and quality of life (QOL) data from an Intergroup study.** *Proc ASCO* 2003:**Abstract 1009.**

Grolleau F et al. **A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels.** *J Neurophysiol* 2001;85:2293-97. **Abstract**

Adjuvant chemotherapy after hepatic resection for colorectal metastases

Ambiru S et al. **Adjuvant regional chemotherapy after hepatic resection for colorectal metastases.** *Br J Surg* 1999;86(8):1025-31. **Abstract**

Belli G et al. **Liver resection for hepatic metastases: 15 years of experience.** *J Hepatobiliary Pancreat Surg* 2002;9(5):607-13. **Abstract**

Berlin J et al. **Phase II evaluation of treatment of complete resection of hepatic metastases from colorectal cancer and adjuvant hepatic arterial infusion of floxuridine: An Eastern Cooperative Oncology Group Study (PB083).** *Am J Clin Oncol* 1999;22(3):291-3. **Abstract**

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Liu LX et al. **Current treatment for liver metastases from colorectal cancer.** *World J Gastroenterol* 2003;9(2):193-200. **Abstract**

Lorenz M et al. **Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer.** *German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen) Ann Surg* 1998;228(6):756-62. **Abstract**

Nonami T et al. **Regional adjuvant chemotherapy after partial hepatectomy for metastatic colorectal carcinoma.** *Semin Oncol* 1997;24(2 Suppl 6):S6-130-S6-134. **Abstract**

O'Connell MJ et al. **Clinical trial of adjuvant chemotherapy after surgical resection of colorectal cancer metastatic to the liver.** *Mayo Clin Proc* 1985;60(8):517-20. **Abstract**

Tono T et al. **Limited but definite efficacy of prophylactic hepatic arterial infusion chemotherapy after curative resection of colorectal liver metastases: A randomized study.** *Cancer* 2000;88(7):1549-56. **Abstract**

Wagman LD et al. **A prospective, randomized evaluation of the treatment of colorectal cancer metastatic to the liver.** *J Clin Oncol* 1990;8(11):1885-93. **Abstract**

James L Abbruzzese, MD

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Edited comments by Dr Abbruzzese

Capecitabine/oxaliplatin trials in patients with metastatic disease

We are involved in a Phase II trial evaluating capecitabine/oxaliplatin in patients with metastatic colon cancer. Similar to what has been found in Europe, we identified very significant activity with response rates in the 40 to 50 percent range. In fact, those results led us to propose a Phase III randomized trial through the Southwest Oncology Group, which will be a head-to-head comparison of the FOLFOX regimen (infusional 5-FU/leucovorin/oxaliplatin) to the oral regimen of capecitabine/oxaliplatin.

This Phase III trial will be a direct test of whether we can substitute capecitabine, a more convenient drug, and whether we'll have similar or even better efficacy with the incorporation of an oral drug. We hope to have that trial up and running this year.

We're expecting that the regimen incorporating capecitabine will have similar efficacy to the standard intravenous FOLFOX regimen. We might be pleasantly surprised and see better activity, but the expectation based on the available Phase II data is that we'll see similar efficacy. Our goal is to demonstrate that within the context of similar efficacy, there is better overall tolerability without the central lines and pumps that are required to administer the FOLFOX regimen.

Practicing oncologists in the United States have been somewhat reluctant to adopt infusional 5-FU regimens because of the frequency of patient visits to the clinic, the unpredictability of the pumps and the complications from the central lines. Therefore, we're hoping to see better patient acceptance and quality of life with the capecitabine regimen in patients enrolled in the Phase III trial.

ASCO 2003 Phase II Capecitabine/Oxaliplatin Trials: Response Rate for First-line Therapy in Patients with Metastatic Disease

Abstracts from Proc ASCO 2003	Number of Patients	Response Rate
Van Custem E et al. Abstract 1023	96	45%
Grothey A et al. Abstract 1022	71	49%
Makatsoris T et al. Abstract 1447	36	31%
Carreca T et al. Abstract 2939	21	43%

Preoperative capecitabine/oxaliplatin trial

We're just finishing a protocol to evaluate a preoperative oxaliplatin-based chemotherapy regimen in patients with potentially resectable liver metastases. We're conducting the trial through the National Cancer Institute and hoping to interest the Southwest Oncology Group (SWOG) and possibly the Eastern Cooperative Oncology Group (ECOG). It's going to be a Phase II trial looking at preoperative capecitabine/oxaliplatin.

Our goal is to try to increase the number of margin-free resections and to render more patients without any evidence of disease at the completion of surgery. We're anxious to see if this type of trial can be conducted in the cooperative group setting, and if the results in that setting mirror those seen in the smaller, single-institution trials that have been reported so far. We're trying to obtain funding to look at tumor markers, but we definitely do want to try to incorporate some biology into the study.

Managing patients in a nonprotocol setting

Many patients with metastatic colon cancer are elderly and may have other significant medical problems, therefore, their performance status may not as good as that of patients enrolled on protocols. In that setting, I frequently utilize single-agent capecitabine as initial therapy. My second choice is the intravenous FOLFOX regimen, based on the N9741 trial.

I think decision-making for the elderly patient has been simplified by the availability of oral capecitabine, but I use cautious dosing.

I've been using other agents, such as irinotecan, more in the second-line setting. This is a very controversial area. Hopefully, the upcoming trials will begin to sort through some of the issues about sequencing and which is the best first-line agent.

Single-agent capecitabine dosing

I generally use a lower dose than is recommended in the package insert. Many patients don't qualify for protocol therapy or have concerns about toxicity. The goal is to maintain efficacy with minimal toxicity. I usually start with a dose of

1 g/m^2 administered twice a day (2 g/m^2 per day), and sometimes I even use a lower dose if, in my judgment, the patient might not tolerate the drug.

I've also adopted a different schedule for capecitabine. I generally give patients an extra week off — I use two weeks on and two weeks off. I've found this regimen seems to really improve patient tolerance. My patients rarely develop severe hand-foot syndrome or severe diarrhea. If they do develop diarrhea, it's usually very easy to manage with loperamide and other antidiarrheals.

I see hand-foot syndrome very infrequently. More frequently, I am confronted by chronic dryness of the skin and scaling of the hands and feet. Patients can easily deal with this by using moisturizers. In the few cases in which we run into problems, I generally reduce the dose of capecitabine by 10 to 20 percent, or, if necessary, give the patient a short drug holiday until the skin changes reverse completely.

Usually, patients do well using those two maneuvers. With the strategies I described, I have had patients in my practice on capecitabine for up to a year and even longer in a few instances. The patients have had excellent tolerance and no cumulative problems.

Capecitabine/oxaliplatin in patients with cholangiocarcinoma and pancreatic cancer

We plan to explore the potential role of capecitabine/oxaliplatin in patients with cholangiocarcinoma or gallbladder cancer and as second-line therapy in patients with pancreatic cancer. In pancreatic cancer, there was very promising Phase II data with single-agent capecitabine published in the *Journal of Clinical Oncology* this past year. Capecitabine's activity was equivalent to that of gemcitabine. I am not aware of any data with capecitabine/oxaliplatin in pancreatic cancer.

In my own practice, I frequently use capecitabine as second-line therapy in patients with pancreatic cancer who have failed gemcitabine or gemcitabine combinations and are not candidates for a clinical trial. Even though some of these patients have difficulty with gastrointestinal function, such as slow gastric emptying, it has never been a major problem with oral agents like capecitabine.

It's a very well-tolerated approach, and we see the patients' tumors having an objective response around 10 percent of the time. A much larger percentage of patients' tumors, an estimated 30 or 40 percent, remain stable for eight to twelve weeks and sometimes even beyond.

Select publications

Publications discussed by Dr Abbruzzese

Cartwright TH et al. **Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer.** *J Clin Oncol* 2002;20(1):160-4. **Abstract**

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Goldberg RM et al. **N9741: Oxaliplatin (oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Updated efficacy and quality of life (QOL) data from an intergroup study.** *Proc ASCO* 2003. **Abstract 1009.**

Capecitabine plus oxaliplatin trials

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Petrovic Z et al. **Oxaliplatin (L-OHP) and capecitabine (X) as second-line chemotherapy in patients with advanced gastric cancer.** *Proc ASCO* 2003. **Abstract 1199.**

Scheithauer W et al. **Intermittent weekly high-dose capecitabine in combination with oxaliplatin: A Phase I/II study in first-line treatment of patients with advanced colorectal cancer.** *Ann Oncol* 2002;13(10):1583-9. **Abstract**

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Thomas RR et al. **Hypersensitivity and idiosyncratic reactions to oxaliplatin.** *Cancer* 2003; 97(9):2301-7. **Abstract**

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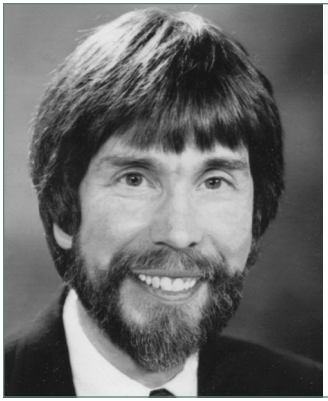

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Professor of Medicine and Director of Clinical Investigations,
Robert H Lurie Comprehensive Cancer Center of Northwestern University
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Edited comments by Dr Benson

Improved survival in metastatic colorectal cancer

Patients with metastatic colorectal cancer are living longer with a better quality of life as a result of combination chemotherapy. More patients are exposed to multiple therapeutic regimens, including irinotecan and oxaliplatin combinations, and are having better survival. A recent European abstract suggested that the long-term sequence of therapy with irinotecan and oxaliplatin results in median survival of 20 to 21 months — almost double the survival of bolus 5-FU regimens. Although we are not where we want to be in terms of outcome, we are making progress.

Oxaliplatin trial in pancreatic cancer

ECOG will soon activate a very large trial for patients with pancreatic cancer comparing fixed-rate infusion gemcitabine combined with oxaliplatin to the standard 30-minute gemcitabine. This will be one of the largest pancreatic trials done in the United States. The rationale for this trial is based on data from French investigators in locally advanced non-surgical disease, and metastatic disease. Both groups actually benefited from the combination of gemcitabine and oxaliplatin with median survivals greater than seven months. The ECOG trial will define the role of oxaliplatin in the combination and whether the combination is truly superior to either fixed-rate or 30-minute dosing of gemcitabine.

Management of oxaliplatin toxicity

We counsel patients about the risks of oxaliplatin, and our patients have actually been fine with it. We've not had a lot of difficulty with cold exposure in our patients receiving oxaliplatin — and Chicago is a cold place to live. Patients will describe a tingling feeling in their hands if they reach in the refrigerator and take out a cold bottle of milk. If they drink very cold liquids or have

exposure to cold air, they can experience difficulty swallowing or shortness of breath. This generally resolves within the first week of treatment, and most of our patients are able to resume drinking cold beverages after this time.

Trials are underway to explore the peripheral neurotoxicity, predictably seen after about eight cycles of therapy. A European trial is evaluating efficacy and tolerability of treating patients with a planned break from oxaliplatin. There are also various maneuvers, such as calcium and magnesium infusions, to control the peripheral neuropathy. We'll have to see how those play out.

Adjuvant therapy

Historically, in oncology, we would expect the response and survival data seen with oxaliplatin and irinotecan in advanced disease to translate into a survival benefit for patients in the adjuvant setting. We have to be careful, however, in the history of clinical research we've made assumptions and then been surprised by how the data unfolds.

We do not know if the efficacy of combination therapy is superior, and there are certainly risks of added toxicity. Two trials designed to answer this question have been completed in the United States. New Intergroup adjuvant trials will further explore the use of combination therapy in the adjuvant setting. We have to wait for the data to emerge from the recently completed trials. We also need to support the future trials looking at this question and the laboratory correlative studies, which hopefully will yield additional biological information that will correlate with tumor response.

Select publications

Calvo E et al. **Bi-weekly triplet combination chemotherapy of oxaliplatin, irinotecan and 5-FU/leucovorin seems to be feasible and safe in metastatic and adjuvant colorectal carcinoma.** *Proc ASCO* 2003;**Abstract 1265.**

Cassidy J et al. **Oxaliplatin (Oxa)/5-FU/LV in first-line metastatic colorectal cancer followed by irinotecan: Interim results of the Life Study.** *Proc ASCO* 2003;**Abstract 1064.**

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.**

De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Safety results of the international randomized MOSAIC trial.** *Proc ASCO* 2003;**Abstract 525.**

Garay CA et al. **Randomized trial of bolus plus infusional 5-FU/leucovorin (LV5FU2) with/without oxaliplatin (FOLFOX4) after sequential fluoropyrimidine and CPT-11 in the treatment of advanced colorectal cancer (ACRC).** *Proc ASCO* 2003;**Abstract 1019.**

Louvet C et al. **Gemcitabine versus GEMOX (gemcitabine + oxaliplatin) in nonresectable pancreatic adenocarcinoma: Interim results of the GERCOR/GISCAD Intergroup Phase III.** *Proc ASCO* 2003;**Abstract 1004.**

Rothenberg M et al. **Final results of a Phase III trial of 5-FU/leucovorin versus oxaliplatin versus the combination in patients with metastatic colorectal cancer following irinotecan, 5-FU, and leucovorin.** *Proc ASCO* 2003;**Abstract 1011.**

Souglakos J et al. **Combination with irinotecan (CPT-11) plus oxaliplatin (L-OHP) as first-line treatment in metastatic gastric cancer: A multicenter Phase II trial.** *Proc ASCO* 2003;**Abstract 1288.**

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Edited comments by Dr Atkins

Phase II trial of pemetrexed and oxaliplatin as first-line therapy

The NSABP developed a foundation to conduct Phase II clinical trials to ensure that novel agents will be available for evaluation in Phase III trials. The first trial evaluated pemetrexed 500 mg/m^2 and oxaliplatin 120 mg/m^2 in patients previously untreated for metastatic colorectal cancer.

Pemetrexed is a multitargeted antifolate that inhibits at least three enzymes — thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase — involved in folate metabolism. Since it's multitargeted, it may have more activity than 5-FU. It is synergistic with a number of other agents, including oxaliplatin, and has activity in a number of cancers, including breast, colon, pancreatic and lung cancer.

Pemetrexed is generally well-tolerated. The major toxicities in our study were neutropenia and thrombocytopenia, but most of this was abrogated by B12 and folate supplementation. The incidence of Grade III-IV neutropenia was 23 percent, which compares favorably with what has been observed with 5-FU/irinotecan and 5-FU/oxaliplatin. No Grade III-IV diarrhea was observed, and there was minimal Grade III-IV neurotoxicity. The incidence of neurotoxicity was three percent, whereas in studies of oxaliplatin/5-FU it is approximately 18 percent. Pemetrexed may actually reduce oxaliplatin-associated neurotoxicity.

The overall response rate in our trial was 23 percent, and another 50 percent of patients had stable disease. Some received up to 18 cycles of therapy, which was given every 21 days. Some patients did extremely well with very minimal toxicity. The response rate may not be quite as high as seen with other 5-FU regimens, and it's possible the dose should be escalated. Another group is conducting a Phase II trial with this combination using much higher doses of the pemetrexed. We chose the 500 mg/m^2 because of the lack of available Phase I data for higher doses. The other issue that needs to be evaluated is using a 14-day schedule.

Importance of clinical trial participation

There are a number of reasons I support clinical trials. First, I believe patients on clinical trials do better than those who are not, and we are starting to see data to support this. The reason may be the regimented follow-up and high likelihood that patients will receive appropriate cancer therapy.

In addition, data from Sloan-Kettering shows that the cost of care for patients on clinical trials is decreased. We drive costs up by ordering unnecessary and expensive tests. Sometimes we do this because we are in a pattern — on "auto pilot." Five or ten years can go by, and we may not change our practice. It's easy to be lulled into complacency and do the things you've always done. But, in the context of a clinical trial, you follow a protocol or a "recipe", which has been developed by the best cancer minds in the world.

I also believe clinical trials are important because physicians are very biased. We don't always know the best treatment for a particular patient. The bone marrow transplant trials in breast cancer are a good example. One thousand women, at a cost of roughly $100,000 each, participated. This works out to a cost of approximately one hundred million dollars. At the same time, 36,000 women had bone marrow transplants outside of clinical trials at a cost of $3.5 billion dollars — for no benefit. Physicians thought it would be better but were obviously wrong.

I practice in a small town, but each year we enter about 150 patients into clinical trials. Many physicians in the community are committed to research. In private practice I have the best of all worlds. I can be as involved as I want in clinical research without the headaches of academic medicine. I work very closely with CALGB and NSABP, and my colleagues work with SWOG and RTOG. Overall, I am very comfortable with the clinical trials process.

Select publications

Publications discussed by Dr Atkins

Atkins JN et al. **Pemetrexed and oxaliplatin for first-line treatment of patients with advanced colorectal cancer: A Phase II trial of the NSABP foundation research program.** *Proc ASCO* 2003;**Abstract 1108.**

Berman E et al. **Financial analysis of patients with newly diagnosed acute myelogenous leukemia on protocol or standard therapy.** *Cancer* 2002;95(5):1064-70. **Abstract**

Gnant M. **Impact of participation in randomized clinical trials on survival of women with early-stage breast cancer — An analysis of 7,985 patients.** *Proc ASCO* 2003;**Abstract 287.**

Post-test: Colorectal Cancer Update, Issue 2, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Radiation therapy is thought to upregulate thymidine phosphorylase.
   a. True
   b. False

2. A proposed ECOG trial will determine the role of combination oxaliplatin and gemcitabine in the treatment of pancreatic cancer.
   a. True
   b. False

3. Oxaliplatin should not be given to patients living in cold climates.
   a. True
   b. False

4. Which of the following strategies are being examined in clinical trials to reduce the neurotoxicity associated with oxaliplatin?
   a. Planned breaks in therapy
   b. Calcium and magnesium infusions
   c. Both of the above
   d. None of the above

5. In Gamelin's study, prophylactic treatment with calcium and magnesium to prevent oxaliplatin-associated neurotoxicity significantly reduced neuropathy (any grade) at the end of oxaliplatin-based therapy.
   a. True
   b. False

6. Phase II trials evaluating capecitabine/oxaliplatin as first-line therapy in patients with advanced colorectal cancer have reported response rates between 40 to 50 percent.
   a. True
   b. False

7. A Phase III trial is being planned to compare the FOLFOX regimen to capecitabine/oxaliplatin in patients with advanced colorectal cancer.
   a. True
   b. False

8. The goal of the Phase II trial evaluating preoperative capecitabine/oxaliplatin in patients with resectable liver metastases is to:
   a. Increase the number of margin-free resections
   b. Increase the number of patients without evidence of disease
   c. Determine if results from single-institution trials will be duplicated by a cooperative-group trial.
   d. All of the above
   e. None of the above

9. In a Phase II trial, single-agent capecitabine had activity similar to gemcitabine in patients with pancreatic cancer.
   a. True
   b. False

10. Which Grade III/IV toxicities occurred most frequently in the NSABP Phase II trial of pemetrexed and oxaliplatin?
    a. Thrombocytopenia
    b. Diarrhea
    c. Neutropenia
    d. Stomatitis

11. Pemetrexed is a multitargeted antifolate.
    a. True
    b. False

Post-test Answer Key: 1a, 2a, 3b, 4c, 5a, 6a, 7a, 8d, 9a, 10c, 11a

Evaluation Form: Colorectal Cancer Update, Issue 2, 2003

NL Communications Inc respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of our completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

GLOBAL LEARNING OBJECTIVES

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

- Describe ongoing clinical trials in colorectal cancer and their potential impact on patient care 5 4 3 2 1
- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment 5 4 3 2 1
- Develop and explain a management strategy for patients with colorectal cancer in the adjuvant and metastatic settings 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 2

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

- Counsel patients regarding the risks and benefits of combination versus single-agent chemotherapy in metastatic colorectal cancer 5 4 3 2 1
- Describe the planned and ongoing trials evaluating capecitabine/oxaliplatin in patients with colorectal cancer 5 4 3 2 1
- Evaluate novel approaches for preventing or ameliorating acute and cumulative oxaliplatin-associated neurotoxicity 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Howard S Hochster, MD	5 4 3 2 1	5 4 3 2 1
James L Abbruzzese, MD	5 4 3 2 1	5 4 3 2 1
Al B Benson, III, MD, FACP	5 4 3 2 1	5 4 3 2 1
James N Atkins, MD	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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What other topics would you like to see addressed in future educational programs?

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