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Colorectal Cancer™ UPDATE

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

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Colorectal Cancer Update

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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

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment, and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriate patients about the availability of ongoing clinical trials.
- Describe the emerging research data on various adjuvant chemotherapy approaches, including the use of oxaliplatin-containing regimens and the use of capecitabine or intravenous 5-FU, and explain the absolute risks and benefits of these regimens to patients.
- Review and evaluate the evolving neoadjuvant radiation and/or chemotherapeutic approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients.
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 5 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Hurwitz, Tepper, Goldberg and Eng on the integration of emerging clinical research data into the management of colorectal cancer.

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INTERVIEW

Herbert I Hurwitz, MD

Dr Hurwitz is Associate Professor of Medicine in the Division of Hematology/Oncology, Clinical Director of the Phase I Program and Co-leader of the GI Oncology Program at Duke University Medical Center in Durham, North Carolina.

Tracks 1-19

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: What do you see as some of the key current issues in the use of adjuvant therapy for patients with colorectal cancer?

DR HURWITZ: The biggest questions regarding chemotherapy in the adjuvant setting have to do with stage, namely lymph node–positive versus

node-negative disease, and to some degree, the existence of any additional risk factors (eg, an inadequate number of lymph nodes). The debate surrounds whether patients with lymph node-negative disease or those with Dukes B_2 — or Stage II — cancer benefit from therapy. I usually address that issue by having a long discussion with the patient. I explain that the relative benefit for these patients is probably similar, but because the absolute risk is less, the absolute benefit is also smaller, but it still may exist.

DR LOVE: How do you approach the treatment of patients with lower-risk disease, and where does capecitabine fit in?

DR HURWITZ: Settings arise in which patients have preexisting neuropathy or have careers or lifestyles for which neuropathy would be a major quality-of-life adjustment. I'll let them know that they have two options: FOLFOX, which probably has a slightly superior outcome, or capecitabine as monotherapy — or if for some reason that would not be available, 5-FU is probably better than nothing from the point of view of disease control and survival.

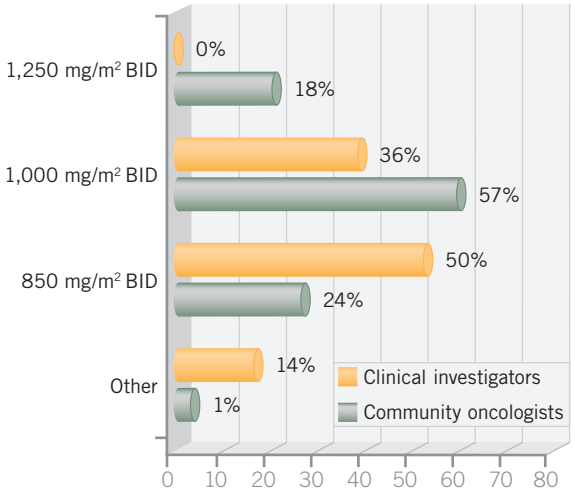
DR LOVE: You mentioned the option of capecitabine monotherapy. How do you dose in that setting?

DR HURWITZ: For monotherapy, most patients in the US will begin with 1,000 mg/m^2 twice daily for two out of three weeks (1.1). The dose will be increased if they don't have problems in the first cycle. For patients with an

1.1

A 2007 National Patterns of Care Study with Community Oncologists (N = 150) and Clinical Investigators (N = 27)

What dose of capecitabine do you routinely use in combination with oxaliplatin in the adjuvant setting?



SOURCE: Love N et al. *Patterns of Care in Medical Oncology* 2007;4(1). Available at: www.PatternsOfCare.com

excellent performance status, it is reasonable to start at the full 1,250 mg/m^2 twice daily.

Tracks 12-13

DR LOVE: How do you go about choosing first-line systemic therapy for metastatic disease?

DR HURWITZ: The main issue in the metastatic setting is whether the patient is a candidate for systemic therapy. The second issue is the presence of any major contraindications to the backbones of therapy, which would be either a fluoropyrimidine or bevacizumab. A quick family history will tell you if any family member has had problems receiving chemotherapy. If a family member has a dihydropyrimidine dehydrogenase (DPD) deficiency and could not metabolize pyrimidines, usually everybody in the family has been alerted.

Another issue would be bevacizumab-specific contraindications. Recent (six months to one year) arteriovascular complications — myocardial infarction, stroke or active disease — are fairly significant contraindications to bevacizumab.

DR LOVE: Is the use of bevacizumab as beneficial with an oxaliplatin-containing regimen as it is with an irinotecan-based regimen?

DR HURWITZ: I don't believe it's an issue of oxaliplatin versus irinotecan. In the second-line FOLFOX study from Dr Giantonio (ECOG-E3200; [Giantonio 2007]) — FOLFOX/bevacizumab versus FOLFOX alone versus bevacizumab monotherapy — the benefits in terms of response rates and survival with the addition of bevacizumab to second-line FOLFOX were significant. The improvements using bevacizumab were as large as those in any other study, and the second-line setting probably includes a harder-to-treat population.

A comparison of other data to those of the first-line NO16966 study of bevacizumab with oxaliplatin (Saltz 2007) is confounded by several clinical study variables. The FOLFOX/CAPOX/bevacizumab data (1.2) do not appear as positive as those using the bolus IFL regimen. However, bolus IFL is not the best platform to use in the first-line treatment of colorectal cancer.

Track 14

DR LOVE: How do you maximize treatment benefit from oxaliplatin in metastatic disease?

DR HURWITZ: One approach is to be preemptive through the use of a calendar schedule. This is the OPTIMOX (Tournigand 2006) approach, by which stopping and starting treatment are based as much on the calendar as they are on the patient's symptoms or disease control.

I find that adjustment based on the patient's symptoms — as long as the threshold of symptoms is lowered — ends up being a nearly identical approach. I have a bias to try to adjust based on how the patient is faring rather than the

1.2

Updated Efficacy Results From XELOX-1/ NO16966: A Randomized, Phase III Trial of Bevacizumab in Combination with XELOX or FOLFOX4 in First-Line Metastatic Colorectal Cancer

Intent-to-Treat Analysis

Outcome	XELOX/FOLFOX4 + bevacizumab (n = 699)	XELOX/FOLFOX + placebo (n = 701)	Hazard ratio (97.5% CI)	*p*-value
PFS	9.4 mo	8.0 mo	0.83 (0.72-0.95)	0.0023
PFS (on treatment)	10.4 mo	7.9 mo	0.63 (0.52-0.75)	<0.0001
TTF	6.9 mo	6.0 mo	0.84 (0.74-0.96)	0.0030
Median OS	21.3 mo	19.9 mo	0.89 (0.76-1.03)	0.0769

PFS = progression-free survival; TTF = time to treatment failure; OS = overall survival

Hazard ratio < 1 favors bevacizumab

Analysis of PFS versus on-treatment PFS suggests that continuation of bevacizumab until disease progression may be necessary to optimize the effect of bevacizumab on PFS.

Therapy discontinuation occurred more frequently in the bevacizumab-containing arm versus the placebo arms (31% versus 21%), mostly due to XELOX/FOLFOX4-related AEs (neurotoxicity, GI events, general disorders and hematological events) rather than bevacizumab-related AEs.

SOURCE: Saltz L et al. *Proc ASCO* 2007;**Abstract 4028**.

calendar, but in practice, the two approaches are most likely similar.

DR LOVE: When you stop oxaliplatin, do you continue the 5-FU or capecitabine and the bevacizumab?

DR HURWITZ: Yes, currently my algorithm is to reduce or stop only the problem agent and to continue the portions of therapy that seem to help, as long as they're well tolerated.

For patients who need a break for personal reasons, or for asthenia, I believe stopping even the fluoropyrimidine and bevacizumab for a period of several weeks to two months is a reasonable approach, as long as the disease burden and patient symptoms allow for the holiday.

Track 16

DR LOVE: What are your thoughts regarding whether or not to continue bevacizumab for patients with disease progression?

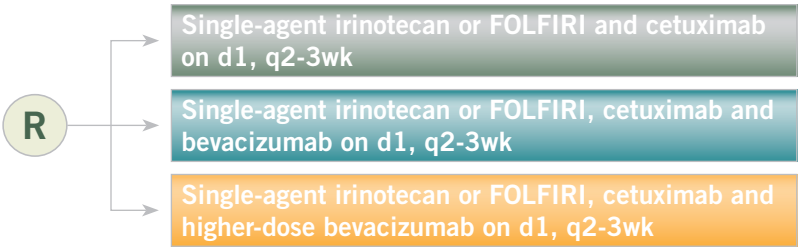
DR HURWITZ: If the disease clearly progresses on therapy, that therapy, whatever it is, should be stopped and patients should receive whatever other options seem reasonable. The difficulty — particularly if progression is slow — is knowing whether the slow progression is attributable to bevacizumab or to indolent disease. That's why we have to use our best judgment until we see better data.

The cooperative groups are running a study known as iBET (1.3). This will address the question of whether patients fare better with bevacizumab continued into that "second-line" setting and whether they respond better to the 5-mg versus the 10-mg dose. ■

1.3

The iBET Trial: A Phase III Study of Irinotecan-Based Therapy and Cetuximab with or without Bevacizumab in Metastatic Colorectal Cancer After Disease Progression on First-Line Therapy

Protocol IDs: SWOG-S0600, CTSU
Target accrual: 1,260 (Open)



Eligibility

- Confirmed metastatic disease with disease progression following first-line therapy with bevacizumab and FOLFOX, OPTIMOX or XELOX
- No prior irinotecan or cetuximab
- Zubrod PS 0-2
- No uncontrolled hypertension (ie, SBP > 150 mmHg or DBP > 90 mmHg)

SOURCE: NCI Physician Data Query, October 2007.

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INTERVIEW

Joel E Tepper, MD

Dr Tepper is Hector McLean Distinguished Professor of Cancer Research in the Department of Radiation Oncology at UNC School of Medicine's UNC/Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Tracks 1-15

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Can you provide an overview of current clinical trials in rectal cancer?

DR TEPPER: The major emphases in clinical trial development in rectal cancer are in two separate areas. One is trying to enhance local control to the point of being able to treat rectal cancer without a surgical resection. Virtually all those trials have included radiation therapy and all include a fluoropyrimidine.

People are also interested in using other agents to enhance response to radiation therapy. The new cytotoxics have been studied to a great extent. Irinotecan has been of some interest but is problematic due to the possibility of

diarrhea associated with irinotecan being additive to the diarrhea already associated with radiation therapy and the fluoropyrimidine.

Much more interest has been shown in oxaliplatin, which has been evaluated in Phase I and II studies. We performed a Phase I study and the initial parts of a Phase II study, which then went into CALGB as a Phase II study (Ryan 2006).

The study's aim was to deliver the oxaliplatin in such a way as to optimize radiation sensitization. We used a once-weekly schedule throughout the course of radiation therapy, which is somewhat different from the schedule typically used with oxaliplatin alone as a cytotoxic. The Phase I study suggested that a dose of 60 mg/m^2 per week would be most appropriate.

Track 3

DR LOVE: Have you made any observations about the potential side effects and toxicity of capecitabine with radiation therapy as opposed to continuous infusion 5-FU?

DR TEPPER: After treating a number of patients, I don't believe the side effects to be much different. Some questions related to timing remain regarding the combination of capecitabine with radiation therapy. Based on some of the available pharmacokinetic data, we try to deliver the capecitabine approximately an hour and a half before the radiation therapy. I don't know if that's better, but it matches up with being at or slightly past the peak concentration of the agent.

DR LOVE: Any reason to believe that capecitabine might be more efficacious than 5-FU when combined with radiation therapy? There has been discussion about whether radiation therapy increases thymidine phosphorylase (TP). Could that in some way synergize with capecitabine better than 5-FU?

DR TEPPER: Yes, the issue of the synergism has been raised, but I'm aware of no clinical data to indicate that it is affecting the overall outcome. The response data appear similar between the agents based on early results, but it's possible that the NSABP-R-04 study will demonstrate the superiority of capecitabine.

Track 5

DR LOVE: What are your thoughts regarding combining bevacizumab with radiation therapy?

DR TEPPER: Bevacizumab is an interesting drug to consider combining with radiation therapy. You would expect that the last thing you would want to do would be to use an anti-angiogenic agent with radiation therapy because shutting down the blood supply could lead to worse results by producing more hypoxic cells and a decreased response to radiation therapy.

That does not appear to be the case because the preclinical data suggest that drugs such as bevacizumab have a beneficial effect when combined with radia-

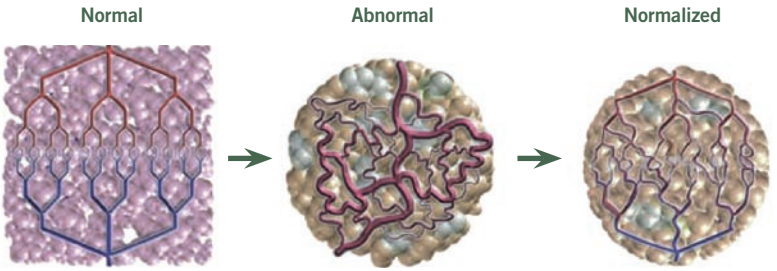
tion therapy. Work from Rakesh Jain has suggested that what is occurring in these tumors treated with bevacizumab is vascular normalization rather than overall vascular shutdown (Jain 2001; [2.1]).

By changing intratumoral pressure, we might actually allow better blood flow, better delivery of chemotherapy and better oxygenation effects for radiation therapy.

Few small studies have used bevacizumab with radiation therapy. Thus far, the toxicity appears to be acceptable, but I believe it's too early to say how encouraged one should be with the results. ■

2.1

Effect of Anti-VEGF on Normalization of Tumor Vasculature



Anti-VEGFR treatment prunes immature blood vessels and decreases the diameter of residual vessels. The tumor vasculature becomes less tortuous and more organized, with improved perivascular cells and basement membrane coverage.

SOURCE: Reproduced with permission from *Nat Med*. Jain R. **Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy.** *Nat Med* 2001;7(9):987-9. **Abstract**

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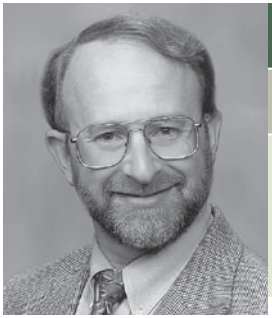

INTERVIEW

Richard M Goldberg, MD

Dr Goldberg is Professor and Chief in the Division of Hematology/Oncology and Associate Director at the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Tracks 1-9

Select Excerpts from the Interview

Track 1

DR LOVE: What's new in adjuvant therapy?

DR GOLDBERG: The most important data regarding adjuvant therapy for colon cancer are from the update of the MOSAIC trial (de Gramont 2007). It hasn't changed what we expected, but it has confirmed what we hoped. Prior to this update, we've had only disease-free survival data. Now we have significant advantage for overall survival at six years.

The good news from MOSAIC was that the patients with Stage III disease definitely gained approximately a five percent survival advantage. The bad news was that the patients with Stage II disease did not appear to gain a significant survival advantage with FOLFOX over 5-FU/leucovorin.

What does that mean? For all comers with Stage II disease, the ASCO guidelines still apply (Benson 2004). You need to have an individualized discussion with those patients, tell them what they can expect and ask them whether that's enough for them to receive adjuvant treatment. I'm always on the fence

about whether to offer FOLFOX or just a fluoropyrimidine to patients with Stage II disease who want treatment.

Track 2

DR LOVE: How do you approach the issue of adjuvant therapy for the older patient?

DR GOLDBERG: I conducted a meta-analysis with Dan Sergeant of four different trials, comparing patients older than age 70 to those younger than age 70 (Goldberg 2006).

We examined the MOSAIC trial, two first-line advanced-disease trials — CALGB-9741 and the de Gramont original study — and the Rothenberg trial in the second-line setting.

Across the board in all three settings, we found that patients benefited equally, regardless of age. Toxicity was minimally elevated in older patients. White blood count and thrombocytopenia were affected.

However, these were laboratory parameters, not clinical parameters. Except in the second-line setting, the superior FOLFOX therapy conferred an advantage of equal value to younger and older patients.

We didn't have many patients over the age of 80, and the people enrolled were the healthiest of the older patients. Taking the data from them and extrapolating to the patient who walks into your office every day is more complicated. My hope is that this study will enable oncologists to think more liberally about the use of FOLFOX for older patients.

In my practice, if I'm worried about a patient's ability to tolerate the regimen, I'll start with 5-FU/leucovorin. If they tolerate that, I'll move up to full-dose oxaliplatin or, if I'm being cautious, I'll initially administer 60 mg/m^2 of oxaliplatin.

If they pass that test, I'll increase it to the full dose. I don't believe you have to make a decision when you first see the patient: "I will administer FOLFOX or only 5-FU."

DR LOVE: What about the patient over the age of 80? Does an age limit exist at which you will stop using adjuvant therapy?

DR GOLDBERG: If patients have comorbidities that suggest they aren't likely to live for more than two or three years, it's reasonable not to administer adjuvant therapy.

I'll give you two examples from my practice. The first is a 90-year-old woman, who's now 92, who received adjuvant FOLFOX.

Even though she walked with a walker because of arthritis, she was going to the pool for water aerobics every day. She went to the senior citizens' center every day, and she was active within the limitations of her arthritis.

The other patient was in her mideighties, and we made a decision not to treat her. Now I'm using FOLFOX to treat her for advanced disease and wishing that I had treated her in the adjuvant setting because she had a high risk for cancer recurrence.

Maybe her cancer would have recurred anyway, but we're at the same point, using the same drugs. She's two years older, and I'm using it with palliative intent rather than curative intent.

Track 3

DR LOVE: Where are we in terms of clinical trials in the adjuvant setting?

DR GOLDBERG: The one trial open in the US is the NCCTG-N0147 study, which is evaluating FOLFOX with or without cetuximab (3.1). It's approximately a third of the way to its final accrual, so it's making progress. I believe this is an important question to answer.

Beyond that, it isn't clear to me what the next chemotherapy/biologic question ought to be. Some discussion took place about five drugs versus four — FOLFOX and bevacizumab with or without cetuximab.

My experience with patients I've enrolled in CALGB-80405 in the metastatic setting is that the ones who are randomly assigned to five drugs have a hard time receiving treatment until disease progression. Most of them have shown responses, but most of them have "said 'uncle'" before they've received the maximum potential benefit.

3.1

A Phase III Study Comparing Oxaliplatin and Leucovorin/5-Fluorouracil with or without Cetuximab After Surgery for Stage III Colon Cancer

Protocol IDs: NCCTG-N0147, CTSU
Target Accrual: 2,300 (Open)

Eligibility

- Curatively resected Stage III colon cancer
- No prior chemotherapy or radiation therapy

Study Contacts

North Central Cancer Treatment Group
Steven Alberts, MD, Protocol Chair
Tel: 507-538-7623
Albert Bernath, MD, Protocol Co-Chair
Tel: 570-214-9290
Frank Sinicrope, MD, Principal Investigator
Tel: 507-538-7623

Eastern Cooperative Oncology Group
Gershon Locker, MD, FACP, Protocol Chair
Tel: 847-570-2515, 888-909-5222

SOURCE: NCI Physician Data Query, August 2007.

Track 6

DR LOVE: What is your decision-making process regarding first-line therapy in the metastatic setting?

DR GOLDBERG: I initially attempt to enroll patients on the CALGB-80405 trial, which is a study of dealer's choice of chemotherapy — FOLFOX or FOLFIRI — combined with either cetuximab, bevacizumab or both.

If a patient is not interested, I'll tell him or her that FOLFOX and FOLFIRI provide basically equivalent outcomes and that, in general, we're adding bevacizumab to first-line therapy.

I don't believe that the NO16966 trial data presented at ASCO will change my first-line approach off study. I will still offer people FOLFOX with bevacizumab as first-line therapy.

The data from the NO16966 trial, which evaluated CAPOX versus FOLFOX with or without bevacizumab, indicated that no difference in response rate appeared when they added bevacizumab (Saltz 2007). Modest differences in survival of about a month were evident.

Does that mean bevacizumab is not worth adding? Not to me. I believe it's worth adding bevacizumab to FOLFOX, but I have my eye on it. I'm watching for additional information to either reinforce or change my opinion. ■

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INTERVIEW

Cathy Eng, MD

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Tracks 1-10

Track 1 Use of adjuvant capecitabine for patients with lower-risk disease

Track 2 Disease-free survival as a surrogate endpoint for overall survival

Track 3 NCCTG N0147: Adjuvant FOLFOX with or without cetuximab

Track 4 New research issues in anal cancer

Track 5 Clinical trial of CAPOX with radiation therapy for anal cancer

Track 6 RTOG-9811: Use of mitomycin C versus cisplatin chemotherapy for anal cancer

Track 7 Clinical trial of cisplatin, fluorouracil, cetuximab and radiation therapy for HIV-associated anal cancer

Track 8 Clinical trial of 5-FU/bevacizumab in combination with radiation therapy for rectal cancer

Track 9 Use of neoadjuvant capecitabine and oxaliplatin for rectal cancer

Track 10 Prognostic value of the ratio of sampled-to-positive lymph nodes

Select Excerpts from the Interview

Track 1

DR LOVE: The X-ACT trial data have led many oncologists to switch to capecitabine when using a fluoropyrimidine alone in the adjuvant setting, when oxaliplatin is not going to be used — for example, in a patient with a lower-risk, Stage II tumor. Is that a strategy you are using?

DR ENG: I have patients at low risk who are only willing to receive capecitabine alone. We discuss the side effects of oxaliplatin-based chemotherapy, which they know will require six months of therapy and is associated with neuropathy. These patients are supposedly free of disease and are trying to work full time. I have been surprised that so many patients are willing to take single-agent capecitabine — they feel that at least they are doing something.

We use the schedule of 1,000 mg/m^2 twice a day on days one through 14 every three weeks. We haven't been able to utilize the dose used by the

Europeans — 2,500 mg/m^2 — due to the hand-foot syndrome that occurs. European patients tolerate the higher dose of capecitabine, even in their combined chemotherapy regimens with oxaliplatin. I agree with Dan Haller's observation that geographic differences exist in the tolerability of capecitabine (Haller 2006).

DR LOVE: What about using capecitabine in the adjuvant setting along with oxaliplatin?

DR ENG: I have colleagues who use adjuvant CAPOX. We now know from the NO16966 study that FOLFOX and CAPOX are equivalent, but that's in the metastatic setting (Cassidy 2007). That may apply just as well in the adjuvant setting. As with any oral chemotherapy, you have to be cautious and make certain the patient is adherent to your recommendations.

Track 5

DR LOVE: Can you discuss the study you are conducting in anal cancer?

DR ENG: A retrospective study conducted by my colleague Christopher Crane at MD Anderson evaluated 5-FU/cisplatin in 92 patients, with no induction. He recorded an impressive five-year survival and disease-free survival rate of 88 percent (Das 2006).

After approval of oxaliplatin and with its use as a radiation sensitizer in rectal cancer, it seemed appropriate to replace cisplatin with oxaliplatin, thus forgoing the nephrotoxicity, electrolyte disturbances, nausea and vomiting associated with cisplatin. Instead of using continuous infusion 5-FU, we utilized capecitabine as a radiation sensitizer. So we are using a CAPOX regimen combined with radiation therapy.

Thus far we've accrued 13 patients. They receive their chemotherapy for the first two weeks of treatment on a Monday-through-Friday schedule, and they take the third week off.

DR LOVE: What are you seeing in terms of side effects and toxicity?

DR ENG: Initially, there were issues with diarrhea. Originally, we administered the chemotherapy every week during radiation therapy, but as the Phase I/II trial was developed in rectal cancer, we amended our schedule to follow that protocol. They didn't provide oxaliplatin and capecitabine in the third week.

So that's what we've done. We've taken it out during the third and sixth weeks. We believe this regimen will be equivalent to historical data with 5-FU and cisplatin but with less toxicity, but it's still early.

Tracks 6-7

DR LOVE: What questions do you receive from doctors in practice regarding the treatment of anal cancer?

DR ENG: The most common one is, "Do I really need to use mitomycin-C?" The majority of physicians prefer using cisplatin to mitomycin-C, but due to the conclusions drawn from the RTOG-98-11 study, they now feel compelled to use mitomycin-C (Ajani 2006). Many of us don't like using mitomycin-C because of its toxicities.

I discuss with them that the design of 9811 makes it difficult to conclude that mitomycin-C is the best option, and many of them then use cisplatin. A lot of them have already been using cisplatin but didn't know whether they needed to change that practice.

DR LOVE: What about the use of oxaliplatin in the clinical setting for anal cancer?

DR ENG: I don't recommend it because it needs to be evaluated as part of a clinical trial. Physicians do cite my abstract and ask if they can use oxaliplatin (Eng 2005). I remind them that toxicities occur that haven't been fully studied, especially because diarrhea and radiation dermatitis are commonly observed in the treatment of anal cancer. Oxaliplatin is being investigated, but I don't believe physicians should assume that it will replace cisplatin. ■

SELECT PUBLICATIONS

Ajani J et al. **Intergroup RTOG 98-11: A phase III randomized study of 5-fluorouracil (5-FU), mitomycin, and radiotherapy versus 5-fluorouracil, cisplatin and radiotherapy in carcinoma of the anal canal.** *Proc ASCO* 2006;**Abstract 4009**.

Cassidy J et al. **XELOX compared to FOLFOX4: Survival and response results from XELOX-1/NO16966, a randomized phase III trial of first-line treatment for patients with metastatic colorectal cancer (MCRC).** *Proc ASCO* 2007;**Abstract 4030**.

Das P et al. **Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: A matched-pair analysis.** *Int J Radiat Oncol Biol Phys* 2006;66(5):1378-83. **Abstract**

Eng C et al. **A Phase II study of capecitabine plus oxaliplatin and radiation therapy, XELOX-XRT, in squamous cell carcinoma (SCCA) of the anal canal: A preliminary analysis.** *Proc ASCO* 2005;**Abstract 4271**.

Giantonio B et al. **Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200.** *J Clin Oncol* 2007;25(12):1539-44. **Abstract**

Haller D et al. **Tolerability of fluoropyrimidines appears to differ by region.** *Proc ASCO* 2006;**Abstract 3514**.

Love N et al. **Patient perspectives on adjuvant systemic therapy of early colorectal cancer.** *Cancer Q & A* 2007;1(1):10-1. Available at: **www.CancerQandA.com**

Tabernero J et al. **An international phase II study of cetuximab in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) in the first-line treatment of patients with metastatic colorectal cancer (CRC) expressing Epidermal Growth Factor Receptor (EGFR). Preliminary results.** *Proc ASCO* 2004;**Abstract 3512**.

Willett CG et al. **Complete pathological response to bevacizumab and chemoradiation in advanced rectal cancer.** *Nat Clin Pract Oncol* 2007a;4(5):316-21. **Abstract**

Willett C et al. **Phase I/II study of neoadjuvant bevacizumab with radiation therapy and 5-fluorouracil in patients with rectal cancer: Initial results.** *Proc ASCO* 2007b;**Abstract 4041**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Trial NO16966 demonstrated a progression-free survival advantage with the addition of bevacizumab to oxaliplatin-based chemotherapy (FOLFOX or CAPOX) as first-line therapy for patients with metastatic colorectal cancer (mCRC).**
   a. True
   b. False

2. **The OPTIMOX strategy involves the planned discontinuation of systemic therapy during the treatment of mCRC.**
   a. True
   b. False

3. **The iBET trial (SWOG-S0600) is evaluating _____ after disease progression on first-line FOLFOX/bevacizumab.**
   a. Single-agent irinotecan
   b. FOLFIRI with cetuximab
   c. FOLFIRI with cetuximab/bevacizumab
   d. Both b and c
   e. a, b and c

4. **The six-year update of the MOSAIC trial demonstrated a survival advantage with adjuvant FOLFOX compared to 5-FU among patients with _____.**
   a. Stage II disease
   b. High-risk Stage II disease
   c. Stage III disease
   d. All of the above

5. **RTOG-98-11 demonstrated that 5-FU/cisplatin/radiation therapy resulted in superior disease-free survival compared to 5-FU/mitomycin/radiation therapy in the treatment of anal cancer.**
   a. True
   b. False

6. **A pooled analysis by Goldberg and colleagues revealed that the relative benefit of FOLFOX did not differ by age (<70 versus >70 years old) among patients with colorectal cancer.**
   a. True
   b. False

7. **The NCCTG-N0147 adjuvant trial will evaluate _____ for patients with resected Stage III colon cancer.**
   a. FOLFOX or FOLFIRI with or without bevacizumab
   b. FOLFOX or FOLFIRI with or without cetuximab

8. **NSABP-R-04 is evaluating the role of _____ as a part of neoadjuvant therapy for patients with rectal cancer.**
   a. Bevacizumab
   b. Oxaliplatin
   c. Both a and b
   d. None of the above

9. **Capecitabine is often administered at _____ doses in Europe than in the US.**
   a. Higher
   b. Lower
   c. Equivalent

10. **According to work conducted by Rakesh Jain, treatment with bevacizumab results in vascular normalization, which is associated with _____.**
    a. Increased blood flow
    b. Improved delivery of chemotherapy
    c. Enhanced radiation therapy effects via improved oxygenation
    d. All of the above

Post-test answer key: 1a, 2a, 3e, 4c, 5b, 6a, 7b, 8b, 9a, 10d

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- Review and evaluate the evolving neoadjuvant radiation and/or chemotherapeutic approaches to rectal cancer and explain the absolute risks and benefits of these regimens to patients. . . . . 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into management strategies for patients with advanced colorectal cancer. . . . . 5 4 3 2 1 N/A

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