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Colorectal Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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Editor's Note

An Important New Treatment Option Becomes Available.

The lead interview for this issue of Colorectal Cancer Update focuses on one of the most exciting new data sets in the field for many years. Richard Goldberg's ASCO presentation in Orlando this May surprised many observers by demonstrating a progression-free and overall survival advantage for the so-called FOLFOX regimen compared to the Saltz regimen and to a combination of oxaliplatin and irinotecan (see page 6).

Oxaliplatin has just been approved by the FDA for use in combination with infusional 5-FU and leucovorin in patients who have progressed after receiving irinotecan and bolus 5-FU/leucovorin. The approval time of seven weeks is the shortest ever for a cancer drug in this country. It must be noted that oxaliplatin is also frequently associated with neurotoxicity, which seems acceptable in the metastatic setting but may be more problematic as adjuvant therapy.

Dr Goldberg notes that from a scientific perspective, the survival data in this new report are challenging to interpret, because patients randomized to irinotecan/5-FU/leucovorin (IFL) generally did not have the opportunity to receive oxaliplatin on progression, while those randomized to FOLFOX were able to receive irinotecan. Perhaps the key conclusion is that the availability of oxaliplatin, irinotecan and some variation of 5-FU is improving the prognosis for metastatic colorectal cancer, and that these advances are likely to have even more impact in the adjuvant setting.

A recurring theme in my recent interviews with colorectal cancer research leaders is that pharmacologic interventions have taken a giant step forward in the last 5-10 years, and practicing oncologists now have available far more options both in the protocol and nonprotocol setting. In addition to developing agents and regimens with greater antitumor activity, current trials are also attempting to develop therapies with fewer side effects and toxicities.

One point of great interest in the FOLFOX presentation at ASCO was that the regimen included infusional 5-FU, which causes more patient inconvenience than bolus therapy. However, speakers interviewed for this program report encouraging phase II trials utilizing capecitabine combinations in lieu of infusional 5-FU. Chris Twelves discusses his work on capecitabine/oxaliplatin, which by indirect comparison seems comparable in efficacy to the FOLFOX regimen and will likely now move into phase III randomized trials.

David Kerr reviews another encouraging data set attempting to substitute capecitabine for 5-FU, specifically in combination with irinotecan. Combinations of capecitabine with either irinotecan or oxaliplatin are considered experimental, and these regimens should not currently be utilized in the nonprotocol setting.

As commented on by John Marshall in the inaugural issue of Colorectal Cancer Update, the key dose-limiting toxicity of capecitabine is hand-foot syndrome, and while this side effect can be minimized with careful attention to dosing and patient education, the ASCO meeting included another presentation that offers an alternative approach to this problem.

Edward Lin performed a retrospective case-controlled study of colorectal cancer patients receiving capecitabine who were also receiving the COX-2 inhibitor, celecoxib, for comorbid conditions. Dr Lin theorized that the hand-foot syndrome and perhaps diarrhea associated with capecitabine might be mediated through COX-2, and his new data set provides encouraging pilot data suggesting that celecoxib might be useful in preventing or treating these side effects. Again, further research is required before this strategy should be used outside a research setting.

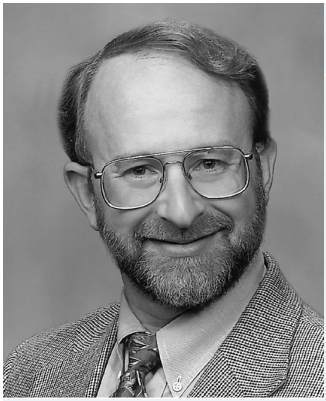
The recent explosion of clinical trial data in colorectal cancer typified by the ASCO meeting also brings to mind the complexities of translating exciting new advances like the FOLFOX data into patient care. I asked Alan Venook to select a patient from his practice who typified this challenge, and he described a patient with the fascinating initial presentation of infected liver metastases. When this young man was stable enough to receive systemic antitumor therapy, a misjudgement in clinical assessment almost had disastrous repercussions.

Specifically, Dr Venook notes that a key predictive factor for toxicity from trials of the IFL regimen has been performance status, and that frightened patients have a tendency to obfuscate their daily difficulties. In this case, in spite of Dr Venook's suspicions that his patient was doing much more poorly than it appeared in the clinic, the IFL regimen was utilized as part of a phase II study evaluating an angiogenesis inhibitor. The patient's performance status rapidly deteriorated, he was removed from the study and switched to a less toxic treatment. Dr Venook notes the important lesson from this case is that efficacy and tolerability data reported from clinical trials must be carefully studied by practitioners before implementing the treatment into nonprotocol care. In particular, he cautions that patients recruited for studies may be younger and in better overall health than those in day-to-day community practice.

Dr Venook's case is an important reminder of the challenge of translating clinical research into patient care, which is the major focus of our educational series. Through 14 years of utilizing the one-on-one interview format, we have learned to pose the difficult questions to investigators for which practicing oncologists seek answers. All of us like to remember the patients who responded well to our therapeutic recommendations, but research "mavens" like Alan Venook also have enough clinical experience to know the pitfalls of incorporating new therapies into patient care.

Those of us who entered oncology before 1990 remember the dreary and very small list of therapeutic options for colorectal cancer treatment, and chemoprevention was rarely even discussed. Today, we now have entered a new era in the field, and it seems likely that a multipronged research approach combining new strategies for prevention, early detection and systemic treatment may result in a significant impact on the morbidity and mortality of this very common disease.

— Neil Love, MD



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Edited comments by Dr Goldberg

Intergroup trial N9741: Irinotecan/5-FU/leucovorin vs irinotecan/oxaliplatin vs oxaliplatin/5-FU/leucovorin

This trial originated in 1997. The first version had four arms, comparing 5-FU/leucovorin (the control arm) to three different ways of giving 5-FU/leucovorin with irinotecan. By March of 1999, the NCI became interested in looking at combinations of oxaliplatin in colon cancer.

It was determined that the most expedient way to test oxaliplatin in the cooperative group setting was to change N9741 from a four-arm to a six-arm trial by adding an oxaliplatin plus irinotecan arm and an oxaliplatin plus 5-FU/leucovorin arm.

The following year several of the arms were closed because of toxicity. In the arms where bolus 5-FU was given either with irinotecan or oxaliplatin, there were very high death rates. So, the six-arm study became a three-arm study. There was a 4.5% 60-day mortality rate for the patients receiving irinotecan/5-FU/leucovorin (IFL) and a 1.8% 60-day mortality rate for the patients receiving irinotecan/oxaliplatin and 5-FU/leucovorin/oxaliplatin (FOLFOX).

The National Cancer Institute convened a group of independent reviewers to review the charts of the patients who died within 60 days. It was found that about half of the patients died of something expected, such as dehydration, diarrhea and neutropenia. But the other half had thrombotic events, such as myocardial infarction, cerebral vascular accident or mesenteric infarction, which was a new toxicity syndrome.

E-N9741, NCCTG-N9741, SWOG-N9741, CLB-89804: Phase III Randomized Study of Combinations of Oxaliplatin, Fluorouracil, Leucovorin Calcium, and Irinotecan as Initial Therapy in Patients with Advanced Adenocarcinoma of the Colon and Rectum Closed Protocol

Eligibility	Locally advanced, locally recurrent or metastatic colorectal adenocarcinoma not curable by surgery or radiotherapy
ARM 1	(Saltz regimen) Irinotecan 125 mg/m^2 + leucovorin calcium 20 mg/m^2 + 5-FU 500 mg/m^2 qw for 4 weeks followed by 2 weeks of rest. Courses repeat every 6 weeks.
ARM 2	(FOLFOX-4 regimen) Oxaliplatin 85 mg/m^2 on day 1 + leucovorin calcium 200 mg/m^2 + 5-FU bolus 400 mg/m^2 + 600 mg/m^2 for 22 hours on days 1 and 2. Courses repeat every 2 weeks.
ARM 3	Oxaliplatin 85 mg/m^2 + irinotecan 200 mg/m^2 on day 1. Courses repeat every 3 weeks.

Treatment continues in the absence of disease progression or unacceptable toxicity.

Trial results

Roughly 800 patients were enrolled in the trial. They were randomized to IFL (the new control arm), FOLFOX or irinotecan/oxaliplatin. The North Central Cancer Treatment Group Data Monitoring Committee released the results of the trial because the time to progression and survival statistics surpassed the early stopping rules that were written into the protocol.

Efficacy

We observed a significant advantage in time to progression (primary end point), response rate and survival with FOLFOX compared to IFL. Although a little lower than reported in other trials, a 28% and 29% response rate was observed for irinotecan/oxaliplatin and IFL, respectively. FOLFOX had a significantly ($p = 0.03$) higher response rate of 38%.

The time to progression was 6.9 months with IFL and 6.7 months with irinotecan/oxaliplatin, compared to 8.8 months with FOLFOX. Although irinotecan/oxaliplatin and IFL were comparable, there was a statistically significant ($p = 0.0009$) difference in time to progression between FOLFOX and IFL.

These data were consistent with those observed in the Saltz trial with IFL and the de Gramont trial with FOLFOX. This was the first randomized comparison of those two regimens.

The survival data was the most interesting; the median survival was 14.1 months with IFL, 18.6 months with FOLFOX and 16.5 months with irinotecan/oxaliplatin. The difference between IFL and FOLFOX was statistically significant ($p = 0.002$). The number of patients alive at one year was

58% with IFL, 71% with FOLFOX and 65% with irinotecan/oxaliplatin. The N9741 trial results confirm the data from the Saltz trial with IFL and from Aimery de Gramont with FOLFOX-4.

Between 59% and 67% of the patients went on to receive second-line therapy. Among the patients randomized to IFL, only 17% received oxaliplatin as second-line therapy. In contrast, 52% of the patients randomized to FOLFOX went on to be treated with irinotecan, and 45% of the patients randomized to irinotecan/oxaliplatin received 5-FU.

Tolerability of the regimens

More patients receiving FOLFOX withdrew from the trial because of toxicity compared to those receiving IFL or irinotecan/oxaliplatin. However, the withdrawals usually occurred late in treatment, after about eight cycles. Most of the patients on FOLFOX who withdrew had neurotoxicity while responding to therapy.

In contrast, patients receiving IFL experienced early toxicity — most often diarrhea, nausea, vomiting and dehydration — that required either dose reductions or drug discontinuation. Some patients receiving IFL died early from toxicity. The toxicity associated with IFL is a little less predictable, occurs earlier and, in my opinion, is more potentially life-threatening than the toxicity associated with FOLFOX.

Our trial had a formal quality-of-life analysis, but we have not been able to analyze it yet. Initially, the toxicity associated with FOLFOX is less severe than the toxicity with IFL. It is particularly noticeable with respect to the hair loss, diarrhea and nausea and vomiting. In my opinion, the statistically significant advantage seen in toxicity with FOLFOX is also a clinically relevant difference.

Time to progression, survival and response rate in N9741

	IFL (n=264)	FOLFOX (n=267)	Oxaliplatin + irinotecan (n=264)
Median TTP (months)	6.9	8.8 HR=0.71 (p=0.0009)	6.7 HR=1.00 (p>0.50)
Median survival (months) 1 year survival	14.1 58%	18.6 71% HR=0.67 (p=0.002)	16.5 65% HR=0.80 (p=immature)
Response rate	29%	38% (p=0.03)	28% (p=0.89)

TTP= Time to progression
Hazard Ratios, 2-sided p-value compared to IFL

Derived from a presentation by RM Goldberg, *ASCO* May 2002, Orlando, FL

Managing patients on irinotecan/5-FU/leucovorin (IFL)

During the first course of therapy, instead of prescribing four weekly treatments of IFL and seeing the patients at six weeks, I now see them weekly. If they have escalating problems with diarrhea, nausea, vomiting and dehydration, I reduce their dose within the first cycle of therapy. Reasons to consider either a dose delay or reduction include incomplete resolution of diarrhea, any signs of dehydration and borderline or low white blood cell counts.

CASE 1: 36-year-old woman treated with FOLFOX followed by hepatic resection

History

At her initial diagnosis, this young speech pathologist was found to have extensive liver metastases, which were not amenable to resection. She had her primary tumor removed at another center, and she was given a bleak prognosis. She was asymptomatic with a performance status of 0.

Follow-up

She enrolled in a clinical trial and was treated with the FOLFOX regimen.

Case discussion

After about six cycles of FOLFOX, she had a dramatic reduction in the number and size of her liver lesions. They were surgically resected, and she is now free of tumor.

She tolerated the therapy very well and was able to continue working during the treatment. She had minimal neurotoxicity of the immediate type. Oxaliplatin regimens seldom cause significant alopecia and have a lower incidence of severe diarrhea, nausea or vomiting and neutropenia than IFL.

She is just passing her second anniversary since resection, has no evidence of disease and obviously is very grateful. She had a six-month-old child at the time of her diagnosis, and she has been able to watch her toddler grow.

Neurotoxicity associated with oxaliplatin

There are two kinds of neurotoxicity observed with oxaliplatin. One occurs within 24 hours of administration and is exacerbated by cold. For instance, if the patient takes a cold beer out of the refrigerator the afternoon after their treatment, he/she will feel like the beer can is electrified. This type of neurotoxicity usually disappears within a day or two of treatment, but it can occur with just a few oxaliplatin doses.

The more problematic and long-lasting neurotoxicity usually occurs after a cumulative dose of about 800 mg/m^2 of oxaliplatin. There is actual damage to the dorsal root ganglion cells. Patients may have a more prolonged, typical neuropathy, where they have difficulty buttoning buttons or picking up coins. In contrast to the taxanes and the vinca alkaloids, oxaliplatin-induced neuropathy improves over time, but it may not resolve completely.

Aimery de Gramont presented results at ASCO from the MOSAIC trial, an adjuvant study, which randomizes patients to 5-FU/leucovorin or 5-FU/leucovorin/oxaliplatin. He found that neuropathy was quite frequent, particularly in patients receiving their ninth, tenth and twelfth cycles of oxaliplatin. In most cases the neuropathy either disappeared or eased dramatically within four months of discontinuing the treatment.

My clinical observation is that the neuropathy improves over time, although it remains more problematic than what Dr de Gramont presented. About 50% of the patients who receive 10 to 12 cycles of oxaliplatin will have some significant amount of neuropathy, although seldom severe. Many patients will say, "I want to keep on treatment, because response is more important to me than this symptom."

Trials evaluating oxaliplatin in combination with capecitabine

There are some phase II data that show promising activity for capecitabine plus oxaliplatin. In the United States, there is some reluctance to embrace infusional 5-FU regimens, based on the need for an indwelling catheter and the potential for catheter-related complications. It would be ideal if we had randomized trial data demonstrating that an oral drug could replace infusional 5-FU.

Sequence of therapy for advanced colorectal cancer

An interesting presentation at ASCO by Axel Grothey compared the Mayo Clinic regimen of 5-FU/leucovorin to FOLFOX. He demonstrated an advantage in survival, response rate and time to progression for FOLFOX compared to 5-FU/leucovorin.

He also looked at the six most recent randomized trials presented at ASCO in advanced colon cancer and demonstrated that survival increases when patients have access to oxaliplatin, irinotecan and 5-FU. In the Saltz trial, only about five percent of the patients received oxaliplatin as second-line therapy, and the median survival was just over 14 months. In the European trials where oxaliplatin and irinotecan were available as second-line therapy, the median survival ranged between 19 and 21 months.

The optimal therapy for patients with advanced colon cancer includes all three drugs (5-FU, irinotecan and oxaliplatin). How they should be sequenced is not yet known, but sequencing is less important than the availability of all three drugs.

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Edited comments by Dr Twelves

Phase II capecitabine/oxaliplatin trial (XELOX)

Objective response rate

Although this was a phase II study, it was not conducted at a single center but rather at a number of different centers. Ninety-six patients were treated, and the key end point was the objective response rate. The combination of capecitabine/oxaliplatin had a 55% overall response rate, similar to what is expected with intravenous 5-FU/oxaliplatin. These are very robust data, because they are from multiple sites in a large study population.

Tolerability

Capecitabine/oxaliplatin was well tolerated. Oxaliplatin in combination with a fluoropyrimidine typically causes neuropathy as the predominant side effect, which is a slightly unusual toxicity for many physicians treating colorectal cancer patients. Nurses and patients must be educated about this neurotoxicity. Once physicians become familiar with the sensory neuropathy — how to identify it and when to reduce or to stop the oxaliplatin — it is easily recognized and treated.

For most patients, the neuropathy manifests as some numbness or tingling in their fingers. Patients may also notice that they must concentrate a little more to carry out fine motor tasks. Patients should also be warned about some other unusual manifestations, which are often precipitated by exposure to cold. There are patients who, if they have a cold drink, get some spasm in their throat. Similarly, some patients experience weakness or a temporary loss in the use of their hands.

The neuropathy is cumulative, and it rarely occurs during the initial cycles. Some patients can continue treatment for six months without significant neuropathy, but quite commonly over that period of time they develop some neuropathy.

Patients often say they have some numbness or tingling in their fingers. When

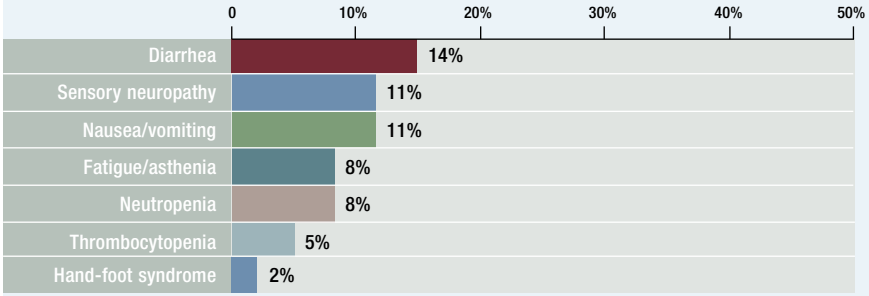
asked if it is troubling them and they say no, then we do not do anything. If they say that they are starting to have some difficulty and that their fingers are not as agile as before, it is determined that they have a functional impairment. At that point, the oxaliplatin dose is reduced or the drug is discontinued. There is a gradual resolution of the neuropathy, which is highly reversible over a period of time.

Neuropathy was also the principal side effect observed when capecitabine was substituted for 5-FU in combination with oxaliplatin, and there was also some diarrhea. About one-third of the patients stopped the oxaliplatin because of the neuropathy. Even when the patients who did not receive the full planned course of oxaliplatin were included in the analysis, there was still a high response rate, encouraging time-to-progression data and survival figures.

Capecitabine/oxaliplatin was much less myelosuppressive than conventional 5-FU/oxaliplatin. The difference in myelosuppression is very striking. It is potentially important for patients, because there is always concern about the risk of infection in patients receiving palliative chemotherapy. As seen in the single-agent trials, 5-FU is much more myelosuppressive than capecitabine. There was virtually no serious myelosuppression with capecitabine/oxaliplatin.

There were only five patients receiving capecitabine/oxaliplatin who had any grade IV toxicity. A slightly lower dose of capecitabine was used, and there was only a 3% incidence of significant hand-foot syndrome. The capecitabine dose was 2,000 mg/m^2/day, rather than 2,500 mg/m^2/day. Only a very small proportion of patients had any symptomatic or functional impairment from the hand-foot syndrome.

Incidence of grade III/IV treatment-related adverse events with XELOX*



XELOX = 3-week cycle of capecitabine (1000 mg/m^2 BID days 1-14) and oxaliplatin (130 mg/m^2 day 1)
Tabernero J et al. *Proc ASCO* 2002;**Abstract 531**.

Research on capecitabine/oxaliplatin compared to 5-FU/oxaliplatin

The two regimens look highly comparable. Although we are comparing two different studies, the data for capecitabine/oxaliplatin match closely the 5-FU/oxaliplatin data from the Intergroup (N9741) trial. Also, the earlier 5-FU/leucovorin/oxaliplatin (FOLFOX-4) study results, by de Gramont, look very similar to our data with capecitabine/oxaliplatin.

The big advantage with capecitabine/oxaliplatin for the patients is convenience. There is also an advantage in terms of reduced myelotoxicity. For the individual patient, the key advantage is that they will only need to come to the hospital for their intravenous infusion of oxaliplatin, while the rest of their treatment can be taken at home.

Patients receiving an infusional 5-FU regimen may require a central venous catheter. In terms of quality of life, substituting infusional 5-FU with oral capecitabine is something the patients will prefer.

My feeling is that, in a few years, capecitabine will replace 5-FU across the board. Clearly, there would be reluctance to substitute on a purely ad hoc basis. Therefore, it is important to explore these combinations accurately and carefully. At the same time, it is impossible to imagine that every single 5-FU regimen, schedule and combination will be the subject of a major randomized trial.

I think with oxaliplatin, if the regulatory authorities do not require a randomized trial, capecitabine could be substituted straightaway. However, a randomized trial will probably be expected by the regulatory authorities, given the incidence of colorectal cancer and the impact this will have in the population.

Trials evaluating adjuvant oxaliplatin in combination with capecitabine or 5-FU

These combinations are quite attractive for the adjuvant setting, partly because of the efficacy data. The recent Intergroup (N9741) trial demonstrated that oxaliplatin was at least as effective as irinotecan and arguably more effective as a partner for 5-FU. The efficacy data clearly indicate the need to explore 5-FU or capecitabine in combination with oxaliplatin in the adjuvant setting. The overall safety profile makes it attractive for patients receiving adjuvant treatment. Neuropathy should not be a substantial obstacle.

Managing advanced colorectal cancer in patients with a poor performance status

Patients enrolled in clinical trials do not accurately reflect the patients seen on a daily basis. It is now clear that combination chemotherapy, arguably with capecitabine/oxaliplatin as a strong contender, represents the gold standard. However, the gold standard may not be appropriate, desirable or chosen by every individual patient with advanced colorectal cancer. There is a proportion of patients who are less fit, do not want intravenous treatments and prefer oral treatments with a fluoropyrimidine, such as capecitabine.

In the coming years, patients will have two or more choices — a more intensive treatment in the form of combination chemotherapy that will impact on response rates and survival or a viable and attractive alternative of single-agent capecitabine. There is a nice distinction between these different approaches. I do not think a one-size-fits-all approach will be the best.

CASE 2:
64-year-old man with extensive metastatic liver disease

History

This man had surgery and adjuvant 5-FU several years previously. He had been well, until he developed some discomfort in his abdomen. He was a slim and relatively fit gentleman. He had not lost a substantial amount of weight and was still eating, but he was a bit less energetic. However, he was still up and about and active. On physical exam, his liver was enlarged and he had right upper quadrant tenderness. His family doctor sent him for a scan, which confirmed the presence of extensive liver metastases. His disease was confined to the liver.

Follow-up

The patient enrolled in the capecitabine/oxaliplatin phase II clinical trial, which he tolerated very well.

Case discussion

This patient had come in with his son, who was very well informed with documents from the Internet. Patients are coming to us with information, and we need to talk to them in a different way to discuss these options. This gentleman really wanted combination chemotherapy, because he wanted the best possible treatment. He was a fit man, so this was appropriate.

There is now a range of different treatment options for metastatic colorectal cancer, a luxury that was unheard of just a few years ago. There is oxaliplatin, irinotecan, capecitabine or intravenous 5-FU.

Since he was concerned about hair loss, diarrhea and other significant toxicities, they preferred oxaliplatin to irinotecan. Fortunately, he was invited to participate in the phase II capecitabine/oxaliplatin trial. Without that clinical trial, he would otherwise have been treated with 5-FU/irinotecan.

As he received capecitabine/oxaliplatin, his performance status was maintained and even improved — partly because of the discomfort in his abdomen resolving. He tolerated the treatment well. He developed some neuropathy, although not severe enough to discontinue the oxaliplatin. He was relieved and pleased to see that he was able to maintain his lifestyle during the trial. He was an active man and an active walker. As with other patients, there was a sense of being involved, because of the oral chemotherapy.

With capecitabine/oxaliplatin, at least half of the patients have a major reduction in their tumor mass and about one-third have either disease stabilization or a minor reduction in their tumor. This patient had a good response. His originally palpable liver was no longer palpable, and his discomfort went away. Additionally, his CEA came down very impressively.

He completed over six months of capecitabine/oxaliplatin and remained off treatment for four months, but eventually his disease progressed. Perhaps reflecting his favorable experience with his initial treatment, he was interested in receiving more chemotherapy, and we treated him with irinotecan. He gained some benefit, albeit less than with oxaliplatin. After the irinotecan, he was still reasonably fit, and he participated in an experimental-drug protocol. He died a few months ago.

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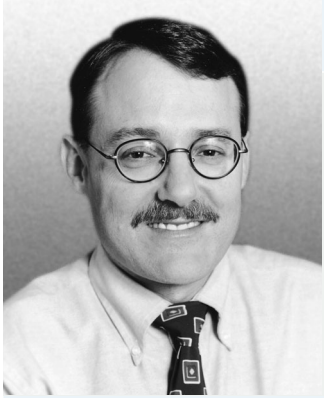

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CASE 3:
45-year-old man presenting with infected liver metastases and colon cancer

History

This patient had about a six-month history of weight loss and abdominal complaints — trouble with intermittent diarrhea and constipation. He acknowledged being ill for a few weeks before being admitted to the hospital with a high fever.

His evaluation revealed large liver metastases, which appeared abscessed, and a large colon cancer as the primary. He had no personal or family history of colorectal cancer. The primary tumor, in the right colon by the hepatic flexure, had seeded bacteria into his metastases. He was treated with antibiotics, and his liver abscess was drained.

When we saw him, he was on antibiotics with a resolved bacteremia and not in very good shape. The primary tumor was minimally symptomatic. It was not obstructed or bleeding actively. He was minimally anemic with a hemoglobin of 12 g/dL. His liver function tests and bilirubin were normal, but his LDH was 900 IU/L. The metastases occupied at least half of his liver.

Clinical course

This patient had a vision of being very aggressive with his therapy. About three months ago, he enrolled on a phase II clinical trial in which he received irinotecan/5-FU/leucovorin and an angiogenesis inhibitor. He did not tolerate the chemotherapy, he experienced tremendous fatigue such that he was bedridden for two weeks after chemotherapy, and he was taken off of the study. Subsequently, he received capecitabine and had a major response.

Case discussion

Infected liver metastases

This patient either denied his symptoms or was in good enough condition that the disease was quite advanced when it was diagnosed. The patient's primary tumor led to bacterial seeding into the bloodstream, infection of the metastases and an abscess. Since bacteria can seed from the bowel into the bloodstream and then infect a heart valve, colon cancer can cause Streptococcus bovis endocarditis. It is a wonder that metastases do not get infected more often. Our group probably sees two or three cases a year of infected liver metastases.

Choice of systemic therapy

The only sites of tumor involvement were the liver and colon. The first question faced was — should his primary tumor be removed? Since his performance status was marginal, he was not obstructed and he had recently been treated for bacteremia, we decided to avoid surgery at that time.

The next question was — how do we optimally treat this young, but relatively debilitated, colon cancer patient? The options included irinotecan/5-FU/leucovorin, 5-FU/leucovorin alone, capecitabine or a phase II study combining irinotecan/5-FU/leucovorin with an angiogenesis inhibitor.

Originally, most of us made the assumption that irinotecan/5-FU/leucovorin should be used in the sickest patients where you needed to make a difference. Surprisingly, the sickest patients are not those who derive the greatest benefit. In our practice, probably a quarter of all patients are not candidates for aggressive, upfront therapy. In those cases, I would use capecitabine as an alternative.

Phase II clinical trial of irinotecan/5-FU/leucovorin and Angiozyme®

This patient and his family wanted to be very aggressive with the therapy. At the first visit, the treatment decision was actually deferred because of his marginal performance status. About two weeks later, the patient insisted he was doing reasonably well, and he did not appear to have an active infection. Therefore, he was offered aggressive treatment.

Barely making the cutoff for performance status, he enrolled in the phase II trial with the angiogenesis inhibitor. Since it was a phase II study, all of the patients were treated with combination chemotherapy (irinotecan/5-FU/leucovorin) and the angiogenesis inhibitor. The angiogenesis inhibitor was Angiozyme® (antiangiogenic ribozyme), a ribozyme to one of the VEGF receptors.

Consistent with what we have learned, he tolerated the treatment extremely poorly. His disease burden made him unable to tolerate the chemotherapy. He did receive an experimental agent, but there was no evidence that Angiozyme® contributed to his toxicity. There is concern that the angiogenesis inhibitors may affect hemostasis and coagulation. This patient had none of those problems. His main problems were horrendous fatigue and some diarrhea. He was bedridden after two weeks of chemotherapy.

Predictors of irinotecan toxicity

It might have been a suboptimal decision to enroll this patient on the clinical trial. In clinical research, the performance status is a very important component of the patient's assessment, but it is a subjective measure. Either the physician overestimates the performance status or the patient, wishing to participate in clinical trials, boosts their performance status and claims to be doing much better than they actually are, in reality. This patient's wife called a week later and said, "He came to see you yesterday and said he was doing fine, but the truth is he can't get out of bed." This emphasizes how critical it is to make an accurate assessment of the patient's performance status.

When discussing the reasons not to use an aggressive three-drug regimen (irinotecan/5-FU/leucovorin), many physicians use age as an important criterion. Age is perhaps a minor criterion, but the key issue is the patient's performance status and overall condition. As one might have expected from this patient's high LDH and marginal performance status, he did very poorly with the irinotecan-based chemotherapy.

It is anticipated that patients treated with prior radiation therapy will experience more irinotecan-related toxicities. There is also concern, not clearly based on data, that patients with a right colon resection may have more toxicity. The diarrhea associated with irinotecan is a small-bowel diarrhea. If a right hemicolectomy is performed, the ileocecal valve is removed; hence, the flow of diarrheal stool into the colon is greater. Therefore, there is more liquid stool without a valve at the ileocecum. Some believe patients with a total colectomy may also have more irinotecan-induced diarrhea.

Capecitabine monotherapy

He was taken off the study. After about three weeks, he recovered to his baseline and was started on capecitabine 1,000 mg/m^2 twice a day (two weeks on, one week off) to which he had a major response. I consistently find the dose of 1,250 mg/m^2 twice a day, to be more toxic than I am willing to accept; therefore, I do not use it in my own practice. Occasionally, I start with a dose of capecitabine as low as 800 mg/m^2 twice a day in patients whom I believe will not tolerate the higher dose (i.e., patients who had pelvic radiation or elderly patients who had prior chemotherapy).

This patient has had six cycles of capecitabine. He tolerated the first four cycles well, the fifth cycle less well and then developed relatively impressive hand-foot syndrome on the sixth cycle. He is currently on a "vacation" from his chemotherapy. His performance status is still not normal, but he is fully functional. It turns out he had understated his side effects all along. In retrospect, he had tingling in his hands and feet.

The question becomes — should capecitabine be continued at a lower dose? He is petrified about taking a "vacation" from the treatment. In patients who achieve a response and in his case a meaningful clinical response, it is often a battle to discontinue the treatment, even for just a few weeks. He had about an 80% reduction in his liver metastases. His primary, however, is still in place. I ultimately convinced him to stop the capecitabine in order to resect his primary.

CASE 3 *(Continued)*

Managing patients with a synchronous primary tumor and metastases at presentation

In colon cancer, the introduction of new agents has somewhat changed the management of patients with a synchronous primary tumor and metastases. Anticipating problems from the primary, for many years it was removed immediately and then the metastatic disease was addressed.

While I have always been a proponent of that idea, I have started edging in the other direction — particularly for patients with bulky disease, because aggressive chemotherapy may have a big impact. Losing a month of time while the patient recovers from surgery may take away that window of opportunity for the patient. The primary concern is the need to wait for wound healing before initiating systemic therapy.

If the primary tumor is removed first, it can be a scheduled operation. In a patient with a nearly obstructing sigmoid colon cancer and metastatic disease, if the primary is not removed, the patient may present late one night with an obstruction. If they have received aggressive chemotherapy, they are neutropenic and thrombocytopenic. Now, a diverting colostomy is required, because the patient is bowel septic.

Obviously, this is a worse case scenario and an extreme example of what happens if the primary is not removed. But, chemotherapy may have enough of an impact that it is important to give it. Previously, 5-FU/leucovorin provided a marginal effect on the cancer. Now, the different chemotherapy options have a major impact.

This patient's tumor had already been a local problem; he had already seeded his liver metastases from the primary. In my mind, it was a problem waiting to happen. In general, right colon primaries are much less problematic, because the stool is liquid in the right side of the colon. So, very rarely do they present as an obstruction. They may bleed, but this patient really had not bled.

On repeat colonoscopy, he had an ulcerated tumor without bleeding in his right colon by the hepatic flexure. It appeared flattened and largely necrotic, compared to what was initially a fungating mass.

After his operation, if all goes well, the decision will be to either go back to irinotecan-based chemotherapy or continue capecitabine. He had horrendous toxicity with irinotecan, and there are no guarantees he would not have that toxicity again. However, his performance status has improved to the point where he may tolerate irinotecan.

Comments on Intergroup trial N9741

This is the first look at the data set, and I think there are some issues with how time to progression and time to failure were presented. This study raises other issues, such as how to best give 5-FU/leucovorin.

One of the differences between treatment groups was the 48-hour infusion for 5-FU with oxaliplatin (FOLFOX) and the bolus 5-FU with irinotecan (IFL). It is possible that this difference contributed to the disparity in the results.

It is not known which subsets of patients are poor candidates for oxaliplatin.

The existing literature might lead one to believe that there are no poor candidates for oxaliplatin, other than those with baseline neuropathies. However, more than half of all patients discontinue oxaliplatin because of neuropathy.

Trials evaluating capecitabine in combination with oxaliplatin

There is a great deal of phase II data for capecitabine/oxaliplatin, which leads us to believe that the combination is at least equivalent to infusional 5-FU/oxalipatin. However, they have not been compared in a head-to-head trial.

It is not a leap of faith to use oxaliplatin in combination with capecitabine, as opposed to a 48-hour infusion of 5-FU. There is a wealth of European data suggesting that capecitabine/oxaliplatin is a reasonable combination.

It is difficult to know from a regulatory perspective where capecitabine fits in this regard. But from a practical perspective, it is hard to see why it would not be incorporated into these regimens.

Phase II study results with capecitabine/oxaliplatin (XELOX) in metastatic colorectal cancer patients

	Treatment setting	Capecitabine/Oxaliplatin doses	CR + PR	Median survival (months)
Borner et al[1]	1st-line (n=43) 2nd-line (n=26)	1,250 mg/m^2 BID*/130 mg/m^2 †	49% 15%	17.1 11.5
Tabernero et al[2]	1st-line (n=96)	1,000 mg/m^2 BID*/130 mg/m^2 †	55%	
Jordan et al[3]	1st-line (n=17)	1,000 mg/m^2 BID*/70 mg/m^2 ‡	41.2%	
Shields et al[4]	1st-line (n=35)	750 mg/m^2 BID*/130 mg/m^2 †	34.3%	

**Capecitabine is administered two weeks on, one week off.*

†Oxaliplatin is administered on day 1 q 3 weeks.
‡Oxaliplatin is administered on days 1, 8 q 3 weeks.

[1]Borner MM et al. *J Clin Oncol* 2002;20:1759-66. **Abstract**

[2]Tabernero J et al. *Proc ASCO* 2002;**Abstract 531**.

[3]Jordan K et al. *Proc ASCO* 2002;**Abstract 2225**.

[4]Shields AF et al. *Proc ASCO* 2002;**Abstract 568**.

Adjuvant oxaliplatin

Although another oxaliplatin regimen has been tested in the adjuvant setting, I believe the data presented at ASCO on N9741 makes it plausible that an adjuvant trial might evaluate infusional 5-FU/leucovorin/oxaliplatin (FOLFOX).

While it is natural to evaluate oxaliplatin in the adjuvant setting, another concern is its long-term toxicities. In the data presented at ASCO, about 50%

of the patients had significant neuropathy. Data on the long-term impact of oxaliplatin-induced neuropathy is needed. If oxaliplatin causes a substantial neuropathy that may affect patients for the rest of their lives, this might be relevant.

Unless we derive a great deal of benefit, we accept much less toxicity in the adjuvant setting than the metastatic setting. I think the adjuvant studies need to be done. However, if adjuvant oxaliplatin leads to cancer survivors who cannot button their shirts or tie their shoelaces because of substantial neuropathy, we will have made a tradeoff.

Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy — *Grade II-IV neurotoxicity after 4, 8 and 12 cycles of an oxaliplatin-based therapeutic regimen plus glutathione (GSH) or placebo*

	After 4 cycles		After 8 cycles		After 12 cycles		
	Placebo (n=26)*	GSH (n=26)*	Placebo (n=19)*	GSH (n=21)*	Placebo (n=8)*	GSH (n=10)*	*p*-Value after 12 cycles
Number of patients with Grade II-IV neurotoxicity	2	1	11	2	8	3	0.004

** Number of assessable patients*

Oxaliplatin regimen = oxaliplatin 100 mg/m² on day 1 concurrent with 6-S-stereoisomer of leucovorin 250 mg/m² as a 2-hour infusion followed by a 24-hour infusion of 5-FU 1,500 mg/m² for 2 consecutive days. Therapy was repeated every 2 weeks.

Glutathione (GSH) = 1,500 mg/m² for 15 minutes immediately before each oxaliplatin administration.

NOTE: The response rate was 26.9% (95% CI 9.8-43.9%) in the GSH arm and 23.1% (95% CI 6.8-39.2%) in the placebo arm, with no reduction in the activity of oxaliplatin.

Derived from: Cascinu S et al. **Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: A randomized, double-blind, placebo-controlled trial.** *J Clin Oncol* 2002;20:3478-3483. Abstract

Clinical relevance of oxaliplatin-induced neuropathy

"In the coming years, there will be an expanding use of oxaliplatin in several other cancers as well as in the adjuvant setting, as indicated by two ongoing randomized trials in colon cancer in Europe (Multicenter International Study of Oxaliplatin 5-FU-LV in the Adjuvant Treatment of Colon Cancer [MOSAIC] trial) and the United States (National Surgical Adjuvant Breast and Bowel Project C-07), oxaliplatin-induced neuropathy will be a growing, relevant clinical problem."

EXCERPT FROM: Cascinu S et al. *J Clin Oncol* 2002;20:3478-3483.

NSABP C-07: Phase III Study of Fluorouracil and Leucovorin Calcium with or without Oxaliplatin in Patients with Stage II or III Carcinoma of the Colon Open Protocol

Eligibility	Previously resected, potentially curable stage II or III carcinoma of the colon (T3,4; N0,1,2; M0)

ARM 1 | Leucovorin calcium + 5-FU qw for 6 weeks

ARM 2 | Oxaliplatin on days 1, 15 and 29 + leucovorin calcium + 5-FU as in Arm 1

Treatment continues every 8 weeks for 3 courses in the absence of disease progression or unacceptable toxicity.

Source: NCI PDQ® Clinical Trials Database

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Rationale for combining capecitabine with irinotecan

When combining drugs, it is attractive to use those with different molecular targets. For irinotecan, the target is topoisomerase-1, and for capecitabine, a prodrug of 5-FU, it is thymidylate synthase. Capecitabine, which starves the cell of thymidine, might synergize with irinotecan, which inhibits DNA topoisomerase-1. If the cell is depleted of thymidine, there is no doubt that irinotecan will be more effective.

Both drugs are active as single agents. There are also data from preclinical, in vitro models suggesting that capecitabine/irinotecan may be synergistic. It makes sense to bring these two mechanistically novel drugs together into a combination regimen.

Phase I/II trials with capecitabine/irinotecan

Working with colleagues in the Netherlands, we have entered 27 chemotherapy-naïve patients with advanced measurable colorectal cancer in our phase I/II trial. In the dose-finding phase I study, the recommended dose was 1,000 mg/m^2 twice daily for 14 days for capecitabine and 250 mg/m^2 every three weeks for irinotecan.

At the recommended dose, there was about a 50% response rate with tolerable side effects. The dose-limiting toxicities were myelosuppression and diarrhea. At the recommended dose, a 10% grade III/IV toxicity rate is projected. Capecitabine/irinotecan has manageable toxicity, is active and is very convenient for patients.

There are two or three other European trials, which have come to very similar conclusions in terms of dose finding. So, the doses of irinotecan 250 mg/m^2

every three weeks and capecitabine 1,000 mg/m^2 twice daily for 14 days every three weeks seem to be the ones that will be included in all the phase III randomized trials. The fact that we have four studies showing very similar conclusions adds weight and certainty to that regimen.

Capecitabine compared to 5-FU/leucovorin

As demonstrated in some very compelling randomized studies in advanced disease, I think capecitabine is much more useful than the bolus administration of 5-FU/leucovorin. There are toxicity and convenience benefits associated with capecitabine.

Since we commonly use infusional 5-FU/leucovorin in Europe and there are no direct comparisons with capecitabine, it would be interesting to study. I would guess that capecitabine is probably as effective with about the same level of toxicity as our rather complicated 48-hour infusional 5-FU/leucovorin regimens, which require pumps and intravenous access.

If we can substitute capecitabine in the combinations with irinotecan or oxaliplatin, then that may be an improvement. There are initiatives in Europe to compare capecitabine/irinotecan to infusional 5-FU/leucovorin/irinotecan.

In pharmacologic terms, such as the degree of inhibition of thymidylate synthase, there are some data suggesting that capecitabine and infusional 5-FU/leucovorin are approximately equivalent. From small patient studies looking at pharmacodynamic end points, they do appear similar.

CASE 4: 66-year-old man treated with irinotecan/capecitabine followed by hepatic resection

History

This active and fit ex-Army brigadier was diagnosed about two years ago, at a different cancer center, with Dukes' C colorectal cancer. At that time, he did not receive adjuvant chemotherapy.

He re-presented to our center with evidence of advanced hepatic metastatic disease. He had bilobular disease with 25% of his liver replaced by tumor. His lungs and the rest of his abdomen were clear. His CEA was ten times the upper limit of normal. His performance status was 1, and he was in good shape. After a multidisciplinary team meeting, it was deemed that he had inoperable disease.

Follow-up

He enrolled on the capecitabine/irinotecan phase I/II trial. He was entered on dose level 3, which consisted of irinotecan 250 mg/m^2 and capecitabine 2,000 mg/m^2/day for 14 days. After four months of therapy, only two out of the original ten metastatic lesions remained, and they were surgically removed.

CASE 4 *(Continued)*

Case discussion

After two months of therapy, a CT scan revealed an excellent partial response. Within the first two months of treatment, his CEA level came down very quickly to normal, consistent with the excellent partial response. After another two months of treatment, the CT scan demonstrated that his disease was now unilobar. He only had two lesions remaining out of what were initially ten.

The patient tolerated the treatment well. He did not require any dose reductions throughout the four-month treatment period. He did, however, have noticeable thinning of his hair.

His performance status was well maintained. He was able to maintain his daily activities — chairman of a local hospital trust and caring for his large house and garden. Since he only came to the hospital once every three weeks, rather than more frequently as is customary with the complicated 5-FU infusion regimens used in Europe, he was freed up. This case illustrates the use of chemotherapy to downsize an inoperable tumor.

The patient underwent resection of his residual disease two months ago. The surgeons performed an intraoperative ultrasound and found nothing to biopsy. His liver has started to regenerate, his two-month postoperative CT scan was completely clear and all tumor markers are normal.

We are not planning to restart chemotherapy at this point. As far as we can tell, he has no residual tumor. Of course, the likelihood is that there is residual disease, but we are giving him a period of time off treatment.

He may be part of a group of patients who now have a five-year survival rate of about 15% to 20%. I believe had we not removed the residual disease, his median life expectancy would have been 12 to 18 months.

Increasingly in patients with isolated hepatic metastases, we may be able to downsize, rather than downstage, their disease with these powerful chemotherapy regimens. Then, I think they should have surgery. We are moving into a very different natural history of this disease.

There are data from neoadjuvant trials with infusional 5-FU/leucovorin/oxaliplatin that look very interesting. In one quite large surgical series from the hospital Paul Brousse in France, patients with initially inoperable disease that was made operable by chemotherapy had as good a survival as patients with initially operable disease. Although it is not a randomized trial, it is a sophisticated anecdote from one of the largest surgical series in the world.

Gene therapy for colorectal cancer

We have manipulated the common cold virus, the adenovirus, so that it only divides in cancer cells — those with a mutant P-53 or some other molecular switch. Then we put new genes into the virus for enzymes that convert nontoxic, inactive prodrugs into fairly cytotoxic species.

We clone the enzyme from a bacteria or a virus, so there is no human

equivalent. Then we put the gene for that enzyme into a viral vector, in our case adenovirus. The enzyme we are interested in is called nitroreductase (NTR). It converts the prodrug, CB1954, into a very toxic bifunctional alkylating agent, which is active in all the colorectal cancer cell lines tested. We have also worked with cytosine deaminase, another bacterial enzyme, which converts the antifungal drug 5-fluorocytosine (5-FC) into 5-FU. Another enzyme, thymidine kinase, converts ganciclovir to a toxic antimetabolite.

We have also made a virus with two enzymes, NTR and cytosine deaminase. We have shown synergistic cell kill through the generation of both 5-FU and the alkylating agent in the same cell. Therefore, we have delivered combination chemotherapy with a single virus.

Phase I gene therapy trial

We have just completed our first clinical trial, which is not published yet. In that trial, we injected the virus directly into the cancers of patients with hepatic metastases. We saw very significant expression of the virus and the enzyme, which was the proof of our principle. Does the virus infect the cells? Are the enzymes made?

In the adjuvant setting, giving the virus via the hepatic artery/portal vein or directly into the peritoneal cavity could be a clever idea. I am a supporter of regional chemotherapy, and it seems logical. No doubt, we are working on developing stealth viruses that can be given intravenously.

In our phase I trial giving the virus directly into the liver tumor nodules, there were no toxicities. Once the prodrug is activated into the cytotoxic species, it has a half-life of only seconds. The cytotoxic species is confined in the cell and does not diffuse into the bloodstream. Therefore, it would be very unlikely to see the systemic toxicity associated with conventional chemotherapy.

Since our virus-directed enzyme prodrug therapy (VDEPT) synergizes with 5-FU/leucovorin and capecitabine, combination studies with the virus, the prodrug and probably chemotherapy will be next. Perhaps some day in the adjuvant setting, we will give a complicated postoperative chemotherapy regimen and adjunctive gene therapy to the liver, administered through the portal vein or into the peritoneal cavity. Gene therapy holds some promise, but it is some ten years away.

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Edited comments by Dr Lin

Role of COX-2 in colorectal cancer

Cyclooxygenase-2 (COX-2), a regulator of inflammation, is also known as the central "playmaker" in tumor angiogenesis. COX-2 is expressed in colorectal cancers, and its expression may be a negative prognostic factor. Furthermore, COX-2 is a very potent angiogenic factor, and it is upstream of VEGF (vascular endothelial growth factor) and PDGF (platelet-derived endothelial growth factor). The exact role of COX-2 in colorectal cancer progression is still being evaluated. However, it is an important target for colorectal cancer treatment.

Phase II trial of chemotherapy in combination with celecoxib for metastatic colorectal cancer

Dr Charles Blanke conducted a phase II trial with triple therapy plus a COX-2 inhibitor (irinotecan/5-FU/leucovorin plus celecoxib) in patients with previously untreated, unresectable or metastatic colorectal cancer. His data suggests a potential improvement in irinotecan-related diarrhea and an increase in vascular syndromes. My interpretation is that the COX-2 inhibitors potentially work through the antiangiogenic pathway. This may be the reason the patients had increased vascular syndromes, such as myocardial infarctions or strokes.

Capecitabine in combination with celecoxib

Capecitabine is activated through thymidine phosphorylase (TP), also known as a platelet-derived endothelial growth factor, which is a very potent angiogenic enzyme. Tumor cells upregulate and turn on the angiogenic phenotype.

Potentially, capecitabine delivers more cytotoxic drug to the tumor cells than normal cells.

Although the combination of capecitabine/celecoxib must be evaluated in prospective clinical trials, the idea is to give two drugs that potentially antagonize their side effects, but also enhance their antitumor activity and improve the delivery of the drug to the tumor.

Etiology of hand-foot syndrome

Hand-foot syndrome only occurs rarely with bolus 5-FU. Other drugs also cause hand-foot syndrome, such as liposomal doxorubicin and docetaxel. Hand-foot syndrome is drug-related — if you do not give the drug, you do not get hand-foot syndrome.

Because of the way capecitabine is metabolized and where it accumulates, I believe hand-foot syndrome is probably due to its metabolites. In fact, in our prospective trial, we will look at COX-2 levels as well as try to determine which metabolites accumulate in the hands and feet. I think the metabolites are probably prostaglandin-like.

The feet seem to have delayed circulation, so there might be a difference in how the metabolites are cleared. Additionally, enzyme expression may vary in different tissues. The hands and feet, like tumor cells, may potentially accumulate more 5-FU. I am not aware of any data demonstrating that patients who develop hand-foot syndrome have a better tumor response. I think hand-foot syndrome is one of the toxicities highly specific to patients who are receiving continuous-infusion 5-FU, capecitabine and some other drugs.

Celecoxib attenuates capecitabine-induced hand-foot syndrome

We thought the hand-foot syndrome might be driven by COX-2, which has been "proven" to be the central regulatory mediator of inflammation. We had also observed that patients taking celecoxib together with capecitabine did not experience any hand-foot syndrome.

Retrospective analysis of patients receiving capecitabine/celecoxib

In a case-controlled retrospective analysis, capecitabine-treated patients with tumor-related pain were given celecoxib (200 mg twice a day) and observed for hand-foot syndrome. Then they were compared to a historical-control group of patients primarily treated with capecitabine alone and not given any other NSAID. Both groups of patients were identified by the pharmacy database and matched according to the capecitabine dose. Most of the

patients received 1,000 mg/m^2 of capecitabine twice a day. The median ages for the capecitabine/celecoxib and control groups were 65 and 55, respectively. Therefore, the control group was a bit younger.

Tolerability

Six months ago when the data was gathered, the capecitabine/celecoxib cohort consisted of about 32 patients. In those patients receiving capecitabine/celecoxib, grade III hand-foot syndrome was almost nonexistent. Only one patient developed grade III hand-foot syndrome while taking celecoxib.

That patient had bilateral DVTs and congestive heart failure with grade III edema at baseline. He actually developed more of a foot syndrome, but no hand syndrome. Other than that patient, we saw very mild hand-foot syndrome — minor erythema and minor pain that did not interfere with the patients' daily work. In the capecitabine-only, dose-matched control group, 34% and 17% experienced greater than grade I and grade III hand-foot syndrome, respectively.

Another interesting observation was related to diarrhea. Approximately 28% of the patients receiving capecitabine alone required hospitalization for hydration. We rarely encountered the need for hydration in the patients taking capecitabine/celecoxib. There were, however, a couple of patients who developed dehydration, but they required only outpatient hydration.

Additionally, the patients receiving celecoxib seemed to have much better pain control. About 30% of the patients had a performance status of 2, but they all universally improved when given celecoxib along with capecitabine.

Case-controlled retrospective analysis of patients receiving capecitabine/celecoxib or capecitabine alone as first- or second-line therapy for metastatic colorectal cancer

Tolerability	Capecitabine/celecoxib (n=32)	Capecitabine (n=35)	*p*-Value
HFS (> grade I)	4 (12.5%)	12 (34.3%)	0.037
HFS (> grade II)	1 (3.1%)	6 (17.1%)	0.11
Diarrhea (> grade I)	5 (15.6%)	10 (28.6%)	0.2
Diarrhea (> grade II)	1 (3.1%)	10 (28.6%)	0.005

HFS=hand-foot syndrome

Lin EH et al. **Celecoxib attenuated capecitabine-induced hand-and-foot syndrome (HFS) and diarrhea and improved time to tumor progression in metastatic colorectal cancer (MCRC)** *Proc ASCO* 2002;**Abstract 2364**.

Efficacy

Although quite a few patients had failed prior chemotherapy (i.e., irinotecan, oxaliplatin and prior 5-FU regimens), capecitabine produced a decrease in CEA and disease stabilization. In the patients who had received prior irinotecan and were treated with capecitabine/celecoxib, there were two partial responses. No partial responses were seen in any irinotecan-experienced patients who were treated with capecitabine alone. However, three chemotherapy-naïve patients had a partial response to capecitabine alone, which lasted about nine months. In contrast, seven patients who received capecitabine/celecoxib had responses that lasted for about 12 months. One patient has been on therapy for approximately 18 months.

Case-controlled retrospective analysis of patients receiving capecitabine/celecoxib or capecitabine alone as first- or second-line therapy for metastatic colorectal cancer

Efficacy	Capecitabine/celecoxib (n=32)	Capecitabine (n=35)	*p*-Value
Partial Response	4 (12.5%)	3 (8.5%)	0.325
Stable Disease	20 (62.5%)	8 (22.8%)	0.001
Progression	6 (18.7%)	25 (71%)	0.028
CEA decline >25%	24 (75%)	8 (22.8%)	0.005
Median TTP	6 months	3 months	—

TTP=time to tumor progression

Lin EH et al. **Celecoxib attenuated capecitabine-induced hand-and-foot syndrome (HFS) and diarrhea and improved time to tumor progression in metastatic colorectal cancer (MCRC)** *Proc ASCO* 2002;Abstract 2364.

Phase II capecitabine/celecoxib trial

The retrospective data are hypothesis-generating and the basis for our large prospective phase II trial that will evaluate full-dose capecitabine with a higher dose of celecoxib. The primary objectives of that trial will be to achieve better tumor response and provide a cohort for comparison to a historical cohort with respect to the dose intensity of capecitabine, quality of life and the incidence of the hand-foot syndrome. The first phase of clinical testing will evaluate the combination for feasibility, toxicity, tolerance, quality of life and clinical benefit.

Capecitabine/celecoxib has the advantage of being a totally oral regimen. Many patients treated with both drugs have maintained a very good quality of life. Patients with a good response have been able to go back to their daily routine activities. To prove the initial observation and hypothesis, our phase II trial will focus on the hand-foot syndrome and tumor efficacy. Then we may consider adding an EGFR (epidermal growth factor receptor) antagonist and "pilot" a targeted-therapy combination.

Capecitabine/celecoxib in clinical practice

Our results were very consistent, and we have treated five or six patients who developed capecitabine-induced hand-foot syndrome with celecoxib (200 mg twice a day). Universally, their hand-foot syndrome has improved.

Recently, we had a patient on a capecitabine/irinotecan trial who developed grade III hand-foot syndrome. Despite reducing the dose of capecitabine from 1,000 mg/m^2 to 750 mg/m^2 twice a day, she still had hand-foot syndrome. At 500 mg/m^2 twice day she did not have hand-foot syndrome, but her tumor progressed.

An option for her was to increase the dose of capecitabine to 900 mg/m^2 twice a day and initiate celecoxib. She actually did well with that option, and the hand-foot syndrome did not return. Of the patients treated with celecoxib for the hand-foot syndrome, four or five have not experienced a recurrence while being able to maintain the capecitabine dose intensity.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
capecitabine	Xeloda®	Roche Laboratories, Inc.
leucovorin	—	Various
irinotecan	Camptosar®	Pharmacia Corporation
oxaliplatin	Eloxatin®	Sanofi-Synthelabo, Inc.
celecoxib	Celebrex®	Pfizer, Inc./Pharmacia Corporation
5-FU	—	Various
antiangiogenic ribozyme	Angiozyme®	Ribozyme Pharmaceuticals, Inc.
5-fluorocytosice (5-FC)	Ancobon®	ICN Pharmaceuticals, Inc.
ganciclovir	Cytovene®	Roche Laboratories, Inc.

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