For decades, the goal of treatment in metastatic colorectal cancer (CRC) was palliative. Palliative treatment relied on chemotherapy with 5-fluorouracil. Later on, leucovorin was added; the combination generated response rates of 10-20% and a median overall survival (OS) of about 12 months. Some patients with metastases that were confined to the liver and deemed resectable underwent liver surgery with curative intent, but this group of patients was small (at best 10-15%) and only 30% of those were alive 5 years after surgery.

The emergence of new, more effective chemotherapy regimens to treat CRC has conceivably changed our approach in three ways:

1. We are now able to allow more patients with metastatic disease to proceed to liver surgery with curative intent by downsizing previously unresectable metastases with highly active neoadjuvant chemotherapy.

2. We should be able to improve the outcome of those patients who undergo surgery by (additional) post-operative chemotherapy, and;

3. The integration of novel chemotherapy drugs, such as irinotecan and oxaliplatin, and biologics, including bevacizumab and cetuximab, into our systemic treatment of advanced CRC has already led to significant prolongation of OS which is now in the range of 2 years.

Today the challenge is to allow more patients to benefit from these advances. We need to inform oncologists, surgeons, and patients of the potential for curative treatment and of the literally once-in-a-lifetime chance they might miss if they fail to consider a curative approach. Furthermore, the medical community must develop clear criteria to identify those patients who are good candidates for the neoadjuvant/resection strategy. Fortunately, we are on our way to meeting these challenges.

Establish a Dialog

The secret is close cooperation and communication between oncologists, surgeons, and patients. Our approach at the Mayo Clinic can be easily introduced at any cancer center or hospital. It begins even before I see a patient. I work closely with one of a group of surgeons to develop a treatment strategy based upon the results of the most recent CT examination. We try to determine whether the patient is a good candidate for resection. If so, we will discuss the option with the patient, and then, with his consent, will begin neoadjuvant chemotherapy.

After 2 months of treatment, the surgeon and I review the new CT results to determine if the metastases have been sufficiently downsized. If we are satisfied with the response, the patient will be admitted for surgery. If not, the patient will complete another 2 month course of chemotherapy and then we make another assessment. Four months is the critical time period; if a patient is not resectable at that point, that status is highly unlikely to change in the future. For those patients, the next course is palliative treatment.

Those whom we are able to resect are evaluated once again after surgery to discuss the option of postoperative chemotherapy to prevent recurrence. At that point, we would use our
knowledge on the tumor's response to the neoadjuvant treatment to decide which regimen to use. For instance, if the tumor responded very well to a certain neoadjuvant chemotherapy, it would make sense to continue to use this regimen again after resection.

One of the advantages of this approach is that it can facilitate communication across long distances. The patient need not be seen in order for the medical team to develop the treatment plan. Right now, we can make a decision based on CT or MRI scans sent to us from other facilities. I can even foresee a time when our team will be able to review a virtual scan of a patient in Omaha via the Internet to determine if curative resection is achievable. In this way, the expertise of leading cancer centers can be available to anyone at the click of a button.

Of course, the suitability of a patient for curative treatment is not always readily apparent. Opinions will differ. When in doubt, I always give the benefit of the doubt to the cure and try to convince the surgeon to try. Missing a patient who could be cured is far worse than having to abandon the laparoscopy in the middle of the procedure. And the patients always agree to be aggressive in their treatment. Everyone wants to be cured, and that, after all, is our objective.

Which patients are good candidates for curative therapy? In the past, only 15% of CRC patients with hepatic metastases were recommended for surgery. A new strategy, known as OncoSurge, was recently developed by a consensus panel of oncologists and liver surgeons (more information can be found at: Alberts S Colorectal Dis 2003;5[Suppl 3]:20-28). Using new and expanded patient selection criteria, and the availability of more effective neoadjuvant and postoperative chemotherapy, OncoSurge should help increase significantly the rate of resectability and long-term survival in our patients.

In fact, curative therapy should now be considered for patients who heretofore would have been deemed to have contraindications to surgery, such as multiple or bilobar metastases, large tumor size, a prior Dukes' stage C or a poorly differentiated primary tumor, synchronous detection of metastases with the primary tumor, age, or a resection margin of less than 1 cm. As the OncoSurge consensus agreed, we can now apply curative resection to a wide range of clinical conditions. We can even re-resect subsequent metastases. The OncoSurge strategy now offers a large population of patients the possibility of prolonged survival and the chance of cure. Indeed, the only circumstances that now serve as an absolute contraindication to resections are non-resectable extrahepatic disease and portal lymph node involvement.

The development and implementation of OncoSurge illustrates the merits of collaboration between clinical oncologists and surgeons. By working together in close cooperation, we can increase survival and give the chance of a cure to patients who in the past would have received little more than a bleak prognosis.

Bevacizumab Plus FOLFOX Improves Survival In Advanced Colorectal Cancer, Say E3200 Researchers

The combination of bevacizumab (Avastin) and FOLFOX improves survival in previously treated patients with advanced colorectal cancer, according to final results of a key phase III trial (E3200) presented in January at a gastrointestinal cancer symposium. The findings suggest that in addition to its role as a valuable supplement to first-line, fluorouracil-based chemotherapy, bevacizumab appears to be effective and safe as part of a second-line combination with FOLFOX.

The trial, which was conducted by the Eastern Cooperative Oncology Group, enrolled 828 patients who had previously received 5FU and irinotecan (Camptosar) regimen and were refractory to treatment. Patients were randomized to 1 of 3 treatment arms: FOLFOX4 (85 mg/m² of oxaliplatin on day 1 only, plus a bolus of 200 mg/m² of leucovorin and 400 mg/m² 5FU, followed by a 22-hour continuous infusion of 600 mg/m² of 5FU, bimonthly for 12 cycles) plus bevacizumab (10 mg/kg q 14 days), FOLFOX4 alone, or bevacizumab alone. The investigators suspended randomization to the third arm at the recommendation of the trial’s data monitoring committee, who found that overall survival seemed likely to be significantly lower than the other 2 cohorts.

The median survival of patients receiving FOLFOX4 plus bevacizumab...
Should patients with stage II colon cancer receive adjuvant chemotherapy? Unlike in stage III disease, for which a 1990 National Institutes of Health consensus development conference recommended the use of 5FU-based adjuvant chemotherapy for all medically fit individuals with fully-resected tumors, the evidence to support any specific adjuvant therapy for stage II patients has been weak. In large part, the dearth of compelling data in this subset of patients stems from the fact that too few stage-II patients were included in the pivotal trials to know if they received benefit from treatment. On the other hand, covariate analysis of the pivotal trials has failed to show a significant treatment by stage interaction. In other words, the proportional decrease in tumor relapse and death resulting from adjuvant chemotherapy in stage II patients is similar to that seen in stage III patients. There were not enough events in the stage II patients for the observed benefit to reach statistical significance. Additionally, substudy findings from the QUASAR trial, which compared 5FU and leucovorin (Wellcovorin) with 5FU/leucovorin and levamisole (Ergamisol), showed a statistically significant survival advantage for chemotherapy in stage II colon cancer patients.

In 2004, an international panel of experts was convened to develop evidence-based guidelines for clinical decision making. Under the direction of co-chairs Al B. Benson III, MD, Northwestern University Feinberg School of Medicine, and Daniel G. Haller, MD, University of Pennsylvania Cancer Center, Philadelphia, PA, the panel attempted to answer 2 primary questions: first, should all medically fit patients with curatively resected stage II colon cancer be offered adjuvant chemotherapy as part of routine prac-
Routine Use of Adjuvant Chemotherapy in Stage II Disease Not Recommended, Although High-Risk Patients Might Benefit

continued from page 3

tice, and second, should patients with curatively resected stage II colon cancer and a poor prognosis be offered adjuvant chemotherapy. After a systematic review of the literature up to that point, including all randomized controlled trials and meta-analyses, the panel decided that:

• The routine use of adjuvant chemotherapy for medically-fit stage II colon cancer patients is not recommended
• For stage II patients at high risk, with poor prognosis, or an inadequate sampling of nodes, the direct evidence does not support the use of adjuvant therapy outside the clinical trials setting. However, as many of the studies included in the analysis were poorly powered, the indirect evidence gleaned from clinical experience might well support the use of adjuvant chemotherapy in this population of patients. That decision should be made by oncologists and patients after a careful review of the individual’s specific medical situation.

Routine Use Unnecessary

Even though the benefits of adjuvant chemotherapy are clear for patients with stage III colon cancer, most of the evidence suggests that treatment does not provide any survival advantage. Why might this be so?

“The failure to document a statistically and clinically relevant benefit is largely attributable to the relatively good prognosis for stage II patients after surgery alone,” said Benson and Haller. As a result, there has been little reason to randomize thousands of patients to demonstrate “a small margin of absolute improvement in survival with adequate statistical power,” they added. Although the panel did find an absolute improvement in disease-free survival ranging from 5% to 10%, depending on the trial, this gain did not translate into a statistically significant difference in overall survival. For these patients, the risks of treatments (significant drug toxicities) clearly outweigh the potential benefits.

Those patients at high risk present a different picture, however. Patients who have provided only a very small sample of lymph nodes (< 13) may well have micrometastic disease and could possibly be helped by adjuvant therapy. In general, the greater the number of analyzed lymph nodes, the more confident physicians can be that a patient does not have residual disease.

Other patients with poor prognostic features, including T4 lesions (those that adhere to or invade local organs), perforation of the colon at the tumor site, peritumoral lymphovascular involvement or poorly differentiated histology also should be considered as candidates for adjuvant chemotherapy.

Based on what is known about the clear efficacy of treatment in stage III colon cancer, the possibility that adjuvant chemotherapy would not provide a similar benefit in stage II disease “seems biologically implausible,” Benson and Haller said. In addition, large phase III trials do not show a significant treatment by stage interaction. Patients and oncologists prepared to act primarily on the indirect evidence — the results of stage III trials — are justified in considering treatment, if they recognize that the benefit as measured in absolute survival is small, perhaps about 5%, they added. This opinion is supported by the updated report of the MOSAIC trial at ESMO 2005 by de Gramont which showed a significant improvement in disease-free survival in stage II patients treated with FOLFOX. The essential point is that the risk-benefit ratio must be considered: high risk stage II patients have a risk of relapse in the 30% range and therefore have potentially more to gain with adjuvant therapy.

In making this choice, the panel stressed, patients must be included in the decision-making process. Physicians must provide all of the information necessary for patients to make an informed selection.
Careful Monitoring and Aggressive Treatment Key to Managing Diarrhea in Colon Cancer: Expert Panel

With an incidence ranging from 50% to 80%, chemotherapy-induced diarrhea is one of the most common, and troubling, side effects associated with modulated fluorouracil (Adrucil)(FU) regimens, single-agent irinotecan (Camptosar), and FU/irinotecan combinations in colon cancer treatment. Indeed, upwards of one-third of all patients may report severe or life-threatening diarrhea. High-dose treatments, particularly irinotecan plus bolus FU plus leucovorin (Wellcovorin) (IFL), can even increase the risk of mortality, compared with other regimens, due to the loss of fluids, electrolytes, and the ensuing renal insufficiency and cardiovascular complications.

Despite the recognition that treatment-related diarrhea may be associated with life-threatening adverse events, until the past few years there have been no standardized guidelines for the evaluation and management of chemotherapy-induced diarrhea. The first recommendations did not appear until 1998; two years later, they were revised based on new research. More recently, in 2003-2004, an independent consensus panel of experts met to update the original guidelines to include, among other evidence, new toxicity data reported in 2 National Cancer Institute (NCI) cooperative group studies. Chaired by Al B. Benson III, MD, Northwestern University Feinberg School of Medicine and The Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, the panel found that vigilant monitoring and aggressive therapy, particularly in patients with early warning signs of severe complications, can reduce the risk of morbidity and mortality due to cancer therapy-induced diarrhea.

Among the most important new developments reported by the panel are:

- **Mortality associated with IFL.** A number of patients in 2 NCI trials—N9741 and C89803—using the IFL regimen had early toxic death. An independent panel of review found that the deaths stemmed from gastrointestinal toxicity and cardiovascular events and recommended more vigilance in monitoring adverse events, especially treatment-induced diarrhea, in patients receiving IFL. In particular, gastrointestinal toxicity should be assessed weekly, particular in older patients.

- **The optimal dose of octreotide.** Recent studies show that in patients who fail loperamide (Imodium) therapy, 500 µg of octreotide (Sandozstatin) TID may be more effective than the lower dose treatment.

- **The role of prophylactic anti-diarrheal therapy in patients receiving irinotecan.** To date, the results of studies have been mixed, although a long-acting, slow-release formulation of octreotide has shown promise. Further research will be necessary to fully evaluate this strategy.

- **Diarrhea induced by radiation therapy.** There do not appear to be any effective pharmacological approaches to preventing diarrhea associated with radiation therapy, although current studies using octreotide are now underway.

The assessment of symptoms should be rigorous and classified as either “uncomplicated” (grade 1 or 2) or “complicated” (grade 3 or 4).

Complicated cases should be managed aggressively with intravenous fluids, dose-titrated octreotide (for severely dehydrated patients) and the administration of antibiotic (such as ciprofloxacin to prevent sepsis resulting from chemotherapy damage to the gastrointestinal mucosa).

The initial management of mild to moderate diarrhea should include dietary modifications (eg, eliminating all lactose-containing products and dietary supplements), the initiation of loperamide, and instructions to patients to record the number of stools and to report immediately any symptoms of life-threatening sequelae, such as fever or orthostatic hypotension.

- If symptoms resolve, dietary modifications should continue, with solid food added gradually. Loperamide may be discontinued when patients have been free of diarrhea for 12 hours.

- If diarrhea persists, increase the dose of loperamide and add oral antibiotics to prevent infection. After 48 hours, loperamide should be discontinued and replaced by subcutaneous octreotide or other second-line agent. If the diarrhea is related to chemotherapy, the patient should be evaluated further by the treating physician.

Again, the panel stressed that careful monitoring, early identification of warning signs and symptoms, and aggressive management is a must.
Making Sense of the Studies: Biologics May Offer Added Treatment Options

The recent approval of 2 biological agents, bevacizumab (Avastin) and cetuximab (Erbitux), give physicians new options in treating patients with colorectal cancer. Although bevacizumab is approved for first-line treatment and cetuximab for second- or third-line therapy, a number of newly published studies have investigated the use of these drugs in other patient populations. The findings suggest the addition of these compounds to standard chemotherapy may increase survival.

METASTATIC CANCER
The Role of Bevacizumab
Bevacizumab is a recombinant monoclonal antibody that targets vascular endothelial growth factor (VEGF), a key regulator of physiologic and pathologic angiogenesis. In addition to having direct antiangiogenic effects, bevacizumab also may alter tumor vasculature and reduce interstitial pressure in tumors, thereby improving the effects of chemotherapy. The final results of the pivotal Phase III trial were published in 2004 (N Engl J Med 2004;350:2335-42) and showed that the addition of bevacizumab to 5-fluorouracil (5FU)-based combination chemotherapy produces statistically significant and clinically meaningful improvement in survival in treatment-naïve patients with metastatic colorectal cancer.

In the study, more than 800 patients were randomly assigned to receive either irinotecan (Camptosar), bolus 5-FU (Adrucil), and leucovorin (Wellcovorin) (IFL) plus bevacizumab (5 mg per kilogram of body weight every 2 weeks) or IFL plus placebo. The median duration of survival was 20.3 months in the bevacizumab group, compared with 15.6 months in the placebo group, a 34% reduction in the risk of death (hazard ratio [HR]: .66, p<.001). In addition, the median duration of progression-free survival was 10.6 months in IFL plus bevacizumab-treated patients, versus 6.2 months in patients receiving IFL plus placebo (HR: .54, p<.001). Furthermore, IFL plus bevacizumab patients showed a median response duration of 10.4 months; in contrast, those given IFL plus placebo showed a significantly shorter response: 7.1 months (HR: .62, p<.001). An important adverse response reported in the bevacizumab arm was hypertension, but this side effect was manageable, according to the investigators. In addition, several patients receiving bevacizumab had bowel perforations. The makers of bevacizumab have recently warned doctors and patients of an increased risk of blood clots in the arteries, as well as heart attacks, strokes, and angina.

“The improvement in the clinical outcome afforded by the addition of bevacizumab to IFL suggests that blocking VEGF may be a broadly applicable approach to the treatment of colorectal cancer,” said Herbert Hurwitz, MD, Duke University Medical Center, Durham, NC. “These results suggest that bevacizumab plus fluorouracil-based chemotherapy should be considered a new option for the treatment of metastatic colorectal cancer.”

It should be pointed out that this trial concluded that the addition of bevacizumab to any fluorouracil-containing drug regimen provides a survival advantage. Even though IFL was used in the clinical trial, discussions between Genentech, the sponsor of bevacizumab, the investigators, and the Food and Drug Administration led to an expanded indication for bevacizumab to include FOLFOX and 5FU and leucovorin.

Cetuximab a Potential First-Line Therapy?
There also is emerging evidence that the addition of cetuximab to FOLFIRI (irinotecan 180 mg/m², day (d)1, and leucovorin 200 mg/m² d1, 5-FU bolus 400 mg/m² d1, followed by 5-FU 46 h continuous infusion 2.4 to 3 g/m² every 2 weeks) may be safe and active as primary treatment for metastatic colorectal cancer. Cetuximab is a monoclonal antibody that targets the epidermal growth factor receptor, a protein that plays a role in regulating cell growth. Although the study led by Philippe Rougier, MD, of the Hôpital Ambroise-Paré, Savigny Sur Orge, France, was small, the investigators said the combination of cetuximab with 2 different FOLFIRI regimens (low- or high-dose 5FU) produced no dose-limiting toxicities in the low-dose group and 3 (n=13) in the high-dose arm. Preliminary efficacy findings were encouraging as well: the median time to progression was 10.9 months. A phase III trial is planned for the future.

ADJUVANT CHEMOTHERAPY
An Oral Substitute
Capecitabine (Xeloda) is an oral fluoropyrimidine that is converted to fluorouracil in tumor sites. Capecitabine often is prescribed in combination with oxaliplatin and irinotecan. It is approved for use in the US as a first-line agent based upon its equivalence with bolus 5-FU plus leucovorin in metastatic colorectal cancer patients. A team of European, Canadian, and Australian researchers compared
capecitabine and bolus 5FU/leucovorin given on the Mayo Clinic regimen in a phase III study of drug-naïve patients with resected Dukes’ C colon cancer reported at ASCO 2004. The primary end point was equal or greater disease-free survival. Nearly 2000 patients ranging in age from 18-75 years were included in the trial and were followed for a median of 3.8 years. There was a strong trend to superior disease-free survival in the capecitabine group (HR: 0.87, p=0.0528) and a trend to superiority for overall survival as well (HR: 0.84, p=0.0706). Moreover, patients receiving capecitabine showed a significant 14% reduction in the risk of relapse (p=0.041). These patients also experienced significantly less diarrhea, stomatitis, nausea/vomiting, alopecia and neutropenia, although they reported more hand foot syndrome than those receiving 5-FU/LV (p<0.001). Patients above age 70 maintained the same results as younger patients, leading the investigators to conclude that capecitabine “should replace 5FU/leucovorin given on the Mayo Clinic regimen in the adjuvant treatment of colon cancer.”

Despite these encouraging findings, there are several caveats. While oral capecitabine is equivalent to 5FU plus leucovorin, it is not superior. The side effects are different; when capecitabine is used in combination with other drugs, the toxicity pattern may be affected, with hand foot syndrome and diarrhea the dose limiting toxicities. Furthermore, the tolerable doses of capecitabine have consistently been lower in the US than in Europe for reasons that are not completely understood. Nevertheless, the introduction of oral capecitabine marks an important addition to the metastatic colorectal cancer drug armamentarium.

Current Chemotherapy Options for Colorectal Cancer
While many American oncologists prefer oral capecitabine along with irinotecan and oxaliplatin to avoid the use of infusion pumps in patients with metastatic colorectal cancer, FOLFOX and FOLFIRI continue to be the mainstays of treatment.

For surgical adjuvant therapy of colon cancer, the multinational MOSAIC trial evaluated the benefit of FOLFOX4 in patients with completely resected stage II or III colon cancer. The results demonstrated that that the 3-year disease-free survival (DFS) rate increased 5.3% with FOLFOX4, compared with 5FU/leucovorin (78.2% vs 72.9%, p=0.002), a 23% reduction in the risk of recurrence for patients receiving oxaliplatin. The researchers observed this benefit in all patient subsets. Moreover, FOLFOX4 was generally well tolerated and did not increase mortality, although a significantly greater number of oxaliplatin patients evidenced neutropenia. Some critics of the study indicated that even though DFS improved after 3 years, overall survival (OS) did not. An update of the MOSAIC trial at a gastrointestinal cancers symposium in January, 2005, which reported 4 years of follow-up, indicated the benefits of FOLFOX in prolonging DFS have been maintained. Further follow-up of MOSAIC will be watched closely to ascertain whether OS increases. Additional trials investigating the use of FOLFOX, with and without bevacizumab, and comparing FOLFOX versus FOLFIRI versus 3 months of each regimen plus cetuximab, bevacizumab, or both, will also help reveal the future course of adjuvant chemotherapy in colon cancer.