Multidisciplinary Management of Colorectal Cancer Metastases

Highlights from a symposium conducted in conjunction with The Society of Surgical Oncology’s Annual Meeting, held in San Diego, California, on March 22–26, 2006.

A symposium conducted in conjunction with the 2006 Annual Meeting of The Society of Surgical Oncology and moderated by Anton J. Bilchik, MD, PhD, FACS, four renowned leaders in medical and surgical oncology discussed the criteria for hepatic resection, downstaging of hepatic metastases, and evolving role of chemotherapy in patients with metastatic colorectal cancer. Special focus included discussion of combining advanced surgical techniques and expanded chemotherapy options to improve resectability and survival rates.

Learning Objectives
Upon completing this review of this symposium, the physician should be able to:
• Review the expanding indications for hepatectomy in metastatic colorectal cancer;
• Determine what methods are available to downstage patients thereby improving the chances for curative resection;
• Discuss the role of novel biologic and systemic chemotherapeutic agents in the adjuvant setting;
• Describe the potential value of molecular profiling to improve the selection of patients for chemotherapy.

Audience
Surgical oncologists, medical oncologists, and other physicians who participate in the care of patients with metastatic colorectal cancer, and researchers who are interested in the investigation of new approaches to the treatment of this disease.

Needs Assessment
Colorectal cancer is the second-leading cause of cancer death in the United States. While appropriate screening may result in prevention and early detection, fewer than 50% of eligible adults are undergoing such screening. Surgical and other treatment advances for advanced or metastatic disease have led to improved survival rates, but more innovative and effective approaches are needed. To provide optimal care to patients with metastatic colorectal cancer, it is essential that clinicians and researchers understand the current standard of care as well as emerging data on newer treatment options and ongoing clinical trials.

Expanding the Criteria for Hepatic Resections: Are Old Criteria Obsolete?

For patients who have colorectal cancer with hepatic metastasis, the utilization of novel combinations of surgery and chemotherapy may offer the best hope of increased long-term survival. “Several questions regarding hepatic resection and medical therapy exist, including which patients are appropriate for hepatic resection, what type of chemotherapy regimen is most effective, and what duration of pre- and postoperative chemotherapy is safe,” said Michael D’Angelica, MD, FACS, assistant attending physician, Memorial Sloan-Kettering Cancer Center and assistant professor, Cornell University, Weill Medical College, New York City. Dr. D’Angelica noted that clinicians need to prepare patients with this stage of disease for repeated recurrence, hepatic resection, and chemotherapy.

Hepatic Resection: What Were the Old Criteria?
According to Dr. D’Angelica, before effective chemotherapy regimens were available for the treatment of colorectal cancer, several studies showed varying prognostic factors related to resection of hepatic metastases. In an early study of liver resection, Adson and colleagues concluded that the presence of extrahepatic disease precluded 5-year survival (1). In 1986, Ekberg and colleagues conducted a multivariate analysis of prognostic factors related to hepatic resection and concluded that the procedure should be indicated only when there are fewer than four liver tumors, no extrahepatic disease (EHD), and an achievable resection margin of at least 1cm (2). Two years later, Hughes and associates reported factors negatively impacting survival, including close margins, stage of disease, disease-free interval, size of the tumor, and CEA levels. While no factor alone was significant enough to contraindicate resection, the authors recommended consideration of multiple factors. Factors that alone appeared to be potential contraindications to resection were the presence of EHD or four or more metastases (3). A 1992 study showed that a CEA > 200ng/mL and surgical margin < 1cm, and presence of four or more tumors were predictive of poor outcome (4). However, in 1995, Fong and Blumgart reported that EHD and inability to resect all hepatic disease were the only absolute contraindications to resection (5). In 1999, Fong and colleagues followed 1001 patients and conducted a multivariate analysis, identifying seven factors that were independently predictive of outcome. The researchers focused on five preoperative criteria, the combination of which could be summed to determine a predictive clinical risk score, with low scores correlating with higher long-term survival and higher scores, lower long-term survival. “The authors concluded that a clinical risk score of 0, 1, or 2 indicated resection, while a score of 3, 4, or 5 warranted experimental adjuvant trials,” Dr. D’Angelica explained. The five criteria included node-positive primary colorectal disease, a disease-free interval < 1 year, presence of > one hepatic tumor, largest hepatic tumor of > 5cm, and CEA > 200ng/mL (6).

“Overall, the criteria for resection of hepatic metastases have been conflicting and confusing, but have evolved with recent progress in surgical technique and more effective chemotherapy agents,” Dr. D’Angelica noted.

Hepatic Resection: What Has Changed?
Since the early research on prognostic factors for outcome after resection of hepatic metastases, both surgery and chemotherapy regimens have progressed. “Ten years ago, the mortality rate for liver resection was approximately 5%. In most current series of resection for colorectal cancer-associated hepatic metastases, the mortality rate is approximately 1%, pointing to a significantly safer operation,” Dr. D’Angelica said. There also exists an expanded capability of resecting extensive hepatic disease, utilizing portal vein embolization, intraoperative ablation, and two-stage operation. In addition, where chemotherapy was relatively ineffective 10 years ago, the addition of agents such as oxaliplatin, irinotecan,
and targeted agents has resulted in significantly increased response rates and median survival times in patients with advanced colorectal cancer (Figure 1). Dr. D’Angelica presented current data on surgical outcomes associated with three key factors: the presence of EHD, the presence of four or more metastases, and size of surgical margins.

### Presence of Extrabdominal Disease

In patients who had metastatic colorectal cancer, Elias and colleagues compared those who had liver resection with and without resection of EHD. The results showed that, while survival rates were significantly better in those without EHD, long-term survival in those with EHD was 20% to 30% (7). In Memorial Sloan-Kettering unpublished data, 1,120 patients underwent hepatic resection, with 136 patients also having simultaneous resection of EHD. The results show a median survival of 34 months and 47 months, and a 5-year survival rate of 26% and 39%, in those with EHD and without EHD, respectively (8). “The outcomes clearly differ between those with and without EHD, but they do not preclude the possibility of resection in those with EHD. Indeed, the survival rates with resection of EHD are similar to those that originally encouraged resection of hepatic metastases. Ultimately, it is the extent of disease that determines outcome,” Dr. D’Angelica explained. He pointed out that long-term survival in these patients will likely include repeat recurrences, resections, ablations, and chemotherapy regimens. These results for concurrent resection of EHD represent highly selected patients with an overall limited disease burden and must be interpreted in this context.

### Presence of Four or More Metastases

The addition of effective chemotherapy agents has resulted in significant improvements in survival rates for patients with colorectal cancer with four or more metastases. In a recent study of such patients by D’Angelica and colleagues, a follow-up of 33 months revealed a 5-year overall survival rate of 33%. “Ultimately these survival rates are similar to or better than those that originally encouraged hepatectomy for metastases; the price is a recurrence rate of about 80% and the need for repeat chemotherapy and resection,” Dr. D’Angelica said (8).

### Size of Surgical Margins

According to Dr. D’Angelica, studies also demonstrate the impact of surgical margins on resection outcomes. Data from D’Angelica and colleagues showed median survival rates of 30 months with involved margins (<1 mm), 42 months with margins 1 to 10 mm, and 55 months with margins >10 mm. “Upon multivariate analysis, close margins appeared less significant, with biology and clinical pathologic factors being more important and a wide margin of >1 cm retaining independent significance,” the speaker said (8). Another study by M.D. Anderson researchers showed that positive margins were associated with poor outcomes and negative margins, regardless of width, with good outcomes. This multivariate analysis showed no significance with posi-
tive margins (9). “Overall, the current evidence suggests that margins do have an impact on surgical outcomes, that there exists a complex inter-relationship between tumor biology and surgical technique, and that close margins should not preclude resection of hepatic metastases,” Dr. D’Angelica said.

In conclusion, Dr. D’Angelica emphasized that, while the ability to predict outcome with standard clinicopathologic data is limited, historically accepted contraindications to resection of hepatic metastases are no longer strictly applicable. “Increased survival rates in patients with hepatic metastases—including those with multiple liver tumors, EHD [limited to one organ site], and close surgical margins—have been made possible due to improvements in surgical technique and systemic therapy,” the speaker summarized. Issues that remain under investigation include the use of neoadjuvant chemotherapy over time, patient fitness for repeat surgery and prolonged systemic therapy with recurrence, and the identification of accurate prognostic markers.

Multimodal Therapy in Downstaging Hepatic Metastases and Improving Resectability

“With the development of more effective chemotherapy agents for the treatment of metastatic colorectal cancer, an increased capability to downstage hepatic metastases and improvements in surgical techniques have led to increased resectability and survival rates. In an era of multiple chemotherapy options, it is imperative that surgical oncologists and medical oncologists work together to ensure the appropriate and optimal use of systemic therapies and sequence of therapies in conjunction with hepatic resection and other treatment modalities,” said J. Nicolas Vauthey, MD, FACS, Professor of Surgery, Chief of Liver Service, M.D. Anderson Cancer Center, Houston. Dr. Vauthey noted that the chemotherapy agents used should be tailored to the individual, with consideration of patient comorbidities and risk factors as well as drug efficacy and safety profiles.

Utilization of Chemotherapy Options

In recent years, the use of systemic chemotherapy agents has dramatically improved response and survival rates in patients with metastatic colorectal cancer (Table 1) (10-13). Whereas the use of 5-fluorouracil/leucovorin (5-FU/LV) alone is associated with a response rate of 21% and median survival time of 13 months, 5-FU/LV/oxaliplatin (FOLFOX) or folinic acid/5-FU/irinotecan (FOLFIRI) regimens are associated with a response rate of 54% to 56% and a median survival time of 20 to 22 months. The addition of targeted therapies, such as bevacizumab or cetuximab, has enhanced treatment further, with response rates of approximately 70% and a median survival time exceeding 2 years. “While improvements in treatment are still needed, the effectiveness of existing chemotherapy agents has played a critical role in increasing the number of patients able to undergo resection of colorectal metastasis,” Dr. Vauthey said (14, 15).

According to Dr. Vauthey, the rationale for use of preoperative chemotherapy of resectable colorectal cancer metastases includes the potential for downsizing of disease, which may result in increased curative resection rates and allow for more conservative surgeries (16). In addition, this treatment approach may assist in the identification of responders. Progression may represent a contraindication to surgery in those with > three metastases (14, 15), while preoperative response may allow tailoring of postoperative chemotherapy use, thus avoiding ineffective treatment (17). Finally, preoperative chemotherapy may allow for the simultaneous early treatment of hepatic and systemic metastases.

| Table 1. Systemic Chemotherapy Options in Metastatic Colorectal Cancer (10-13) |
|--------------------------|--------------------------|--------------------------|
| Treatment                | Response %               | Median Survival (mos)    |
| No treatment             | 0                        | 7                        |
| 5-FU/LV alone            | 21                       | 13                       |
| Irinotecan alone         | 18                       | 12                       |
| Irinotecan + bolus 5-FU/LV | 39                      | 15                       |
| FOLFOX or FOLFIRI        | 54-56                    | 20-22                    |
| FOLFIRI plus bevacizumab or FOLFOX plus cetuximab | 70 | >24 |

Limitations to Resectability

“Despite great improvements in treatment options and techniques, there is a limit to resection of liver metastases,” Dr. Vauthey said. The increased risk of complications in patients with a future liver remnant (FLR) of ≤ 20% is well known (18). For this reason, several preoperative treatment modalities—including portal vein embolization (PVE) and chemotherapy—have been utilized to increase the size of the FLR and to downsize hepatic metastases.

In a study of intrahepatic liver volume, for example, 75% of patients undergoing extended right hepatectomy had a left lateral bisegment II/III of < 20% of the total liver volume (19). “To address this issue, our candidates for extended right hepatectomy or major hepatectomy at risk for complications undergo CT scanning of the liver with 3-dimensional reconstruction to determine the volume of the anticipated FLR. We take the measured FLR volume divided by the calculated total liver volume using a formula based on body surface area to obtain the size of the anticipated liver remnant,” Dr. Vauthey explained (20). Based on the results of this standardized method of calculation, patients whose anticipated FLR size is too small may be referred for PVE. “We emphasize PVE of the entire tumor-bearing liver to avoid accelerated tumor growth and optimize the size of the future liver remnant,” he explained. This procedure may result not only in increased FLR, but also in increased liver function. Indeed, in comparisons of patients who had and did not have preoperative PVE, postoperative liver function tests were improved in the PVE group (20). After extensive chemotherapy, PVE is now being considered in patients with a FLR ≤ 30%, and in patients with cirrhosis it is considered with a FLR ≤ 40%. In a series by Vauthey and...
In patients with solitary colorectal cancer liver metastasis, radiofrequency ablation (RFA) is being evaluated as an alternative to resection. However, studies comparing resection versus RFA for solitary liver metastasis have shown significantly higher local recurrence and significantly lower survival rates in the RFA group (22). “At M.D. Anderson, our preferred approach to treatment is to utilize sequential multimodality therapy with preoperative oxaliplatin/irinotecan-based chemotherapy, followed by varying sequences of resection, two-stage resection, PVE, and postoperative chemotherapy, depending on the individual case. Indeed, we have reduced the number of RFAs performed by more than 50% over the past 2 years,” Dr. Vauthey noted.

Safety Considerations with Chemotherapy and Resection

While preoperative and postoperative chemotherapy options offer potentially improved outcomes for many patients with colorectal cancer with liver metastases, clinicians need to be cautious of the potential risks of chemotherapy, including steatosis and steatohepatitis. In an early study, 47% of patients receiving 5-FU had CT findings demonstrating fatty changes in the liver (23). In another study, 30% of those receiving alpha-interferon and 5-FU experienced reversible steatosis. More recently, an evaluation by Kooby and associates pointed to an increase in complications and infection as well as a trend toward an increase in mortality associated with marked steatosis in patients undergoing hepatectomy (24). This finding was associated with a high body mass index (BMI) and preoperative chemotherapy. The authors suggested that steatosis was not a contraindication to major resection, but recommended “due caution.”

In addition, steatohepatitis can also be observed in association with chemotherapy use. Steatohepatitis is associated with impaired hepatic regeneration and may lead to fibrosis, to cirrhosis, and to an increased risk of hepatocellular carcinoma. In an M.D. Anderson series of 34 patients with steatohepatitis, 4% of patients had received no chemotherapy, 5% 5-FU, 6% oxaliplatin, and 20% irinotecan. In those with steatohepatitis, 90-day mortality was 15% compared with 2% in those without steatohepatitis (25).

Another risk with chemotherapy use is sinusoidal dilatation. The recent M.D. Anderson series showed this complication in 22 patients, 2% of whom were receiving no chemotherapy, 0% 5-FU, 4% irinotecan, and 20% oxaliplatin. “In another study (26), an increased incidence [49%] of sinusoidal dilatation was observed in a subset of patients who were receiving primarily oxaliplatin, and developed sinusoidal dilatation after undergoing major hepatectomy with total vascular exclusion,” the speaker noted. The study also showed that surgical complications increased with prolonged preoperative chemotherapy. The higher incidence of sinusoidal dilatation in the study by Karoui and colleagues compared to the M.D. Anderson series may be due, he said, to the use of total vascular exclusion, leading to congestion of the liver. Prolonged FOLFOX treatment of ≥6 months has also been shown to be associated with splenomegaly.

“Overall, the use of chemotherapy may be predictive of distinct hepatic injuries—including sinusoidal dilatation, steatosis, steatohepatitis—and associated with morbidity and mortality after extensive surgery. While steatohepatitis appears to be the main factor in increasing morbidity and mortality, it needs to be determined whether irinotecan alone is associated with this injury, or whether BMI, diabetes, metabolic syndrome, and other factors play a role. Further study is needed to determine the associated morbidity and mortality after major resection or extensive surgery in patients with these conditions,” Dr. Vauthey explained.

Future Directions

In closing, Dr. Vauthey suggested that researchers and clinicians exercise vigilance by reviewing CT imaging to map metastatic disease, utilizing unenhanced CT imaging to assess liver and spleen density, and considering PVE in appropriate patients. “In addition, surgeons need to work closely with their medical oncologist colleagues to achieve resection as soon as possible, to avoid irinotecan use in patients with high BMI or preexisting steatosis, to consider pathologic evaluation as well as laparoscopy to assess the non-tumorous liver, and to use standardized criteria to report volumetry and any complications or injury. It is hoped that, in combining new options in chemotherapy, innovations in surgery, and other novel modalities, outcomes will continue to improve in the treatment of metastatic colorectal cancer,” the speaker concluded.

A New Era in Colorectal Cancer Treatment: Agents That Work

With the availability of numerous chemotherapy agents and combinations of agents for the treatment of metastatic colorectal cancer, research continues in the assessment of which agents, in which combinations, in which sequences, in which patients will afford optimal outcomes and minimal toxicity, according to Lee S. Rosen, MD, Premiere Oncology affiliated with the John Wayne Cancer Institute and St John’s Health Center, Santa Monica, California. Dr. Rosen provided an overview of the current and emerging chemotherapy regimens being used in the treatment of metastatic colorectal cancer.

Efficacy of New Chemotherapy Regimens

“The treatment of metastatic colorectal cancer is an area in which tremendous progress has been made over the last 10 years, and yet more effective therapies are still needed. In 2006, numerous treatment modalities are being used, alone and in combination, to fight this disease,” Dr. Rosen said (Table 1). The use of chemotherapy for metastatic colorectal cancer began with 5-fluorouracil (5-FU) alone, achieving response rates of only approximately 20% and survival times of 6 to 9 months. Since then, several new agents have been developed.

Capecitabine, an orally administered prodrug of 5-FU, has been shown to be at least as effective as intravenous 5-FU in patients with this disease, and is a more convenient alternative to 5-FU infusion in the adjuvant and metastatic settings (27). “However, we know that a combination of agents, rather than a fluoropyrimidine alone, is a more effective treatment for colorectal cancer,” Dr. Rosen noted.

One recent phase III trial compared three first-line combination regimens, irinotecan/5-FU/leucovorin (IFL) versus 5-FU/leucovorin/oxaliplatin (FOLFOX) versus irinotecan/oxaliplatin (IROX), in patients with metastatic colorectal cancer. The results showed response rates of 31%, 45%, and 34%, respectively, and overall survival times of 14.8 months, 19.5 months, and 17.4 months, respectively. Based on these data, the authors concluded that the FOLFOX regimen was more effective than an irinotecan-based combination (27-29).

In another phase III trial, researchers studied the sequencing of combination regimens by randomizing patients with advanced colorectal cancer to receive either first-line folinic acid/5-FU/irinotecan (FOLFIRI) until progression followed by FOLFOX6 until progression, or the opposite sequence. These findings showed that those beginning with the oxaliplatin regimen may have had a higher
In patients with metastatic colorectal cancer but poorer performance status, bevacizumab plus 5-FU/LV resulted in significantly improved overall survival rates in the arm containing 5-FU/LV alone (35). Potential toxicity issues related to VEGF-based therapies include increased risk of hypertension, bleeding/clotting events, proteinuria, wound healing and perforation issues, fatigue, hypothyroidism, and hoarseness. Some of the anti-VEGF agents have associated dizziness and ataxia, possible cardiotoxicity, and rare posterior reversible leukoencephalopathy syndrome ( PRES; occurring only in the setting of uncontrolled hypertension) (32, 36-38).

“Further study of available and emerging chemotherapy and biologic agents is essential to identify optimal treatment combinations, sequences, and durations; to determine appropriate treatment settings whether first-line or refractory, adjuvant or metastatic; to minimize toxicity; and to tailor treatment regimens to the individual patient with colorectal cancer.”

Another biologic agent, cetuximab, is used to target the epidermal growth factor receptor (EGFR), which is overexpressed in a number of malignancies. “However, it appears that even patients with EGFR-negative tumor types may benefit from this agent,” Dr. Rosen noted.

In one study of EGFR-positive patients with colorectal cancer for whom irinotecan treatment had failed, the use of cetuximab with irinotecan produced significantly greater overall response rates than the use of cetuximab alone (23% vs 11%) and longer times to progression (39, 40). In addition, Saltz and colleagues conducted the BOND-1 trial, showing similar and significantly improved partial response and median time to progression with irinotecan plus cetuximab than with cetuximab alone, and the BOND-2 trial, demonstrating even greater improvement with the addition of bevacizumab to these regimens (41). These patients all were “bevacizumab-naive” with the ongoing BOND-3 trial seeing what happens to patients who progress on another bevacizumab-containing regimen and then are randomized to cetuximab-bevacizumab versus irinotecan-cetuximab-bevacizumab. The main side effects of cetuximab include an acne-like rash, changes to nails and fingers, and rare hypersensitivity reactions.

With such a wealth of options for metastatic colon cancer, treatments must be optimized based on the multidisciplinary physician team’s goals for a particular patient. Current standard of care would most often include a combination oxaliplatin- or irinotecan-based regimen plus bevacizumab in the first line. Newer studies will hopefully clarify the role of the biologic agents in first-line metastatic and adjuvant disease, schedules and lengths of treatment.

In closing, Dr. Rosen emphasized that great strides have been made in the medical treatment of metastatic colorectal cancer, but there remains a need for improvement. “Further study of available and emerging chemotherapy and biologic agents is essential to identify optimal treatment combinations, sequences, and durations; to determine appropriate treatment settings whether first-line or refractory, adjuvant or metastatic; to minimize toxicity; and to tailor treatment regimens to the individual patient with colorectal cancer,” he concluded.

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### Table 1. Metastatic Colorectal Cancer Treatment Options in 2006

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<th>Chemotherapy</th>
<th>Radiation Therapy</th>
<th>Targeted agents</th>
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<td>• 5-FU</td>
<td>• SIR spheres</td>
<td>• Bevacizumab</td>
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<td>• Radiofrequency ablation</td>
<td>• Capecitabine</td>
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<tr>
<td>• Hepatic arterial infusion</td>
<td>• Irinotecan (IFL/FOLFIRI)</td>
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<td>• SiR spheres</td>
<td>• Oxaliplatin (bFOL/FOLFodox)</td>
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**Addition of Targeted Therapies**

Two targeted therapies have been approved for the treatment of advanced colorectal cancer: bevacizumab and cetuximab. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) (93% human, 7% murine). This agent is believed to act by inhibiting tumor angiogenesis or perhaps normalizing aberrant tumor blood flow, although the exact mechanism of action is not clear.

In an early phase III trial, Hurwitz and colleagues found that first-line bevacizumab plus IFI produced significantly greater median survival, progression-free survival, and duration of response times than IFI alone (32). In addition, Hochster and colleagues conducted the TREE-1 and TREE-2 trials, studying the use of bevacizumab/oxaliplatin combinations (Figure 1) (33, 34). “These findings showed that the addition of bevacizumab improved outcomes in all oxaliplatin regimens studied,” he said.

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**Figure 1. Trials of Bevacizumab Plus Oxaliplatin Regimens in Patients with Metastatic Colorectal Cancer (MCRC): Study Schemas (33, 34)**

- mFOLFOX6
  - Oxaliplatin 85 mg/m² q2w with modified LV5FU2
- bFOL
  - Oxaliplatin 85 mg/m² q2w plus bolus 5-FU/LV (500/20 mg/m²) d1,8,15 q28d
- CapeOx
  - Oxaliplatin 130 mg/m² q21d plus Capecitabine 1000 mg/m² bid x 14 d

- Previously untreated MCRC (N=158)
- Previously unresected and MCRC (N=225)

- mFOLFOX6 + Bevacizumab
  - 5 mg/kg, q2w (n=75)
- bFOL + Bevacizumab
  - 5 mg/kg, q2w (n=74)
- CapeOx + Bevacizumab
  - 7.5 mg/kg, q3w (n=74)

- Treatment until disease progression
- Primary end point: Incidence of grade 3/4 AEs (first 12 weeks)
- Secondary end points: OS, ORR, TTP, TTF
Tailoring Chemotherapy in Metastatic Colorectal Cancer Using Molecular Profiling: Are We There Yet?

“Emerging evidence suggests great potential benefit in the development of molecular profiling approaches to identify prognostic and predictive factors to assist in guiding treatment decisions in patients with metastatic colorectal cancer,” said Robert B. Diasio, MD, Departments of Medicine, Pharmacology/Toxicology, and Genetics, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham. “To continue to advance medical science in this area, it is highly important to collect tissue specimens for correlative laboratory studies and clinical trials. Essential to this process is that surgical oncologists talk to their patients with colorectal cancer to obtain informed consent, ensure appropriate collection and storage techniques, and ensure assay validation,” said Dr. Diasio.

According to Dr. Diasio, both predictive and prognostic markers are under study for potential benefit in choosing optimal treatment regimens in patients with metastatic colorectal cancer. “Several prognostic markers—including chromosomal instability, TGFβRI, microsatellite instability, TS, and thymidylate synthase—appear promising for their potential value in the adjuvant setting. For other markers, such as the presence of methylation phenotype [CIMP], the role continues to be unclear,” Dr. Diasio said (42).

In terms of predictive markers (predicting response to chemotherapy), potentially valuable markers include UGT1A1 with irinotecan to predict toxicity as well as TS, dihydropyrimidine dehydrogenase (DDP), and thymidylate phosphorylase (TP) with fluoropyrimidine agents, ERCC1 with oxaliplatin, and other genes identified by microarray to predict efficacy (42).

In closing, Dr. Diasio emphasized the need for confirmation of the value of molecular markers in larger, prospective, cooperative group studies. With the progression of research in molecular profiling, it is hoped that chemotherapy regimens may be tailored specifically to the individual, allowing for improved treatment responses and ultimately reduced morbidity and mortality rates in patients with colorectal cancer.

References

1. What were the most commonly cited contraindications to hepatic resection for metastatic colorectal cancer prior to the modern era?
   a. Greater than 4 metastases
   b. Extrahepatic disease
   c. Sub-centimeter margins
   d. All of the above

2. What should patients with extensive hepatic metastases who are being counseled about the outcome of resection be told?
   a. Long-term cure is at least 33%.
   b. No follow up is necessary since the tumors are unlikely to recur.
   c. While long-term survival occurs in about 33% of patients, recurrence is common but there are effective surgical and medical treatments.
   d. When and if the tumor recurs there is no treatment.

3. In patients with colorectal metastases who are candidates for major hepatectomy, and have a high BMI and pre-existing liver steatosis, which of the following drugs should be avoided in a preoperative chemotherapy regimen?
   a. 5-FU
   b. Irinotecan
   c. Oxaliplatin
   d. Bevacizumab or cetuximab

4. Current data on chemotherapy-associated hepatic injuries suggest that:
   a. Surgical complications increase with the duration of chemotherapy.
   b. Steatohepatitis but not steatosis increases mortality.
   c. Steatohepatitis does impair hepatic generation.
   d. All the above

5. In 2006, treatment options for a patient with newly diagnosed metastatic colorectal cancer, excellent performance status, and desiring “aggressive care” include:
   a. Fluoropyrimidine (e.g. 5-fluorouracil or capecitabine) alone
   b. Irinotecan- or oxaliplatin-containing regimen
   c. A or B plus bevacizumab
   d. All of the above

6. Patients with liver-only metastatic colorectal cancer (regardless of the number of lesions at diagnosis) should consider the following at some point in their care, when appropriate:
   a. Combination chemotherapy
   b. Surgical resection
   c. Radiofrequency ablation
   d. All of the above

7. Which of the following have been suggested as potential prognostic markers in stage II colon cancer?
   a. Deletion of chromosome 1
   b. Epidermal growth factor receptor
   c. Vascular endothelial growth factor
   d. Microsatellite instability
Multidisciplinary Management of Colorectal Cancer Metastases

Made possible through an unrestricted educational grant from sanofi-aventis, U.S.

Objectives
Upon completion of this program, participants should be able to: a) Review the expanding indications for hepatectomy in metastatic colorectal cancer; b) Determine what methods are available to downstage patients thereby improving the chances for curative resection; c) Discuss the role of novel biologic and systemic chemotherapeutic agents in the adjuvant setting; and d) Describe the potential value of molecular profiling to improve the selection of patients for chemotherapy.

Program Evaluation

1. How well organized was the program? (1 = poor; 2 = fair; 3 = good; 4 = excellent) _________

2. How would you rate the clarity of the program? (1 = poor; 2 = fair; 3 = good; 4 = excellent) _________

3. Overall, how would you rate the importance of this program? (4 = very; 3 = moderate; 2 = little; 1 = not at all) _________

4. Do you intend to make any changes in your practice or patient care as a result of this program? Yes No

   If Yes, how? Comment ____________________________

5. Did the program include proper disclosure of speakers’ potential conflict of interest and relationship with industry? Yes No

6. Did the program include proper disclosure of speakers’ discussion of FDA Off-Label use of medications or products? Yes No

   If NO, please comment ____________________________

7. Was this a fair and balanced program? Please comment on the scientific rigor, fairness, and balance of the material.

   Comment ____________________________

8. What related topics would you find useful for future SSO programs and publications? ____________________________

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