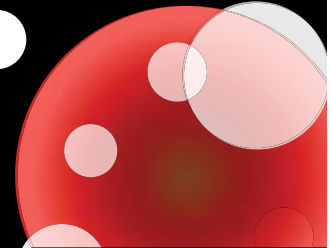




CME On-Demand Webcast

Translating Clinical Trial Data into the Community Setting: A Case-Based Approach to Metastatic Colorectal Cancer



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Syllabus

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Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424

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Robert S. Stern

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Introduction

After decades of having only one effective agent, 5-fluorouracil/leucovorin, for use in treating metastatic colorectal cancer, clinicians now have a wide variety of new chemotherapy combinations, novel targeted biologics, and combination chemotherapy/biologic regimens from which to choose. As a result of these new options, median overall survival has now exceeded 2 years in clinical trials of some regimens. Welcome as these advances are, clinicians are now faced with complex decisions in determining which of the many regimens are most appropriate in individual cases and how to best administer them.

In *Translating Clinical Trial Data into the Community Setting: A Case-Based Approach to Metastatic Colorectal Cancer*, three experts in the field discuss a multidisciplinary approach for incorporating knowledge gained from clinical trials into actual community practice. Their discussion focuses on issues such as whether adjuvant

therapy should be delivered in combination or sequentially, the use of biomarkers in matching patient and therapy, maintenance versus chemotherapy-free intervals, the benefits of perioperative chemotherapy for resectable hepatic metastases, the use of conversion chemotherapy, the role of biologics, whether radiologic complete response indicates a cure, and the management of side effects that differ from those associated with traditional chemotherapy.

We welcome you to this timely and informative webcast and hope that this discussion is useful to you in incorporating the new treatment options into your own practice.

Program Information

Target Audience

This CME activity is designed for clinicians involved in the treatment of patients with metastatic colorectal cancer.

Activity Goal

The goal of this activity is to provide clinicians involved in the treatment of metastatic colorectal cancer patients with state-of-the-science information on current treatment options.

Learning Objectives

- Evaluate the efficacy and toxicity profiles of combination chemotherapy/targeted biologic regimens to determine the most appropriate first-line and second-/third-line therapy for your individual patients with metastatic colorectal cancer.
- Apply your knowledge of the adverse events associated with available combination chemotherapy/targeted biologic regimens for metastatic colorectal cancer to effectively manage side effects and maintain patients on treatment.
- Integrate knowledge of surgical options, the role of adjuvant chemotherapy, and the timing of targeted biologic regimens to provide optimum multidisciplinary treatment of your patients with metastatic colorectal cancer.

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Bristol-Myers Squibb, ImClone Systems Inc, and Genentech BioOncology.

Faculty Biographies

CHAIR



Axel Grothey, MD
Professor of Oncology
Department of Oncology
Mayo Clinic College of Medicine
Rochester, Minnesota

Axel Grothey, MD, is a professor of Oncology and Senior Associate Consultant in the Division of Medical Oncology in the Department of Oncology at the Mayo Clinic in Rochester, Minnesota. He is the vice chair of the North Central Cancer Treatment Group (NCCTG) and the co-chair of the GI committee.

After receiving his medical degree from Ruhr-University Bochum in Germany, Dr. Grothey completed his residency in internal medicine at the West-German Tumorcenter at the University of Essen. He also completed residencies in pathology and internal medicine at prestigious universities in Germany and

was awarded a fellowship in the Department of Hematology-Oncology at the University of Bochum. Subsequently, Dr. Grothey was awarded a postdoctoral research fellowship to address the effect of kinase-mediated signaling on the actin cytoskeleton and phenotypic properties of cancer cells at the M.D. Anderson Cancer Center at the University of Texas.

Dr. Grothey is a member of the Association of German Internists, the American Association of Cancer Research, the European Association for Cancer Research, the American Society for Cell Biology, the American Society of Clinical Oncology, and the European Society for Medical Oncology. He serves on the review board of numerous professional journals. In addition, he is widely published in many peer-reviewed journals. Dr. Grothey's major areas of clinical interest are GI malignancies—in particular, colorectal cancer, unknown primaries, and neuroendocrine tumors.

FACULTY



Cathy Eng, MD
Assistant Professor
Department of Gastrointestinal
Medical Oncology
The University of Texas
M.D. Anderson Cancer Center
Houston, Texas

Cathy Eng, MD, is an assistant professor in the Department of Gastrointestinal Medical Oncology at the University of Texas M. D. Anderson Cancer Center in Houston, Texas. After completing a BA in psychobiology with an international politics minor at New York University, New York, Dr. Eng was awarded an MD from Hahnemann University School of Medicine in Philadelphia, Pennsylvania. She completed her residency training in PGY-2 Diagnostic Radiology at St. Barnabas Medical Center in Livingston, New Jersey and in internal medicine at

Rush-Presbyterian St. Luke's Medical Center in Chicago, Illinois. She also completed her hematology/oncology fellowship at the University of Chicago Medical Center. Dr. Eng is board certified in internal medicine and medical oncology. Dr. Eng is highly involved in clinical research, primarily focusing on colorectal cancer, and is the principal investigator or co-investigator of numerous clinical trials. In recognition of her research accomplishments, Dr. Eng received the SWOG Young Investigator Award in 2005. She is an active member of SWOG's Gastrointestinal Committee, the ASCO Career Development Committee, the ASCO Scientific Program Committee Gastrointestinal Cancer-Colorectal/Liver track, and a liaison to the ASCO Health Services committee. Dr. Eng has authored dozens of peer-reviewed publications, abstracts, and book chapters. She is also a reviewer for several publications including the *Journal of Clinical Oncology*, *Cancer*, and *Clinical Cancer Research*.

FACULTY



J. Philip Kuebler, MD, PhD
Principal Investigator
Columbus Community
Clinical Oncology Program
Columbus, Ohio

J. Philip Kuebler, MD, PhD, is Medical Director of Cancer Research at Grant/Riverside Methodist Hospitals in Columbus, Ohio, and Principal Investigator of the Columbus Community Clinical Oncology Program. In addition to his research responsibilities, he is also in private practice with Columbus

Oncology Associates, Inc. Dr. Kuebler received both his medical and doctorate degrees at Case Western Reserve University, Cleveland, Ohio, and then went on to complete a fellowship in medical oncology at the University of Wisconsin Hospitals in Madison, Wisconsin. His research interests have focused on genitourinary cancer, head and neck cancers, biologic response modifiers, and more recently on colorectal cancer. Dr. Kuebler is currently involved in the National Surgical Adjuvant Breast and Bowel Project as a member of the Colorectal Executive Committee, and he also serves as a member of the NCI Gastrointestinal Steering Committee.

Overview of MCRC

Axel Grothey, MD

The approval of new agents, the development of new combination chemotherapy regimens and chemotherapy/biologic regimens, and an improved understanding of the best ways in which to deliver these therapies have greatly expanded the options for treating colorectal cancer, resulting in significantly increased progression-free and overall survival. Among the first of these new combination chemotherapeutics were IFL (irinotecan + bolus 5-fluorouracil/leucovorin) and FOLFOX (5-fluorouracil/leucovorin + oxaliplatin). In a trial comparing IFL and FOLFOX, the FOLFOX regimen resulted in significantly greater response rates, progression-free survival, and overall survival. Another of the new combination chemotherapy regimens to gain attention is the combination of infusional 5-fluorouracil/leucovorin + irinotecan (FOLFIRI).

As both FOLFOX and FOLFIRI have proven effective and able to extend survival over that obtained with earlier regimens, the question has arisen as to which of the two should be utilized first. In a comparison of first-line FOLFOX/second-line FOLFIRI versus first-line FOLFIRI/second-line FOLFOX, there was no significant difference between the two arms in overall survival (20.6 months and 21.5 months, respectively), although the toxicities associated with the two sequences were different. A study investigating the related question of whether chemotherapeutic regimens should be combined or delivered in sequence compared the sequence of first-line capecitabine/second-line irinotecan/third-line capecitabine + oxaliplatin versus first-line capecitabine + irinotecan/second-line capecitabine + oxaliplatin. Again, there was no significant difference between the two arms in median overall survival (16.3 months and 17.4 months, respectively). However, the combination of oxaliplatin + FOLFIRI (FOLFOXIRI) as first-line treatment has resulted in significant increases in response rates, hepatic resection rates, progression-free survival, and overall survival. The benefit of exposure to all three drugs—5-FU/LV, irinotecan, and oxaliplatin—was documented in a retrospective analysis of 11 phase III studies in 5768 patients, which found a direct relationship between the percentage of patients having been treated with all three drugs and median overall survival.

The availability of novel biologic agents with different

mechanisms of action than those of traditional drugs has further increased the options for treating metastatic colorectal cancer. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), and bevacizumab, a monoclonal directed against the vascular endothelial growth factor, have further increased progression-free survival when added to standard chemotherapy regimens. For example, response rates and 1-year progression-free survival were significantly increased from 38.7% and 23%, respectively, with FOLFIRI alone to 46.9% and 34%, respectively, with the combination of cetuximab + FOLFIRI. In several trials, the addition of bevacizumab to IFL, FOLFIRI, FOLFOX, or capecitabine + oxaliplatin (XELOX) resulted in significantly increased progression-free and/or overall survival compared with that of chemotherapy alone. The latest biologic to be approved for metastatic colorectal cancer is panitumumab, a monoclonal antibody targeting EGFR. Recent studies have identified the K-ras mutation as a biomarker for response to panitumumab, making it possible to predict which patients may benefit from treatment with this agent. A trial exploring the combination of panitumumab with either FOLFOX + bevacizumab (phase III) or FOLFIRI + bevacizumab (phase II) has recently been completed. Although final results are not yet available, preliminary progression-free survival data do not suggest an advantage with the addition of panitumumab.

Other researchers have investigated the possible benefits of maintenance therapy. In a comparison of modified FOLFOX7 with chemotherapy-free intervals versus modified FOLFOX7 with intervals of maintenance 5-FU/LV, the maintenance regimen resulted in an overall survival of 26 months, compared to an overall survival of 19 months with chemotherapy-free intervals, indicating that treatment should not be stopped before disease progression. Although results of these and other trials currently under way are greatly expanding our ability to treat metastatic colorectal cancer, the challenge now is to incorporate this new information into actual clinical practice.

Suggested Readings

Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25:1670-1676.

Fuchs CS, Marshall J, Barrueco J. Randomized controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. *J Clin Oncol*. 2007;25:4779-4786.

Grothey A, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. *J Clin Oncol*. 2005;23:9441-9442.

Hecht J, Chidiac T, Mitchell E, et al. An interim analysis of efficacy and safety from a randomized, controlled trial of panitumumab with chemotherapy plus bevacizumab (BEV) in metastatic colorectal cancer (MCRC). Proc 9th World Congress on GI Cancer. Barcelona. 2007. Abstract 33.

Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007;357:2040-2048.

Koopman M, Antonini NF, Douma J, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomized controlled trial. *Lancet*. 2007;370:135-142.

Maindault-Goebel F, Lledo G, Chibaudel B, et al. Final results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MMCRC): a GERCOR study. Presented at: 43rd ASCO; June 1-5, 2007; Chicago, Ill. Abstract 4013. Updated from oral presentation.

Van Cutsem E, Nowacki M, Lang I, et al. Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial. Presented at: 43rd ASCO; June 1-5, 2007; Chicago, Ill. Abstract 4000.

Case Study: Stage IV Metastatic Colon Cancer in a Patient with Ulcerative Colitis

J. Philip Kuebler, MD, PhD

With the advent of targeted biologic therapies, the development of more effective chemotherapy regimens, and new combinations of the two modalities, treatment options for patients with unresectable metastatic colorectal cancer have greatly increased. As demonstrated in several phase III trials, progression-free survival has reached 8 to 9 months with chemotherapeutic regimens utilizing combinations of 5-fluorouracil (5-FU)/leucovorin (LV)/oxaliplatin (FOLFOX4 or FOLFOX 6) or 5-FU/LV/irinotecan (FOLFIRI), compared with the progression-free survival of 4.3 to 6.2 months achieved with older 5-FU/LV regimens. If the data from 21 phase III trials are placed on the same graph, a clear correlation is noted between overall survival and the percentage of patients receiving all three drugs—5-FU/LV, irinotecan, and oxaliplatin.

The addition of biologic agents to established combination chemotherapy regimens has increased progression-free survival even further. Depending on the particular trial, combinations of bevacizumab with either irinotecan/5-FU/LV (IFL), capecitabine/oxaliplatin (CAPEOX), FOLFOX, or FOLFIRI have resulted in progression-free survival of 9.4 to 11.2 months. Although the addition of cetuximab to FOLFOX did not increase progression-free survival over that achieved with FOLFOX alone in a trial closed early due to poor accrual, FOLFIRI + cetuximab has resulted in significantly increased progression-free survival compared with that of FOLFIRI alone. In light of these and other trial data, either bevacizumab or cetuximab in combination with a biologic agent is recommended as first-line therapy, so the 71-year-old patient with unresectable metastatic colorectal cancer discussed in this presentation was placed on FOLFOX + bevacizumab.

The ability to manage the adverse events associated with these powerful therapies is obviously an important factor in overall outcome. Although this patient had a marked response to FOLFOX + bevacizumab and was still responding at 11 cycles of therapy, neurotoxicity associated with the oxaliplatin component of his therapy resulted in unacceptable disability, necessitating a change in approach. As the cumulative effects of oxaliplatin sometimes require therapy to be stopped in patients who are still responding, studies have investigated possible options to deal with this circumstance. In two separate trials, one utilizing chemotherapy-free intervals and the other a non-oxaliplatin-containing maintenance therapy, cross-study comparison noted that the maintenance therapy resulted in significantly longer overall survival (26 months) than chemotherapy-free intervals (19 months). In light of these results, the patient was placed on maintenance with infusional 5-FU/LV. Unfortunately, after 4 months, his disease progressed and it became necessary to discuss options for second-line treatment.

In summary, FOLFOX, FOLFIRI, CAPEOX, or 5-FU/LV with either bevacizumab or cetuximab are all acceptable choices for first-line therapy, with the decision as to the most appropriate treatment based on the individual patient's situation. Bevacizumab in maintenance or second-line therapy is an option, as is cetuximab plus irinotecan in second- or third-line treatment. Panitumumab, a new biologic agent, has recently been approved for second-line treatment of EGFR-expressing metastatic colorectal cancer, providing another option. Other future possibilities for relapsed disease may include chemotherapy + two biologics. Results of a trial currently under way exploring the combination of FOLFIRI + cetuximab with or without bevacizumab in second-line treatment of patients with relapsed metastatic colorectal cancer should help to determine the feasibility of this strategy.

Suggested Readings

Grothey A, Sugrue M, Hedrick E, et al. Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): results from a large observational study (BRiTE). *J Clin Oncol*. 2007;25(suppl):4036.

Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350:2335-2342.

Kozloff M, Hainsworth J, Badarinath S, et al. Management of hypertension (HTN) in patients (pts) with metastatic colorectal cancer treated with bevacizumab (BV) plus chemotherapy. (Abstract 364). Presented at: 2007 ASCO Gastrointestinal Cancers Symposium.

Kuebler JP, Colangelo L, O'Connor MJ, et al. Severe enteropathy among patients with stage II/III colon cancer treated on a randomized trial of bolus 5-fluorouracil/leucovorin plus or minus oxaliplatin: a prospective analysis. *Cancer*. 2007;110:1945-1950.

Land SR, Kopec JA, Cecchini RS, et al. Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer SNSABP C-07. *J Clin Oncol*. 2007;24:2205-2211.

Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first-line treatment of metastatic colorectal cancer (MCRC) (Abstract 238). Presented at: 2007 ASCO Gastrointestinal Cancers Symposium.

Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229-237.

Venook A, Niedzwiecki D, Hollis D, et al. Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin/5FU/LV (FOLFOX) +/- cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (MCRC): CALGB 80203 preliminary results. *J Clin Oncol*. 2007;24(suppl)3509.

Case Study: Surgically Resectable Metastatic Colorectal Cancer

Cathy Eng, MD

The need for a multidisciplinary approach in treating resectable metastatic colorectal cancer is clearly illustrated in this case of a 49-year-old woman with newly diagnosed metastatic disease. Following successful right hemicolectomy for T3N2M1 right-sided colon cancer, a variety of options were considered to manage the patient's hepatic metastases, including immediate surgical resection, neoadjuvant systemic chemotherapy, and conversion chemotherapy. With immediate surgical resection, the question remains as to the role and duration of adjuvant chemotherapy, since no large prospective randomized trials of surgical resection followed by adjuvant chemotherapy versus observation have been completed. On the other hand, recent studies have provided clinical data on the benefit of neoadjuvant chemotherapy in patients with resectable metastases. In a large prospective phase III trial comparing perioperative FOLFOX (FOLFOX4 for 3 months, followed by surgery, then an additional 3 months of FOLFOX) versus surgery alone, patients receiving perioperative chemotherapy had +8.1% difference in 3-year progression-free survival compared with those undergoing surgery only, and perioperative patients who were actually resectable had +9.2% difference in progression-free survival, compared with surgery-only patients. Although the incidence of postoperative complications was greater in patients receiving perioperative chemotherapy, only one patient in this arm died postoperatively, compared with two in the surgery-alone arm. A third possible approach to the treatment of colorectal metastases is conversion chemotherapy, the use of systemic chemotherapy to decrease tumor burden, thereby increasing the likelihood that surgical resection can be performed. In a trial comparing conversion therapy with FOLFIRI versus FOLFOXIRI, 36% of those receiving FOLFOXIRI were able to undergo hepatic resection, a significantly greater percentage than the 12% of those receiving FOLFIRI.

The combination of biologics and chemotherapy has further increased success rates in treating liver metastases. In a trial comparing FOLFIRI + cetuximab versus FOLFIRI alone, a significantly greater percentage of those receiving cetuximab had no residual tumor after hepatic resection. Similarly, the addition of bevacizumab to either capecitabine + oxaliplatin (XELOX) or FOLFOX also resulted in a greater percentage of patients undergoing liver resection than seen with chemotherapy alone.

Several points are important to keep in mind when using chemotherapy and/or biologic agents in the management of metastatic colorectal cancer. First, chemotherapy may induce hepatic toxicities. 5-FU and oxaliplatin are associated with steatosis and irinotecan is associated with steatohepatitis, adverse effects that result in an increase in 90-day postoperative mortality. Since these events usually occurred after a median of 4 months of chemotherapy, shorter periods of 2 to 3 months of chemotherapy are advisable. (In determining the duration of neoadjuvant therapy, it should be remembered that the goal is not to cure metastatic disease with chemotherapy alone but to make it surgically resectable for curative intent.) Second, because of the risk of postoperative complications, bevacizumab should not be administered for 4 to 8 weeks prior to surgical resection. Finally, radiologic complete response does not necessarily indicate a cure. As seen in a study of 66 liver lesions with radiologic complete response, 55 (83%) were not pathologically cured. Thus, surgical resection should be considered regardless of whether there is radiographic evidence of complete response.

Based on clinical trial results and the above considerations, the patient received six cycles of FOLFOX + bevacizumab (with bevacizumab held on the last cycle) and then underwent successful right hepatic resection. Because of her excellent response to chemotherapy, she opted for an additional 4 to 6 months of postoperative FOLFOX + bevacizumab.

Suggested Readings

Cassidy J, Clarke S, Diaz-Rubio E, et al. XELOX compared to FOLFOX4: Survival and response results from XELOX-1/NO16966, a randomized phase III trial of first line treatment for patients with metastatic colorectal cancer. *J Clin Oncol*. 2007;25(suppl):4030.

Nordlinger B, Sorbye H, Collette L, et al. Final results of the EORTC intergroup randomized phase III study 40983 (EPOC) evaluating the benefit of perioperative FOLFOX chemotherapy for patients with potentially resectable colorectal cancer liver metastases. *J Clin Oncol*. 2007;25(suppl):LBA5.

Nordlinger B, Brouquet A, Penna C, et al. Complete radiological response of colorectal liver metastases (LM) after chemotherapy: Does it mean cure? *J Clin Oncol*. 2006;24(suppl):3501.

Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol*. 2006;24:2065-2072.