New NCCN Treatment Recommendations for Colon and Rectal Cancers

The National Comprehensive Cancer Network published its first of the 2003 NCCN Clinical Practice Guidelines. These updated guidelines contain new treatment recommendations regarding the use of the recently approved agent, oxaliplatin, and of radiation therapy in Stage II, III and IV disease. The recommendations are:

Rectal Cancer

- for patients with distant, unresectable, or multiple metastatic lesions, combination chemotherapy with 5-FU/leucovorin/oxaliplatin is now included as one of several treatment options found to be effective as palliative therapy.
- for Stage IV patients with distant resectable metastases, radiation therapy to the pelvic area should now be considered as a therapeutic option as adjuvant therapy after combination chemotherapy and resection of the metastases and the rectal lesion.

Colon Cancer

- for patients with unresectable or multiple metastatic lesions, 5-FU/leucovorin/oxaliplatin is now included as one of several options found to be effective as palliative therapy.
- for Stage II and III patients, combination regimens including irinotecan, oxaliplatin and capecitabine cannot be considered as standard adjuvant therapy at this time but may be administered in the context of a clinical trial.
- for Stage II or Stage III patients with localized perforation or with close, indeterminate, or positive margins, radiation therapy is recommended as part of a therapeutic adjuvant regimen.
- for Stage IV patients with resectable liver metastases, 5-FU/leucovorin/oxaliplatin is now included as one of several treatment options that is effective as neoadjuvant or adjuvant therapy.

(continued on page 97)
Celltech Pharmaceuticals has Selected RxHope to Centralize and Web-enable Their Patient Assistance Program

The Patient Assistance Program agreement between Celltech Pharmaceuticals and RxHope will give healthcare providers the opportunity to offer their financially disadvantaged patients the following products at no cost: Dipentum®; (osalazine sodium capsules), Gastrocrom®; (cromolyn sodium, USP), Mykrox®; (metolazone tablets, USP), Semprex®; (acivastine, pseudoephedrine hydrochloride) and Zaroxolyn®; (metolazone tablets, USP). Physicians and patients can either log onto www.rxhope.com or contact the RxHope Customer Service Center toll free at 1.866.523.3994 to obtain further information about the program.

“Celltech Pharmaceuticals has a long standing commitment of providing Celltech-marketed prescription medicines free of charge for patients who might not otherwise have the financial resources to access them,” said John Temperato, Director National Healthcare and Trade Relations for Celltech Pharmaceuticals.

Santi Corsaro, worldwide president of ASP, said that CIDEX OPA Solution has been well received since its U.S. launch in 1999. “Almost half of American hospitals today safely, effectively, and conveniently utilize the solution as part of their instrument processing practice,” Corsaro said. “CIDEX OPA Solution now allows healthcare facilities to reduce instrument processing time up to 75 percent compared with traditional glutaraldehyde disinfectants, improving staff efficiency and eliminating the need for redundant instruments.”

Medical facilities can also manually process instruments in CIDEX OPA Solution—it provides high level disinfection with a 12-minute soak time at room temperature (20°C)—increasing efficiency by allowing facilities to standardize their use of high level disinfectants.

CIDEX OPA Solution requires no activation or mixing and has a 14-day reuse life, a 75-day open-bottle life, and a two-year shelf life. CIDEX OPA Solution is a proprietary formulation that destroys 100 percent of Mycobacterium tuberculosis.

Advanced Sterilization Products Announces FDA Clearance of Shorter Processing Time with Cidex® OPA Solution

Glutaraldehyde-Free Solution Now Provides High Level Disinfection in Just Five Minutes at a Minimum of 25 Degrees C in Automatic Endoscope Reprocessors

Advanced Sterilization Products (ASP), a Johnson & Johnson company, has received U.S. Food & Drug Administration 510(k) marketing clearance for a five-minute processing time for its CIDEX® OPA Solution when used in automatic endoscope reprocessors at a minimum of 25°C (77°F). This reduction in processing time—from 12 to five minutes—makes CIDEX OPA Solution the fastest non-glutaraldehyde high level disinfectant available for medical device reprocessing.

CIDEX OPA Solution, a low vapor and low odor solution, is compatible with a wide range of endoscopes and medical devices. Its ease of use and shortened processing time allow high-volume patient care areas, such as GI labs, to avoid delays in procedures and decrease inventory costs by rapid throughput of endoscopes and medical instrumentation.

Kimberly-Clark Expands Feeding Tube Product Offering

Kimberly-Clark Health Care introduced the KIMBERLY-CLARK MIC-KEY® Low-Profile Transgastric-Jejunal Feeding Tube. The new feeding tube is designed for pediatric and adult patients requiring simultaneous jejunal feeding and gastric decompression. Produced with the patient in mind, the new low-profile design is unobtrusive and easy to conceal.

The low-profile feeding tube features multiple feeding exit ports to help improve flow and minimize clogging. A tungsten weighted jejunal portion with high columnar strength maintains jejunal position and a radiopaque stripe aids in catheter visualization. The feeding tube also features clearly marked gastric and jejunal ports for ease of identification and an in-line jejunal port to aid in over-the-wire placement.

The low-profile feeding tube is constructed of high-clarity medical grade silicone and includes a tapered distal tip for non-traumatic tube insertion and is available in low-profile and conventional designs in a wide range of sizes and lengths.
Chemoembolization in HCC
A systematic review was carried out to assess the evidence of the impact of medical treatments on survival on resectable hepatocellular carcinoma (HCC). Sixty-one randomized trials were reviewed, but only 14 met the criteria to perform a meta-analysis, assessing arterial embolization. Arterial embolization improved two years survival, compared with control, and showed a significant benefit with Cisplatin or Doxorubicin. There was no improvement in survival with embolization alone. Overall, induced objective responses in 35 percent of patients were noted. Tamoxifen showed no antitumoral effect and no survival benefits.

It was concluded that chemoembolization improves the survival of patients with unresectable HCC and may become the standard treatment. Tamoxifen in treatment did not modify the survival of patients with advanced disease. (Lovet JM, Bruix J, Barcelona-Clinic Liver Cancer Group. “Systematic Review of Randomized Trials For Unresectable Hepatocellular Carcinoma: Chemoembolization Improves Survival.” Hepatology, 2003; Vol. 37, pp. 429-442.)

Treatment of Portal Hypertension
Twenty-three portal hypertensive cirrhotics, 8 of them under propanolol therapy, were randomized to receive orally 5-isosorbide mononitrate 10mg or placebo and a standard liquid meal 15 minutes later, investigating the effects on increased portal pressure with postprandial hyperemia. Hepatic venous pressure gradients, mean arterial pressure and hepatic blood flow were measured at baseline at 15, 30 and 45 minutes after a meal. The isosorbide as a nitric oxide supplier significantly attenuated the postprandial increase in portal pressure as compared with placebo, and these effects were also observed in patients on chronic propanolol therapy.

It was concluded that hepatic nitric oxide supplementation by low dose isosorbide mononitrate effectively reduces the postprandial increase of portal pressure and cirrhotics, with only a mild effect on arterial pressure and that this effect was also present in patients already on propanolol. This supported therapeutic strategies, based on selective hepatic nitric oxide delivery in treatment of portal hypertension. (Bellis L, Berzigotti A, Abraldes JG, et al. “Low Doses of Isosorbide Mononitrate Attenuate the Postprandial Increase in Portal Pressure in Patients With Cirrhosis.” Hepatology, 2003 Vol. 37, pp. 378-384.)

Colon Polyp Recurrence
Eight thousand, eight hundred and sixty-five individuals with an index polypectomy were evaluated using computerized data from a large Midwestern health maintenance organization, identifying patients 50 years or older who underwent a polypectomy between 1/1/89 and 12/31/99 and following up these patients to identify subsequent polypectomies through 9/1/01, Overall, 2,704 patients (30.5 percent), were diagnosed as having recurrent polyps. Kaplan-Meier projections estimate that 50 percent of the patients will have a recurrence within 7.6 years. Among patients who underwent colon screening at least 9 months after the index polypectomy, Kaplan-Meier projections estimate that 50 percent will have a recurrent polyp within 3.9 years.

It was concluded that even when screening and treatment are received by those who need it, the risk of colon polyp recurrence is high and many patients do not undergo additional screening. Efforts to increase and monitor ongoing screening of postpolypectomy patients are warranted. (Yoood MU, Oliveria S, Boyer G, et al. “Colon Polyp Recurrence in a Managed Care Population.” Archives of Internal Medicine, 2003; Vol. 163, pp. 422-426.)

Adefovir Dipivoxil in Hepatitis B Antigen-Negative Disease
One hundred and eighty-five patients with chronic hepatitis B who were negative for hepatitis B antigen, were randomly assigned to receive either 10mg of adefovir dipivoxil or placebo once daily for 48 weeks. The primary end point was histologic improvement.

At week 48, 64 percent of the patients who had baseline liver biopsy specimens available in the treatment group had improvement in histologic liver abnormalities, compared with 13 percent of patients in the placebo group. Serum hepatitis B virus DNA levels were reduced to fewer than 400 copies per mL in 51 per-

(continued on page 100)
cent of the patients in the treatment group and zero percent of those in the placebo group. The median decrease in log-transformed HBV DNA levels was greater with the treatment than with placebo. ALT levels had normalized at week 48 in 72 percent of the patients receiving the treatment, compared with 29 percent of those receiving placebo. No HBV polymerase mutations associated with resistance to the drug were identified. Safety profile of the drug was similar to that of placebo.

It was concluded that for patients with HBeAg-negative chronic hepatitis B, 48 weeks of adefovir dipivoxil treatment resulted in significant histologic, virologic and biochemical improvement, with an adverse event profile similar to that of placebo. There was no evidence of the emergence of resistant mutations. (Habiyannis SJ, Tessopoulos NC, Heathcote EJ, et al for the Adefovir Dipivoxil 438 Study Group. New England Journal of Medicine, 2003; Vol. 348, pp. 800-807.)

Adefovir Dipivoxil For The Treatment of Hepatitis Be Antigen-Positive Disease

Five hundred and fifteen patients were randomly assigned, all of whom had chronic hepatitis B, positive for hepatitis Be antigen, to receive 10mg of adefovir dipivoxil 30mg or placebo daily for 48 weeks. The primary end point was histologic improvement, compared with the placebo.

After 48 weeks of treatment, significantly more patients who received 10mg or 30mg of the drug had histologic improvement (53 percent, 59 percent and 25 percent, respectively). A reduction in serum HBV DNA levels by a median of 3.5, 4.7 and 0.55 copies per mL were noted, respectively. Undetectable levels (fewer than 400 copies per mL) of HBV DNA, 21 percent, 39 percent and zero percent, respectively, normalization of ALT 48 percent, 55 percent and 16 percent, respectively and HBeAg seroconversion 12 percent, 14 percent and 6 percent, respectively, were noted. No resistant mutations were identified. Safety profile in a 10mg dose of the drug was similar to that of placebo, but there was a higher frequency of adverse effects and renal laboratory abnormalities in the group given 30mg of the drug.

It was concluded that in patients with HBeAg positive chronic hepatitis B, 48 weeks at 10mg or 30mg of adefovir dipivoxil per day resulted in histologic liver improvement, reduced serum HBV DNA and ALT levels and increased rates of HBeAg seroconversion. A 10mg dose has a favorable risk/benefit profile for long term treatment. No resistant mutations were identified. (Marcellin P, Chang PT, Lim SG, et al, for the Adefovir Dipivoxil 437 Study Group. New England Journal of Medicine, 2003 Vol. 348, pp. 808-816.)

Infected Acute Pancreatitis

Three cases of severe acute pancreatitis seen in one institution were prescribed, in which the patient developed aspirate-proven pancreatic infections. The patients were otherwise stable and were treated with long courses of antibiotics known to penetrate the pancreas and emergent surgery was deferred.

In two patients, surgery was completely avoided with good clinical outcome. In the third patient, elective surgery was undertaken 12 weeks after the episode of acute pancreatitis to perform necrosectomy on organized pancreatic necrosis and to evaluate the patient’s biliary tree. There were no postoperative complications.

It was concluded that a subset of patients with severe acute pancreatitis, complicated by infections, can be successfully managed with long-term antibiotics and other supportive measures. High risk necrosectomy can, in some instances, be delayed or avoided entirely. (Adler DG, Chari S, Dahl T, Farnell M, Pearson RK. “Conservative Management of Infected Necrosis Complicating Severe Acute Pancreatitis.” American Journal of Gastroenterology, 2003; Vol. 98, pp. 98-103.)

Colchicine in PBC

Three patients with symptomatic, biopsy-proven antimitochondrial antibody-positive PBC failed to respond to UDCA and then to the addition of methotrexate. Colchicine was eventually added to the regimen. Biochemical tests and liver function and percutaneous liver biopsies were done at baseline and after treatment. All three patients responded after colchicine was added to UDCA and methotrexate. Symptoms, (continued on page 102)
biochemical tests, liver function and liver histology improved and blood tests normalized in two patients.

It was concluded that colchicine may be an effective treatment in some symptomatic patients with PBC who respond incompletely to UDCA alone, or in combination with methotrexate, colchicine may be tried in such patients. (Lee YM, Kaplan MM. “Efficacy of Colchicine in Patients With Primary Biliary Cirrhosis, Poorly Responsive to Ursodiol and Methotrexate.” American Journal of Gastroenterology, 2003; Vol. 98, pp. 205-208.)

**Sphincterotomy Vs. Balloon Dilatation For Bile Duct Stones**

Two hundred and eighty-two patients with bile duct stones were enrolled and randomized to an endoscopic sphincterotomy or endoscopic papillary balloon dilatation group. The success rate for duct clearance, as well as the frequency and types of complications were evaluated prospectively. Endoscopic sphincterotomy was performed in a standard manner. Endoscopic papillary balloon dilatation was carried out with gradual inflation of 4mm, 6mm or 8mm diameter balloons. Complete duct clearance was achieved in 100 percent in the sphincterotomy group and 99.3 percent in the balloon dilatation group. Complications occurred in 11.8 percent of patients in the sphincterotomy group and 14.5 percent of those in the endoscopic dilatation group. No complication was severe and there was no mortality.

The frequency of acute pancreatitis was higher in the balloon dilatation group than the sphincterotomy group (10.9 percent versus 2.8 percent). Hemorrhage occurred only in the sphincterotomy group.

It was concluded that endoscopic sphincterotomy and endoscopic papillary balloon dilatation were approximately equal in terms of successful clearance of bile duct stones. They were also similar with respect to complications. Endoscopic papillary balloon dilatation is an alternative to endoscopic sphincterotomy as a treatment of bile duct stones. (Maguchi H, Komatsu Y, et al for the JESED Study Group. “Endoscopic Sphincterotomy and Endoscopic Papillary Balloon Dilatation For Bile Duct Stones: A Prospective, Randomized, Controlled, Multi-center Trial.” Gastrointestinal Endoscopy, 2003; Vol. 57, pp. 151-155.)

**SSRI and GI Bleeding**

All users of antidepressants in the county of North Jutland, Denmark, from 1/1/91 to 12/31/95 were identified and hospitalizations for upper GI bleeding researched among the 26,005 users of antidepressant medications and compared with the number of hospitalizations in the population of North Jutland who did not receive prescriptions for antidepressants.

During the period of SSRI use without the use of other drugs with upper GI bleeding, 55 upper GI bleeding episodes were identified, which was 3.6 times more than expected, corresponding to a rate difference of 3.1 per 1,000 treatment years. Combined use of an SSRI and NSAID or low dose aspirin increased the risk to 12.2 and 5.2, respectively. Non-SSRIs increased the risk of upper GI bleeding to 2.3, while antidepressants without action on the serotonin receptor had no significant effect on the risk of upper GI bleeding.

The risk with SSRI use returned to unity after termination of that medication, while the risks were similarly increased during periods of use or nonuse of non-SSRIs.

It was concluded that selective serotonin reuptake inhibitors increase the risk of upper GI bleeding and this effect is potentiated by concurrent use of non-steroidal, antiinflammatory medications or low dose aspirin, whereas an increased risk of upper GI bleeding could not be attributed to other types of antidepressants. (Dalton O, Johansen C, Mellenkjoer L, et al. “Use of Selective Serotonin Reuptake Inhibitors and Risk of Gastrointestinal Bleeding: A Population-Based Cohort Study.” Archives of Internal Medicine, 2003; Vol. 163, pp. 59–64.)

Murray H. Cohen, D.O., editor of “From the Literature” is a member of the Editorial Board of Practical Gastroenterology.
Barrett’s Esophagus
H. W. Tilanus and S. E. A. Attwood, Editors
395 pages; ISBN: 1-4020-0102-9; $159.00

As titled, this book and its table of contents suggest that it would be an international treatise on Barrett’s esophagus. Certainly the first chapter is very entertaining and informative about the life and career of Norman Barrett. We learn he was actually an Australian who migrated to England in his early teens and had the nickname of “Patsy” because of his ruddy complexion. Other recommended chapters include those on the cell biology of esophageal epithelium, genetic alterations in Barrett’s esophagus, short segment Barrett’s esophagus and intestinal metaplasia at the gastroesophageal junction, ablation of Barrett’s esophagus, and the role of bile and reflux disease. The last chapter was interesting because the authors (both British surgeons) give a balanced view on this subject not accepting a traditional surgical doctrine that bile reflux is the “root of all evil” in the proton pump inhibitor era. On the other hand, eight of 31 chapters cover routine facets of esophageal physiology and gastroesophageal reflux disease and five other chapters review the multiple operations for esophageal adenocarcinoma and their complications. This selection of chapters is not unusual as the two editors are well known European esophageal surgeons, but distracting if you wanted a text which concentrates on Barrett’s esophagus.

Other features of this book make it not as readable as one might like. Individual paragraphs are not indented or separated from other paragraphs by increased spacing. Therefore, some paragraphs seem to run on for two to three pages unless separated by figures. All the figures and photographs are in black and white. The use of color certainly would have improved the quality of the endoscopic and histologic photographs.

This book may be of interest to “Barrettphiles.” On the other hand, other recent books such as Barrett’s Esophagus and Esophageal Adenocarcinoma by Sharma and Sampliner are much more focused and readable for the gastroenterologist or general physician interested in Barrett’s esophagus.

Joel E. Richter, M.D.
Department of Gastroenterology/Hepatology
Cleveland Clinic Foundation
Cleveland, OH

Drug Induced Liver Disease
Kaplowitz N and DeLeve LD, editors
Marcel Dekker, New York, Basel, October 2002
ISBN: 0-8247-0811-3; $195.00

There are two premises of this exciting new tome on drug induced liver disease. First, the liver is a common target for damage caused by drugs. Therefore, every individual taking medication (prescribed, over-the-counter, or alternative medicines) is at risk, and every physician needs a place to turn to get precise, accurate, detailed information. Second, the past twenty years has produced an explosion of knowledge and technology that has allowed scientists to explore, as never before, the deleterious effect of certain drugs on P-450 isoenzymes, bile acid transport, and mitochondrial function. New concepts in drug induced apoptosis and the role of non-hepatocyte liver cells in drug-induced liver damage are also increasingly important.

The book is divided into three main sections. The first comprises 10 chapters dealing with mechanisms of injury (e.g., oxidative stress, mechanisms of cell death, immunologic mechanisms, etc). A short second section addresses clinicopathological patterns of drug-induced liver disease, and histopathologic features. Seventeen chapters in the third section provide a detailed discussion of specific drugs. This will be the most frequented portion of the book by clinicians, and it is helpfully divided by therapeutic drug category (nonsteroidal anti-inflammatory drugs, cancer chemotherapy, anticonvulsants, etc). There is even a chapter on alternative medicines, vitamins, and natural hepatotoxins.

Throughout, chapters are written by experts in their field. Fifty two authors, one third of them from outside the United States, collaborated. Tables and diagrams are used extensively. Photomicrographs are concentrated in a single chapter, printed only in black-and-white. The discussions are robust. References (over 4,100, according to the publisher) are as recent as 2001, but the majority are from published works from 2000 and before. The quality of the chapters is consistently high. For the most part, brand names are used alongside the generic names, both in the text and in the index.

A few poorly substantiated opinions have slipped through. For example, in the excellent chapter on hepatox-
The authors state that doses of acetaminophen in daily doses as low as 2–6 g have been associated with fatal hepatotoxicity in heavy drinkers. The references provided are based on poorly documented, retrospective estimates of drug ingestion; moreover the authors do not reference published prospective studies in which known doses of acetaminophen (up to 4 g per day) have been administered to alcoholics without inducing hepatotoxicity. The management of the patient with acetaminophen overdose is succinct, accurate, and helpful.

Sections of this book will be of interest to a diverse audience. The clinician will have an up-to-date (at least for now) authoritative tool providing guidance through a maze of literature, providing specific information about the type of liver injury caused by thousands of medications. Scientists, pharmacologists, and students with an interest in the laboratory methodologies for exploring the effects of drugs on the liver, or on mechanisms of actions of drugs on the liver will find this a great resource. It should find a home on the shelf of all medical libraries.

William Carey, MD
Cleveland, OH

Dilation Techniques in the Esophagus
On DVD; Zephyr Medical Enterprises (www.zephyrmedical.com); $35.00

Dilation Techniques in the Esophagus introduces the viewer to the various methods used to treat a variety of esophageal conditions that lead to dysphagia. The video assumes the viewer is familiar with upper GI anatomy and pathology as well as the basics of upper endoscopy. Easy to use menus allow one to choose from four commonly encountered esophageal anatomic problems.

Dr. James DiSario discusses “Through the Scope” balloon preparation and dilation in long esophageal strictures. Throughout the video, split screen views of endoscopy, fluoroscopy, and actual procedural footage are employed to help the viewer follow the narration. Dr. David Fleischer demonstrates the use of a Maloney dilator for a distal Schatzki’s ring. Tips are given by all the experts to promote setup, efficiency, and safety. Dr. H. Worth Boyce reveals the secrets to balloon dilation for achalasia. And finally, Dr. Ken Binmoeller demonstrates Savary bougienage for peptic strictures. After the conclusion to each of these four sections, five multiple-choice questions are asked and answers are given to help viewers remember key points that were discussed.

In just over one hour, the viewer can gain familiarity with the primary modalities used by endoscopists to treat dysphagia. The DVD format helps one to skip or review particular techniques with ease. Overall, this is a well produced video that teaches the novice and refreshes the expert.

The Good: DVD format menus, questions after each session, split screen format incorporating endo/fluoro/procedure.

The Bad: Question session won’t allow you to skip.

Trinetra Vaidya, MD
Gastroenterology Fellow
University of California Davis

George W. Meyer, M.D., Book Editor, is on the Editorial Board of Practical Gastroenterology