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Clinical Oncology

A monthly update of developments in cancer treatment and research [ALERT]

ABSTRACT & COMMENTARY

Cetuximab Adds No Benefit to Adjuvant Chemotherapy in Stage III Colon Cancer

By Gary Shapiro, MD
Director of Medical Oncology, Cancer Center of Western Wisconsin
Dr. Shapiro reports no financial relationships relevant to this field of study.

SYNOPSIS: This randomized Phase 3 clinical trial found that adding cetuximab to standard mFOLFOX6 adjuvant chemotherapy did not improve either overall survival or disease-free survival in patients with resected stage III colon cancer, including those with wild-type KRAS tumors.

SOURCE: Alberts SR, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer. *JAMA* 2012;13:1383-1393.

In this North Central Cancer Treatment Group (NCCTG) study (N0147), 2686 patients with lymph node positive (stage III) colon cancer were randomized to receive 12 biweekly cycles of postoperative mFOLFOX6 (fluorouracil, leucovorin, and oxaliplatin) chemotherapy with or without cetuximab. The N0147 trial began in 2004 before KRAS testing was widely available. Once it was found that patients whose colon cancer had mutations in exon 2 of the KRAS gene were refractory to cetuximab, the study was modified and powered to assess the effect of cetuximab only in patients with normal (wild-type) KRAS tumors. The trial was stopped early, after a planned interim analysis showed that adjuvant cetuximab had no benefit over the mFOLFOX6 regimen.

In patients with wild-type KRAS, the 3-year disease-free survival for those treated with mFOLFOX6 alone was 74.6% compared to 71.5% in those who also received cetuximab (hazard ratio [HR], 1.21; 95% confidence interval [CI], 0.98-1.49; $P = 0.08$). It was 67.1% vs 65.0% (HR, 1.12; 95%CI, 0.86-1.46; $P = 0.38$) in patients with mutated KRAS. Similarly, both time-to-recurrence and overall survival were not significantly different between the two treatment groups. There was no evidence that cetuximab benefited any particular

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subgroup of patients (stratified by age, gender, race, histologic grade, T stage, N stage, obstruction/perforation). On the other hand, patients aged 70 years or older with wild-type KRAS treated with mFOLFOX6 alone had significantly better overall 3-year survival (86.2% vs 72.5%) than those who also received cetuximab (HR 2.00; 95% CI, 1.05-3.78; *P* = 0.03).

Regardless of age, toxicity (≥ grade 3) was significantly higher in those treated with cetuximab in addition to mFOLFOX6 (51.1% vs 73.3%). Those aged 70 years or older who received cetuximab experienced more toxicity (81%) than their younger counterparts (72%). This was primarily due to increased rates of diarrhea, dyspnea, nausea, fatigue, infection, neutropenia, and mucositis in the older aged patients. Younger patients had higher rates of acne/rash than older patients (21.7% vs 10.4%, *P* = 0.002).

COMMENTARY

Although studies have clearly demonstrated the efficacy of adding cetuximab to FOLFOX in treating metastatic colon cancer,[1] the N0147 trial failed to show a similar benefit in the adjuvant setting. This study's authors conclude that cetuximab did not work as they had expected because the "molecular characteristics of micrometastases appear to differ from established metastases." The lack of response to cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, may be due to a transient loss of EGFR dependence and may well apply to other agents directed against EGFR.

In an accompanying *JAMA* editorial, Segal and Saltz note that many clinicians and patients extrapolated the positive results from the metastatic studies to the adjuvant setting choosing regimens with cetuximab because they "apparently could not afford to wait for the data." In addition to their well-taken warning against such "off study" practices, they conclude that it should also not be assumed that agents that are ineffective in macrometastatic setting will not be active in the adjuvant setting.[2]

The N0147 authors devote much of their discussion to the group of patients 70 years of age or older who received cetuximab and had worse outcomes than those who received mFOLFOX6 alone (in contrast to the younger group that simply showed no added benefit with cetuximab). Though these findings should remind us about the potential pitfalls in caring for older patients with cancer, it is important not to generalize them to all older individuals or to all chemotherapy regimens. Clinical studies have established the efficacy and safety of adjuvant chemotherapy and palliative cetuximab in elderly colon cancer patients, but they often lack sophisticated geriatric assessments that help determine risk and benefit in this heterogeneous group.[3,4] Older adults are under-represented in clinical trials[5] and new tools[6] are on the horizon to control for frailty and other geriatric factors that may confound study results.

Thus, in addition to the headline "Adjuvant Cetuximab Does Not Improve Survival in Stage III Colon Cancer," the take home message from N0147 is a reminder to us all about the importance of data. In this era of evidence-based medicine, we should remember that clinical trials have been the cornerstone of oncology care since its inception, and now is not the time to stray from that path. ■

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ABSTRACT & COMMENTARY

Occult Axillary Node Metastasis in Early-stage Breast Cancer: Important or Not?

By William B. Ershler, MD

SYNOPSIS: In a retrospective review of 267 patients evaluated at M.D. Anderson Cancer Center with apparent early-stage, node-negative breast cancer, 15% were found to harbor "occult" metastases upon more intensive scrutiny of the axillary node specimens. In this series, long-term follow-up indicates that such discovery was not associated with a greater frequency of recurrence or poorer survival.

SOURCE: Wu Y, et al. Occult axillary lymph node metastases do not have prognostic significance in early stage breast cancer. *Cancer* 2012;118:1507-1514.

Axillary node involvement is well known to be of prognostic importance in patients with breast cancer. However, it is now appreciated that as many as one-third of patients who are considered axillary node negative by routine examination of typically prepared hematoxylin and eosin (H&E)-stained slides will in fact harbor evidence for metastatic involvement when subjected to more rigorous examination, including the use of immunohistochemistry (IHC).[1] Such "occult metastases" are defined as those not identified in the original H&E section but detected by additional sampling of paraffin blocks, including serial sectioning and/or IHC staining for cytokeratin. Although studies have reported that occult metastases can be identified in 9% to 33% of patients who were considered lymph node negative by standard pathologic processing, the significance of such for the individual patient in terms of prognosis remains to be established.

In the current study, the authors identified 267 patients who underwent axillary lymph node dissection (ALND) between 1987 and 1995 and were lymph node negative according to a routine pathologic evaluation, which included the complete submission of all lymph nodes and an examination of one H&E-stained section per paraffin block. As was the standard of care at that time, patients considered lymph node negative did not receive systemic chemotherapy or hormone therapy. All of the dissected lymph nodes from these patients were re-evaluated by intensified pathologic methods (serial sectioning with H&E levels plus IHC). Occult metastases were categorized by detection method and size. These findings were examined in the context of recurrence rates and overall survival.

Of the 267 patients, 39 (15%) who had lymph node-negative results on routine evaluation of their axillary lymph node dissection specimens had occult metastases identified. Eight of these patients (20%) had macrometastases > 2.0 mm, 15 (40%) had micrometastases (range, > 0.2 mm to 2 mm), and 16 (40%) had isolated tumor cells (≤ 0.2 mm). When compared to the patients without occult metastases, the presence of occult metastases and the size of metastases did not affect recurrence-free or overall survival.

COMMENTARY

The importance of occult metastases has been a controversial topic, with a number of reports indicating negative prognostic implications,[1-3] whereas several others, like the current report, indicate a lack of clinical importance.[4,5] The topic has been the subject of a recent meta-analysis including 27 studies that demonstrated a small increased risk for disease recurrence and death in patients with breast cancer who have occult lymph node metastasis compared with lymph node-negative patients at 10 years of follow-up.[6] Nonetheless, the included studies were quite variable with regard to patients reported, the intensity and techniques used to identify occult disease, and whether they received systemic therapy. In the current report, most patients had small tumors (T1 or T2) and none received systemic

[The clinical oncologist with a breast cancer patient for whom an addendum to the axillary node pathology report includes the discovery of cancer cells should consider the patient node positive and proceed accordingly.]

therapy. The authors found the presence of occult metastasis did not have clinical significance in terms of recurrence or survival. This finding is in distinct contrast to a very similar study from Memorial which, when compared to the current study was remarkably similar in design, pathological techniques, and length for follow-up.[3] Yet, the study population was slightly different. The Memorial cohort included more patients with somewhat larger primary tumors, many of whom presented with symptomatic disease. Thus, they found a greater percentage with occult metastases (23% vs 15%) and such patients had a less favorable prognosis.

Thus, clinicians should be aware that additional more intensive pathological examination of node specimens from patients in whom the routine examination was negative is likely to define a number (between 10-30%) who harbor what is now termed occult metastases. The current report would suggest that such occult metastases are not of clinical importance. However, other reports seem to indicate the opposite conclusion. For the clinical oncologist with a breast cancer patient for whom an addendum to the axillary node pathology report includes the discovery of cancer cells (by IHC, or by additional sectioning), the most likely response will be to consider the patient node positive and proceed accordingly. Although provocative from the perspective of tumor biology, it will take more than this retrospective review for clinicians to have sufficient confidence to ignore such a finding. ■

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ABSTRACT & COMMENTARY

Randomized, Double-Blind, Placebo-Controlled Trial of Bevacizumab Therapy for Radiation Necrosis of the Central Nervous System

By Samir P. Kanani, MD

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Dr. Kanani reports no financial relationships relevant to this field of study.

SYNOPSIS: In a small, single-institutional, prospective, randomized, placebo-controlled trial, 14 eligible patients (median age 47 years) with clinical and radiographic evidence of radiation necrosis secondary to prior head-and-neck or CNS irradiation were randomized to receive intravenous saline of bevacizumab at 3-week intervals. Patients were followed with serial MRI scans, neurologic examinations, and formal neuropsychological examinations. No patients receiving placebo responded by MRI scans while five of five (100%) of patients who received bevacizumab responded on MRI with a decrease in necrosis as estimated on T2-weighted fluid–attenuated inversion recovery scans and T1-weighted gadolinium-enhanced scans. Crossover was allowed in patients receiving placebo who did not respond after two cycles; seven of seven patients crossed over and all of them were found to have a radiographic response. All bevacizumab-treated patients — and none of the placebo-treated patients — showed clinical improvement. At a median of 10 months after the last bevacizumab dose, two patients had a recurrence of radiation necrosis and both of those patients were retreated with 1-2 doses of bevacizumab with success. This provided class I evidence of the efficacy of bevacizumab in the treatment of symptomatic central nervous system radiation necrosis.

SOURCE: Levin VA, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiation Biol Phys* 2011;79:1487-1495.

Chemoradiotherapy is the standard of care in the management of in high-grade gliomas and advanced-stage head and neck cancers, while fractionated radiotherapy and high-dose stereotactic radiotherapy often are used as an alternative to neurosurgical resection in benign CNS diseases. The rates of symptomatic radiation necrosis are generally less than 5-10% and correlate to the dose of radiotherapy administered as well as the volume of tissue irradiated. The mechanism of action responsible for radiation necrosis is currently felt to be triggered by local cytokine release resulting in an increase in capillary permeability and extracellular edema ultimately leading to tissue hypoxia, demyelination of neurons, and necrosis. Treatments to date have included corticosteroids, antiplatelet agents, anticoagulants, hyperbaric oxygen, high-dose vitamins, and surgery.[1] Preclinical studies have demonstrated that vascular endothelial growth factor (VEGF) plays a role in the process of disrupting the blood-brain barrier and the cascade of events that follow resulting in radiation necrosis. The investigators hypothesized that blocking VEGF with bevacizumab would reduce the movement of plasma water through "leaky" brain capillary endothelium.

This Phase 3 trial was conducted at the University of Texas M.D. Anderson Cancer Center. Fourteen patients were randomized to either receiving bevacizumab or placebo infusions. Patients were considered eligible for the trial if there was MRI evidence of radiation necrosis and/or biopsy confirmation. In addition, all patients were required to have neurologic symptoms consistent with the location of necrosis and no prior bevacizumab therapy. Concurrent dexamethasone was allowed in the study as long as the dose was stable for at least a week prior to enrolling. Concurrent warfarin was allowed on study as long as INR was therapeutic. Patients were considered ineligible if they had clinically significant cardiovascular disease such as hypertension, CVA, MI, arrhythmias, unstable angina, or CHF < 6 months of study entry. Patients in Group A received IV bevacizumab at a dose of 7.5 mg/kg at 3-week intervals for two treatments and if patients were responding clinically and radiographically they received another two doses separated by 3 weeks. Patients in Group B received placebo (normal saline). Since none of the placebo-treated patients had a response, all seven were allowed to crossover and received bevacizumab. Failure was defined as an increase in radiation necrosis on MRI, no reduction on MRI, or insufficient reduction and progression of neurologic symptoms. MRI studies included pre- and post-gadolinium administered sequences on a 3.0T scanner. Post-contrast images included 3D dynamic contrast-enhanced MRI images (DCE-MRI). All images were reviewed by a blinded team of neuroradiologists. Serial neurologic examinations, formal neurocognitive testing, dexamethasone dosing records, and self-reports of symptoms using the M. D. Anderson Symptom Inventory (MDASI) were also performed on all patients.

The majority of the patients enrolled in the trial had CNS malignancies and presenting symptoms of radiation necrosis varied from headaches to hemiparesis to decreased vision. Of the seven patients randomized to placebo, five had progression of neurologic symptoms and two demonstrated only progression on MRI. All patients then crossed over and received bevacizumab. For patients randomized to bevacizumab, all demonstrated MRI responses and none progressed clinically. The median increase in volume of FLAIR abnormality was +14% in patients receiving placebo and the median decrease in volume of FLAIR abnormality was 59% in those assigned to bevacizumab (P = 0.0149). The median increase in volume of enhancing tissue was +17% in patients receiving placebo, while patients in the bevacizumab arm had a median decrease in volume of enhancing issue of -63% (P = 0.0058). At a median follow-up of 10 months after the end of treatment, three of 12 patients (25%) required retreatment with one to four doses of bevacizumab and all patients demonstrated radiographic improvement. Of the entire cohort, five patients were on dexamethasone at baseline and four of five were able to reduce their dexamethasone. The one patient who was not able to reduce dexamethasone was found to have progression of his astrocytoma to glioblastoma. Six of 11 patients receiving bevacizumab experienced an adverse event and three were classified as serious: one aspiration pneumonia, one PE secondary to DVT, and one superior sagittal sinus thrombosis. Neurocognitive testing demonstrated a trend toward improvement in the aspects of learning and memory after 6 weeks of therapy despite increasing deficits in memory retrieval. Also, there was some evidence for a reduction in severity of symptoms and improved everyday functioning.

COMMENTARY

This study provides excellent data and justification for the use of bevacizumab in the treatment of symptomatic radiation necrosis. One salient point is the data are drawn from a population with symptomatic not asymptomatic radiation necrosis. A number of patients will develop radiographic changes on an MRI after CNS directed chemo-

radiotherapy. It is important to distinguish mere MRI changes and symptomatic radiation necrosis. Too often in my experience, patients are receiving scans for vague or mild symptoms 2-4 weeks after completing radiotherapy. Invariably the reading neuroradiologist will describe progression of disease and/or radiation necrosis in the radiographic findings. Differentiating radiation necrosis can be difficult. Other imaging, such as FDG PET,

[De-escalating the dose of bevacizumab to 5 mg/kg and incorporating low-dose anticoagulants would be an appropriate regimen to investigate for symptomatic radiation necrosis.]

methionine PET, or thallium chloride-201 PET, can help differentiate tumor growth from necrosis.[2] In addition, magnetic resonance spectroscopy can differentiate necrosis from tumor growth.[3] The concept of "pseudoprogression" has been well documented in a number of cases for patients treated with temozolomide and radiotherapy for GBM and should not be confused with radiation necrosis and/or progression of disease. It should be pointed out that all patients in this trial were at least 6 months out from radiotherapy.

Administering bevacizumab 4-8 weeks after chemoradiotherapy should be done with great caution. Not only does bevacizumab result in adverse events (6/11 on this trial alone), but it precludes patients from enrolling in a number of clinical trials investigating new agents for the treatment of refractory gliomas.

Complications of therapy included superior saggital sinus thrombosis, DVT, and ischemic changes. The authors hypothesize that low-dose anticoagulation might be appropriate with bevacizumab. This could potentially help with some of the discussed complications but may increase risk of hemorrhage. The optimal regimen has yet to be established, but I think potentially de-escalating the dose of bevacizumab to 5 mg/kg and incorporating low-dose anticoagulants would be an appropriate regimen to investigate. Decisions regarding the management of symptomatic radiation necrosis should be made in a multidisciplinary fashion with consultation from neurosurgery, medical oncology, radiology, hyperbaric medicine, and radiation oncology. ■

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ILLUSTRATIVE CASE SERIES

Solitary Colorectal Pulmonary Metastasis

By William B. Ershler, MD

A 61-year-old small business owner was seen in consultation for advice regarding management of a newly discovered pulmonary mass. Seven years previously, he had a 3.5 cm moderately differentiated adenocarcinoma of the sigmoid colon resected along with four regional nodes, all of which were negative for metastatic involvement. The tumor had been discovered at routine colonoscopy, and preoperative imaging studies, including CT scan of the abdomen and chest, were negative for apparent metastatic disease; carcinoembryonic antigen level (CEA) was mildly elevated at 3.8 ng/mL. After an uneventful recovery from his colon surgery, he was treated with eight 3-week cycles of capecitabine (750 mg/m^2 po bid x 14 days every 21 days). Subsequent follow-up evaluations including periodic CT, screening chemistries, and occasional colonoscopies were not indicative of disease recurrence. However, at a recent follow-up visit, CEA titer was noted to be elevated (8 ng/mL). CT scan revealed a normal appearing abdomen and pelvis without lymphadenopathy or abnormalities in the liver or other organs. Colonoscopy also revealed no abnormality. However, CT of the chest revealed an oval-shaped density in the left

lung measuring 3.5 cm in greatest diameter that had not been apparent on CT obtained 14 months previously. PET/CT identified the same lesion, but no others. A CT-guided lung biopsy revealed metastatic adenocarcinoma with histological and cytochemistry pattern consistent with colorectal primary. *Kras* mutation studies revealed no mutations at codons 12 and 13. The patient, otherwise healthy, non-smoker, and robust on physical examination, is referred for a second opinion regarding treatment options.

Discussion

This asymptomatic, otherwise healthy middle-aged man has what appears to be metastatic colon cancer, presumably from a primary lesion resected 7 years previously. There are several aspects of this case that are unusual and worthy of note.

First, 7 years ago after the original resection, the decision to treat with adjuvant chemotherapy for clinical stage II disease presumably was based on an insufficient number of resected nodes (only four, well below the number that confers confidence of adequate staging). Nonetheless, there has been a resurfacing of enthusiasm for adjuvant treatment for stage II disease these days, based primarily upon the findings from the QUASAR study demonstrating modest but significant improvement in survival for patients treated with fluorouracil and folinic acid compared to placebo.[1]

Second, both the long disease-free interval and the pattern of spread must be considered unusual. Certainly, the primary physicians were aware of this, and pursued other explanations, including colonoscopy and CT and PET/CT imaging studies. Perhaps the long disease-free interval relates to more indolent tumor growth characteristics, possibly influenced by adjuvant chemotherapy. But, appearing as an isolated focus in the lung would seem distinctly uncommon. However, it is not completely rare. In fact, by carefully examining a fairly large database of patients with colorectal cancer, Tan and colleagues found the incidence of isolated lung without liver metastases in patients with colon cancer to be approximately 6%, compared with 12% for patients with primary rectal cancer.[2] Thus, although certainly less common than with rectal cancer, isolated recurrence in the lung without liver involvement should not be considered rare.

However, despite this, there basically are no data derived from randomized studies to guide subsequent treatments. This is not to say there have not been sufficient published reports in the surgical literature describing outcomes for patients after pulmonary metastasectomy. Pfannschmidt and colleagues reported on outcome factors for pulmonary resection in metastatic colorectal cancer.[3] Their systematic review included 15 articles and 1539 patients. Overall 5-year survival after complete surgical resection was 40% to 68%. Five-year disease-free survival ranged from 19.5% to 34.4%. For patients having both hepatic and pulmonary metastasectomy, overall survival was between 31% and 60.8%; estimated disease-free survival at 3 years was 8%. Completeness of resection was the most important prognostic indicator. Kanemitsu and colleagues developed a predictive model for estimating long-term outcome.[4] Primary histopathology, hilar or mediastinal lymph node involvement, number of metastases, preoperative carcinoembryonic antigen level, and the presence of extrathoracic disease were factors used in the calculation of a clinical risk score, which was highly predictive of long-term outcome.

For the patient under discussion, it would seem that the most logical next step would be surgical excision. After the long disease-free interval, the solitary nature of the disease recurrence as defined by PET/CT and his overall performance status, the expectation is that he would have a good outcome in terms of protracted disease-free survival. For me, the question is not whether to proceed with surgery, but what to do after recovery. Although there is no trial-derived evidence for chemotherapy in this second adjuvant setting, studies are now underway employing adjuvant chemotherapy after liver metastases resection.[5] These findings may ultimately be applicable to the post-pulmonary metastastectomy adjuvant therapy question. Until such data are available, recommendations must be based on best clinical judgment. In this case, my recommendation would be to proceed to surgery and upon recovery a full course of oxaliplatin-based adjuvant chemotherapy. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

CME Instructions

To earn credit for this activity, please follow these instructions:

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CME Questions

1. Which is an appropriate adjuvant treatment option for patients with stage III (lymph node positive) colon cancer?

a. FOLFOX
b. FOLFOX + cetuximab
c. Cetuximab
d. All of the above

2. Pulmonary metastases in the absence of liver metastases occurs in approximately what percent of all patients with colon cancer?

a. < 1%
b. 6%
c. 12%
d. 25%

3. Upon more intensive examination of lymph nodes from axillary dissections of early breast cancer patients, a percentage (between 10% and 30%) of those, who by routine pathology evaluation were considered negative, will be found to harbor occult metastases. What are the overall prognostic implications in terms of disease recurrence?

a. Recurrence is more likely than node-negative patients without occult metastases.
b. Recurrence is less likely than node-negative patients without occult metastases.
c. There is no influence on recurrence rate.
d. The answer is not in yet.

4. Which of the following comments regarding the treatment of radiation necrosis is NOT true?

a. Bevacizumab significantly reduces the radiographic changes associated with radiation necrosis.
b. Bevacizumab should be used within 2 weeks of completing XRT if an MRI appears abnormal and radiation necrosis is suspected.
c. Bevacizumab given every 3 weeks for a total of four doses is usually sufficient to resolve symptomatic radiation necrosis.
d. Corticosteroids, vitamins, anticoagulants, surgery, hyperbaric oxygen, and bevacizumab have all demonstrated some benefit in managing symptomatic radiation necrosis.

[IN FUTURE ISSUES]

Free Light Chain Levels Offer Predictive Value for Both Myelofibrosis and Myelodysplasia

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Does Aspirin Prevent Cancer?

In this issue: Aspirin and cancer prevention; rivaroxaban for pulmonary embolism; new rhinosinusitis practice guidelines; and FDA actions.

Is recommending aspirin next?

Should aspirin be recommended to prevent cancer? Many lines of evidence have suggested that regular low-dose aspirin reduces the risk of colorectal cancer. Can the inexpensive wonder drug reduce the risk of other cancers as well? Researchers in England led by Dr. Peter Rothwell recently published three meta-analyses that looked at aspirin use and long-term cancer incidence and metastasis, as well as the short-term effect on cancer incidence and mortality, and the effect of aspirin on cancer metastasis. More than 200 studies were included in the meta-analyses, which were initially done to assess aspirin's benefit on vascular disease. The three new studies used a combination of case-control, cohort, and randomized clinical trials.

In the long-term study, the 20-year risk of cancer death and metastases was evaluated whereas the short-term study looked at a 3-5 year time frame. The trial for prevention of metastatic disease included five large, randomized trials of daily aspirin vs control in patients who had new solid cancer diagnosed during the trial. In the long-term study, the odds ratio for colon cancer incidence was 0.62 in favor of aspirin, and the odds ratio was 0.58 for death from colon cancer in favor of aspirin. There were similar reductions in the rates of esophageal, gastric, biliary, and breast cancer. The rate of distant metastases was also reduced. The other two studies also showed reduced rates of cancer and reduced rates of metastatic disease.

In the short-term study, cancer rates were 24% lower with aspirin use at 3 years. Curiously, aspirin did not reduce the risk of vascular events but there was no increased risk of major bleeding, including intracranial hemorrhage.

In the meta-analysis of five trials looking at the rate of metastatic disease, a 36% reduction in cancer metastasis was noted, including a 46% reduction in metastatic adenocarcinoma (all three studies published online in *Lancet* and *Lancet Oncology* March 21, 2012.) An accompanying editorial points out that these studies show that aspirin at any dose reduces nonvascular deaths by 12% and cancer death by 15% with benefits seen within 3 years for higher doses (> 300 mg/day) and at 5 years for lower doses (< 300 mg/day). The major critique of the studies comes from the United States where the Women's Health Initiative Study and the Physicians' Health Study both failed to show benefit from aspirin on cancer mortality. Both of these studies used low-dose aspirin every other day, a dose that may be too low to show biological effect on cancer. Another critique suggests that aspirin may lead to earlier diagnosis of colorectal cancer since it may cause earlier gastrointestinal bleeding, explaining the lower mortality rate. Despite these concerns, the editorialists suggest that this "impressive collection of data moves us another step closer to broadening recommendations for aspirin use. Moreover, future evidence-based guidelines for aspirin prophylaxis can no longer consider the use

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of aspirin for the prevention of vascular disease in isolation from cancer prevention." (*Lancet* published online March 21, 2012). ■

Rivaroxaban for pulmonary embolism

Rivaroxaban, Janssen's oral factor Xa inhibitor, may be an effective alternative to heparin/warfarin for treatment of symptomatic pulmonary embolism, according to a new study. The drug is currently approved for the prevention of stroke in patients with nonvalvular atrial fibrillation and for deep vein thrombosis (DVT) prophylaxis following hip replacement. It has also been shown to be an effective treatment for DVT, although it is not approved for this indication. The new study was a randomized, open-label, event-driven, noninferiority trial comparing rivaroxaban to standard therapy with enoxaparin followed by adjusted-dose vitamin K antagonist for 3, 6, or 12 months for the treatment of pulmonary embolism. The primary outcome was symptomatic recurrent venous thromboembolism with a secondary safety outcome of clinically relevant nonmajor bleeding. In more than 4800 patients who were randomized, rivaroxaban was noninferior to standard therapy with 50 events in the rivaroxaban group (2.1%) vs 44 events in the standard therapy group (1.8%) (hazard ratio [HR], 1.12; confidence interval [CI] 0.75 to 1.68, noninferiority margin 2.0; $P = 0.003$). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard therapy group, while major bleeding occurred in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard therapy group (HR 0.49; 95% CI, 0.31 to 0.79; $P = 0.003$). The authors conclude that a fixed-dose regimen of rivaroxaban was noninferior to standard therapy with enoxaparin and warfarin for the initial and long-term treatment of pulmonary embolism, and potentially showed an improved benefit-risk profile (*N Engl J Med* published online March 26, 2012). The doses of rivaroxaban used in the study were 15 mg twice a day for 3 weeks followed by 20 mg once daily for the duration. Rivaroxaban offers the advantage of oral therapy compared to enoxaparin and the lack of need for blood test monitoring compared to warfarin. ■

New practice guideline for rhinosinusitis

The Infectious Diseases Society of America has published its first Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. The guideline points out the difficulty in distinguishing bacterial vs viral sinus infections. The following are suggestive of bacterial infection: persistent symptoms of sinusitis lasting more than 10 days without evidence of improvement; onset of severe symptoms or signs with high fever, purulent discharge, or facial pain lasting at least 3-4 consecutive days; or onset with worsening symptoms or signs characterized by new onset of fever, headache, or increased nasal discharge following a viral URI. The guideline recommends empiric antibiotic therapy with amoxicillin-clavulanate rather than amoxicillin alone in both children and adults. Children should be treated for 10-14 days while adults should be treated for 5-7 days. The guideline further recommends beta-lactam agents for treatment of sinusitis rather than respiratory floroquinolones, macrolides, trimethoprim-sulfamethoxazole, or second- or third-generation oral cephalosporins due to emerging resistance patterns. Doxycycline may be used as an alternative. (*Clin Inf Dis* 2012;54:e72-e112. DOI: 10.1093/cid/cis370). ■

FDA actions

The FDA has approved the first new erythropoiesis-stimulating agent in more than 10 years. Peginesatide is approved to treat anemia associated with end-stage renal disease in patients on dialysis. The approval was based on two randomized, active-controlled, open-label trials which showed that the drug was as effective as epoetin in maintaining hemoglobin levels. The drug is not approved for chronic kidney disease patients who are not on dialysis or for cancer-related anemia. Peginesatide is marketed by Affymax Inc. as Omontys.

The FDA has approved the first generic ibandronate (Boniva), the popular once-monthly bisphosphonate to treat or prevent osteoporosis in postmenopausal women. Three companies have received approval to manufacture the drug including Apotex Inc., Orchid Healthcare, and Mylan Pharmaceuticals. The generic as well as the brand is dispensed with a medication guide regarding the possible risk of esophagitis, hypocalcemia, bone or muscle pain, osteonecrosis of the jaw, and atypical femoral fractures.

The FDA has also recently approved generic escitalopram (Lexapro), a selective serotonin reuptake inhibitor (SSRI) to treat adults with depression and generalized anxiety disorder. Teva Pharmaceuticals will be the first to market the generic in 5-, 10-, and 20-mg strengths. Like other SSRIs, escitalopram carries a box warning regarding increased risk of suicidal thinking and behavior in children, adolescents, and young adults. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Donepezil and Memantine for Moderate-Severe Alzheimer's Disease

Source: Howard R, et al. *N Engl J Med* 2012;366:893-903.

THE CHOICE OF IF AND WHEN TO EMPLOY pharmacotherapy in the management of Alzheimer's disease (ALZ) is not an easy one. Early in the disease process (mild-moderate ALZ) — where clinical trials have demonstrated beneficial outcomes, albeit of debatable clinically relevant magnitude — clinicians and caregivers may be least motivated to treat, since disease status is relatively less problematic and measureable benefits are smaller. In moderate-severe ALZ, memantine (MEM) has demonstrated beneficial effects. A single, never-replicated trial of the addition of MEM to donepezil (DON) in mild-moderate ALZ had favorable outcomes. Data on whether cholinesterase inhibitors provide improved outcomes as the disease progresses to the moderate-severe stages have been lacking. Indeed, there is some support for discontinuation of cholinesterase inhibition when ALZ progresses to the severe stage.

Howard et al randomized patients (n = 295) with moderate-severe ALZ already on treatment with DON to one of four groups: continued DON alone, MEM alone, continued DON plus MEM, or placebo alone. Patients were followed for 1 year, measuring outcomes by means of the Standardized Mini-Mental State Examination (SMMSE) and Bristol Activities of Daily Living Scale (BADLS). The minimum clinically important difference on these scales is 1.4 points and 3.5 points, respectively.

At 1 year, scores in the group that continued DON were superior to the placebo group as measured by the SMMSE (1.9 points difference); on the BADLS, the score was statistically significantly improved but failed to meet the minimum clinically important difference threshold. Neither substitution of MEM for DON nor addition of MEM to DON provided clinically important improvement.

In moderate-severe ALZ, these data support continuation of DON, but not substitution or augmentation with MEM. ■

Treating Hyperhidrosis with Systemic Therapy

Source: Walling HW. *J Am Acad Dermatol* 2012;66:387-392.

EVEN THOUGH HYPERHIDROSIS (HHD) HAS a prevalence almost three times as great as rheumatoid arthritis (± 3% vs ± 1%), clinician awareness and management of this disorder are often suboptimal. Although the palms of the hands and plantar surfaces of the feet are the most commonly involved sites, axillary, craniofacial, and multisite involvement is reported. The HHD disease severity scale describes moderate HHD as "tolerable but sometimes interferes with daily activities," and severe as "barely tolerable to intolerable, that frequently to always interferes with daily activities." HHD is not just a quality-of-life issue; skin infections are more common in HHD sufferers.

The mainstay of HHD treatment for several decades has been topical drying agents, especially with those containing aluminum chloride. Iontophoresis, botulinum toxin, and even sympathectomy have demonstrated some efficacy, but the expense and inconvenience of such interventions is an obstacle.

Walling performed a chart review of HHD patients seen in an academic department of dermatology who had received one of three systemic agents to treat HHD: glycopyrrolate, oxybutynin, or clonidine.

Glycopyrrolate was effective in 30 of 45 patients; among glycopyrrolate treatment failures, six of 15 were non responders, and nine had adverse anticholinergic effects (e.g., dry mouth). Clonidine was effective in six of 13 patients; among clonidine treatment failures, three were noresponders and four experienced hypotension. A single patient responded favorably to oxybutynin (an anticholinergic typically used for overactive bladder).

Because no one treatment for HHD is uniformly effective, clinicians must become aware of alternative therapies. Previous literature has suggested that systemic treatments might not be well tolerated, yet efficacy in this data set was good with no serious adverse effects. Systemic treatments may help patients with HHD. ■

A New Intervention for Actinic Keratoses: Ingenol Mebutate Gel

Source: Rosen RH, et al. *J Am Acad Dermatol* 2012;66:486-493.

ACTINIC KERATOSES (AK) IS BIOLOGICALly in situ squamous cell carcinoma,

with the potential to become invasive in a minority of cases. However, because an individual patient may have many AK and it is not possible with certainty to identify which lesions are more likely to progress, it has been recommended that removal of AK be performed whenever possible. In the primary care setting, the three most prominent methods of destruction are cryotherapy, immune activators (e.g., imiquimod cream), and antimetabolites (e.g., 5-fluorouracil cream). Each of these methods has substantial limitations; for instance, the inflammatory response to appropriate use of imiquimod or 5-fluorouracil may be both painful and (at least transiently) cosmetically unwieldy. Additionally, traditional regimens of commonly used topicals require multiple applications over several weeks or more.

Ingenol mebutate (ING) is a recently approved topical agent that works by induction of lesion necrosis as well as by activation of antibody-directed cellular cytotoxic pathways. What this does for AK is produce a prompt and immediate kill effect on abnormal cells (within a few hours), which is coupled with a drug-mediated activation of B-cells that binds to abnormal (precancerous) cells over subsequent days and destroys them. This dual mechanism provides for short treatment regimens (2-3 days), with persistent post-treatment effects that obliterate evolving AK. The tolerability profile of ingenol, coupled with its dual mechanism of action and ease of administration, may give it a priority role in topical therapies for AK, although the clearance rates with the new product are not yet established to be at parity with older agents until head-to-head comparator trials are performed. ■

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Colon Cancer Screening: Getting the Right Test Done

Source: Quintero E, et al. *N Engl J Med* 2012;366:697-706.

In its most recent update on colorectal cancer screening (CCS), the American Cancer Society, in concert with other interested parties, suggested that the best screening test for CCS is the one a person can get done. This is because in comparison to the other more widely used screenings (e.g., mammography, PAP testing, PSA), adoption of colonoscopy has been somewhat disappointing.

Fecal immunochemical testing (FIT) of the stool incorporates many of the advantages and circumvents some of the limitations of other screening tools. For instance, the specificity of FIT for human hemoglobin eliminates special dietary restrictions. Additionally, the presence of blood from the upper GI tract does not typically induce a positive result with FIT, eliminating unnecessary evaluation of the colon when upper GI blood is the cause.

Quintero et al report on initial results of the first wave of a comparison between FIT and colonoscopy in a very large population (n = 53,102) of asymptomatic adults age 50-69 years who were randomized to either traditional colonoscopy every 10 years or FIT every 2 years. FIT-positive patients were followed up with colonoscopy.

As is perhaps not surprising, compliance with FIT was about 30% greater than with colonoscopy. Colon cancer was detected in 0.1% of each group; however, the rate of detection of advanced adenomas was more than twice as high in the colonoscopy group (1.9% vs 0.9%).

These preliminary results are encouraging that a method for which patients find more advocacy — FIT — might find a more prominent role in CCS, especially when patients find other screening tools unacceptable. Because these results are preliminary (first 2-3 years of follow-up), we will likely need to wait until final results are completed in 2021 before the question of the role of FIT can be definitively answered. ■

Can Male Pattern Baldness Predict BPH?

Source: Arias-Santiago S, et al. *J Am Acad Dermatol* 2012;66:401-408.

Aside from genetic influences, testosterone (TST) and dihydrotestosterone (d-TST) play an important role in both benign prostatic hyperplasia (BPH) and male pattern baldness (also known as androgenetic alopecia). For BPH, conversion of TST to d-TST by means of 5-alpha-reductase (5-AR) results in stimulus for prostate gland growth. In the prostate, 5-AR of both type 1 and type 2 are operant. 5-AR blockers (e.g., finasteride, dutasteride) have been shown to shrink prostate size.

In the scalp, only 5-AR type 2 is functional. In susceptible individuals, conversion of TST to d-TST in the scalp results in follicular diminution, producing hair loss. Might the same susceptibility to male pattern baldness be reflected in an increased incidence or severity of BPH?

Arias-Santiago et al compared metrics pertinent to BPH in men with and without early-onset male pattern baldness. Although there was no difference between groups in levels of testosterone, prolactin, other gonadal steroids, or testosterone-binding proteins, the men with early male pattern baldness had significantly greater levels of PSA, more lower urinary tract symptoms consistent with BPH, greater prostate gland size as measured by ultrasound, and lower urinary flow rates.

Clinicians may wish to look for BPH-related symptoms in men with early androgenetic alopecia. ■

Clinical Oncology Alert

2012 Reader Survey

In an effort ensure *Clinical Oncology Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. *T*he results will be used to ensure you are getting the information most important to you.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 1, 2012.**

In future issues of *Clinical Oncology Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. appropriate treatment regimens	O A	O B	O C
2. quality-of-life treatments	O A	O B	O C
3. management of clinical symptoms	O A	O B	O C
4. uninsured patients	O A	O B	O C
5. new drug development	O A	O B	O C
6. breast cancer	O A	O B	O C
7. lung cancer	O A	O B	O C
8. prostate cancer	O A	O B	O C
9. cervical cancer	O A	O B	O C
10. FDA regulations	O A	O B	O C

11. What other topics would you like to see discussed in *Clinical Oncology Alert*? _____

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12. Are the articles in *Clinical Oncology Alert* newsletter written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

13. What type of information not currently provided in *Clinical Oncology Alert* would you like to see added?

Please rate your level of satisfaction with the the items listed:

	A. excellent	B. good	C. fair	D. poor
14. monthly case study	O A	O B	O C	O D
15. Rapid Review	O A	O B	O C	O D
16. the new look of *COA*	O A	O B	O C	O D
17. quality of newsletter	O A	O B	O C	O D
18. article selections	O A	O B	O C	O D
19. timeliness	O A	O B	O C	O D
20. quality of commentary	O A	O B	O C	O D
21. clearness of abstracts	O A	O B	O C	O D
22. overall value	O A	O B	O C	O D
23. customer service	O A	O B	O C	O D

24. Please describe your work place:

○ A. private practice ○ B. hospital ○ C. government institution ○ D. research

○ E. Other_____

25. Do you benefit from having important points highlighted in the articles? ○ A. Yes ○ B. No

26. To which other publications or information sources about oncology do you subscribe?

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27. Which publication or information source do you find most useful, and why? _____

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28. Please list the top three challenges you face in your job today.

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29. What do you like most about *Clinical Oncology Alert*?

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31. Has reading *Clinical Oncology Alert* changed your clinical practice? If yes, how? _____

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