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ABSTRACT & COMMENTARY

Radioembolization for Neuroendocrine Liver Metastases: Safety, Imaging, and Long-Term Outcomes

By Samir P. Kanani, MD

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

SYNOPSIS: In a retrospective series, 40 patients with liver-dominant metastatic neuroendocrine tumors were treated with 90Y radioembolization between 2003 and 2007 at a single institution. Response to therapy was assessed by World Health Organization (WHO) guidelines for size and European Association for the Study of the Liver disease (EASL) guidelines for necrosis. Time to response and overall survival were calculated using the Kaplan-Meier method. The median dose was 113 Gy. Clinical toxicities included fatigue (63%), nausea/vomiting (40%), abdominal pain (18%), fever (8%), and diarrhea and weight loss (5%); Grade 3 and 4 bilirubin toxicities were experienced by two patients and one patient, respectively. Different responses were noted by WHO (complete response, 1.2%; partial response, 62.7%) and EASL (complete response, 20.5%; partial response, 43.4%). Median time to response was 4 and 4.9 months by lesion and patient, respectively. The 1-, 2-, and 3-year overall survival rates were 72.5%, 62.5%, and 45%, respectively. Eastern Cooperative Oncology Group (ECOG) performance score 0 ($P < 0.0001$), tumor burden ≤ 25% ($P = 0.0019$), albumin > 3.5 g/dL ($P = 0.017$), and bilirubin ≤ 1.2 mg/dL ($P = 0.002$) prognosticated survival on univariate analysis; only ECOG performance score 0 and bilirubin ≤1.2 mg/dL prognosticated better survival outcome on multivariate analysis ($P < 0.0001$ and $P = 0.02$). The authors conclude that Yttrium-90 therapy for hepatic neuroendocrine metastases leads to satisfactory tumor response and patient survival with low toxicity, in line with published national guidelines.

SOURCE: Memon K, et al. Radioembolization for neuroendocrine liver metastases: Safety, imaging, and long-term outcomes. *Int J Radiat Biol Phys* 2012;83:887-894.

Forty patients with liver-dominant metastatic neuroendocrine tumors (mNETs) were enrolled in this study between 2003 and 2007. This study represents a retrospective review of prospectively collected data. The study inclusion criteria included 1) unresectable mNETs refractory to systemic treatment as determined by oncology and interventional radiology with

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imaging-confirmed progressive disease, 2) Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2, and 3) adequate hematologic, renal, and liver function (bilirubin ≤ 2.0 mg/dL). Exclusion criteria included: 1) significant extrahepatic disease, 2) evidence of uncorrectable gastrointestinal shunting observed on angiography or technetium-labeled macroaggregated albumin scans, 3) the possibility of estimated lung dose to be > 30 Gy in a single session, and 4) concurrent chemotherapy or radiotherapy. One-third of the patients had minimal extrahepatic disease, 62% had symptoms of carcinoid, and 22% had prior liver directed therapy. In patients taking octreotide, this agent was not stopped for 90Y therapy.

The patients' treatment consisted of a pretreatment angiogram to determine aberrant shunting of blood from the liver to the lung and also embolization of aberrant vessels. Patients also underwent a nuclear medicine scan consisting of Technetium-labeled macoaggregated albumin to estimate the lung shunt fraction. Patients were then treated with 90Y using a lobar approach with 38/40 patients receiving bilobar therapy. Prophylactic octreotide (200 mg subcutaneous) was administered to all patients immediately before radioembolization.

All patients were evaluated by history, physical examination, laboratory values, and radiologic imaging 4 weeks after treatment and then every 2 to 3 months. The toxicity included fatigue in 25 (63%), abdominal pain in 7 (18%), nausea and vomiting in 16 (40%), fever and chills in 3 (8%), and diarrhea and weight loss in 2 (5%) patients. One patient experienced Grade 4 bilirubin toxicity, and 15 (38%) experienced Grade 3 lymphocyte toxicity. One patient experienced radiation cholecystitis requiring cholecystectomy. Of all lesions, 94% showed at least some decrease in size, whereas 64% of lesions showed > 50% reduction in size. The median time to response (WHO) was 4 months by lesion and 4.9 months by patient. Of 25 patients symptomatic at baseline, 21 (84%) reported subjective improvement after treatment. The median follow-up time was 27 months. The median overall survival time was 34.4 months.

The 1-, 2-, and 3-year survival rates for all patients were 72.5%, 62.5%, and 45%, respectively, from 90Y treatment. On multivariate analysis, only ECOG performance score 0 and bilirubin < 1.2 mg/dL independently predicted better survival.

COMMENTARY

Well-differentiated gastroenteropancreatic neuroendocrine tumors generally are considered indolent tumors with a prolonged natural history. However, among patients with liver metastasis the survival can be variable. We all have these patients at our clinics who survive many years without symptoms or progression and others who progress rapidly. Most patients who have liver metastasis are symptomatic from hypersecretion rather than the presence of tumor in their liver. These symptoms are often controlled with octreotide. Systemic options such as streptozocin, dacarbazine, temozolomide, oxaliplatin, capecitabine, bevacizumab, and small molecule TK inhibitors all have been investigated after progression on octreotide and show limited potential. Recent studies evaluating everolimus have demonstrated some promise.[1]

Yttrium-90 device (TheraSphere, MDS Nordion, Canada) currently is FDA-approved for patients with unresectable hepatocellular carcinoma.[2] It consists of 20-30 micrometer-sized nonbiodegradable glass microspheres in which Yttrium is the integral constituent. Yttrium-90 is a pure beta emitter with a half-life of 64.1 hours. The current study demonstrates an encouraging median survival in a group of patients who remain symptomatic after initiating octreotide therapy. The current study compares favorably with other reports in the literature using Y90 radioembolization. In a multi-institutional study with 42 patients treated with Y90, Rhee et al found a median survival of 25 months, with 50% demonstrating radiologic response.[3] In another retrospective multi-institutional study, Kennedy et al investigated Y90 microsphere treatment in 148 patients. They reported a median survival time of 70 months, with a radiographic response rate of 60.5%.[4] This study, along with a number of previous studies, demonstrates the safety and efficacy

of radioembolization in the management of patients with metastatic carcinoid. The procedure should be considered an option in symptomatic patients who progress on octreotide. In my opinion, it is better tolerated than other locoregional therapies, such as chemoembolization or bland embolization, although they have never been compared in a randomized fashion. ■

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ABSTRACT & COMMENTARY

An Increased Risk of Non-Hodgkin Lymphoma in Chronic Fatigue Syndrome Patients

By William B. Ershler, MD

SYNOPSIS: Chronic fatigue syndrome (CFS) is common in community practice and it has been speculated that it is the result of chronic immune proliferation or infection. In a review of Surveillance, Epidemiology, and End Results registry data, coupled with Medicare claims data, an association of CFS with non-Hodgkin lymphoma is clearly demonstrated.

SOURCE: Chang CM, et al. Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults. *Cancer* 2012;118:5929-5936.

The epidemiological characterization of chronic fatigue syndrome (CFS) remains challenging due to a lack of standard disease biomarkers. Criteria established by the Centers for Disease Control and Prevention include the presence of fatigue lasting for at least 6 months, reduction in the activities of daily living, and a constellation of persistent symptoms including impaired memory, sore throat, tender lymph nodes, muscle or joint pain, and/or headache.[1] This definition excludes patients with major depressive disorder, schizophrenia, alcoholism, or chronic medical conditions including autoimmune disease, cancer, and cirrhosis. Studies have estimated the prevalence in the United States to be between 0.2-0.4% and to account for more than $7 billion in medical expenses per year.[2,3] CFS is more common in women, in middle age, in non-whites, and in those of middle-income status.[2,3]

The cause of CFS remains unknown but it is thought to be associated with chronic immune stimulation or infection. In recent years, a number of publications suggested an association of CFS with a specific retrovirus (xenotropic murine leukemia virus-related virus), but these studies most recently have been refuted.[4] Nonetheless, there have been a number of studies linking CFS with chronic immunoproliferation,[5,6] and as such, its association with incipient malignancy has been questioned.

To address this, Chang and colleagues performed a population-based, case-control analysis capitalizing on Surveillance, Epidemiology, and End Results (SEER) registry data of approximately 1.2 million cancer cases and 100,000 controls (age range, 66-99 years; 1992-2005). CFS was identified in the period more than 1 year prior to selection, using linked Medicare claims. Unconditional logistic regression was used to estimate the odds ratios (ORs) comparing the CFS prevalence in cases and controls, adjusting for age, sex, and selection year. All statistical tests were two-sided.

Although CFS was present at the same level in the total population of cancer patients when compared with controls (0.05%), more in-depth analysis revealed an association with non-Hodgkin lymphoma (NHL) (OR, 1.29; 95% confidence interval [CI], 1.16-1.43; $P = 1.7 \times 10^{-6}$). Among NHL subtypes, CFS was associated with diffuse large B cell lymphoma (OR, 1.34; 95% CI, 1.12-1.61), marginal zone lymphoma (OR, 1.88; 95% CI, 1.38-2.57), and B cell NHL not otherwise specified (OR, 1.51; 95% CI, 1.03-2.23). CFS associations with NHL overall and NHL subtypes remained elevated after excluding patients with medical conditions related to CFS or NHL, such as autoimmune conditions (rheumatoid arthritis, Sjogren's syndrome), hepatitis B or C, or prior transfusion. CFS also was associated, although not after multiple comparison adjustment, with cancers of the pancreas (OR, 1.25; 95% CI, 1.07-1.47), kidney (OR, 1.27; 95% CI, 1.07-1.49), breast (OR, 0.85; 95% CI, 0.74-0.98), and oral cavity and pharynx (OR, 0.70; 95% CI, 0.49-1.00).

COMMENTARY

By using SEER data linked to Medicare claims, an association of CFS with NHL was clearly demonstrated. Although other associations were demonstrated (i.e., increased risk for pancreatic and renal cancer and reduced risk for breast and oral-pharngeal cancers), these were marginal, especially when considering the level of statistical significance for NHL ($P = 10^{-6}$). This confirms the findings from an earlier report[7] and expands it to include NHL subtypes.

CFS is a heterogeneous disorder and diagnosis is often challenging. For those who meet diagnostic criteria, the current report demonstrates a robust association of an increased risk for lymphoma, particularly B cell NHL. By using Medicare claims data, the findings are restricted to those over the age of 65 years, whereas CFS is most common in middle age. Nonetheless, the finding is of value, both in increasing diagnostic surveillance for incipient lymphoma in CFS patients and also in providing an increased awareness of the likely link of immunoproliferative dysregulation in the pathogenesis of both disorders. ■

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ILLUSTRATIVE CASE SERIES

Vaccination Considerations for Chemotherapy Patients

By William B. Ershler, MD

A 58-year-old female patient with non-Hodgkin lymphoma is seen in the medical oncology clinic for the initiation of the fourth cycle of chemotherapy (R-CHOP). She had presented approximately 3 months earlier with asymptomatic lymphadenopathy. Computerized tomography revealed enlarged lymph nodes throughout the chest and abdomen and an axillary node biopsy revealed follicular large B-cell lymphoma. A bone marrow biopsy was negative for lymphoma involvement. The first three cycles of chemotherapy were tolerated very well with resolution of all palpable disease. On the occasion of initiation of her fourth cycle, she inquired about the advisability of receiving both influenza and shingles vaccines.

The patient's past medical history was significant for insulin-requiring diabetes mellitus and hypertension for which she received metoprolol 12.5 mg bid. She had remained without constitutional complaints throughout therapy and continues to work full time as a waitress.

DISCUSSION

Patients with cancer in general, but particularly those with hematologic malignancies, are at increased risk for infectious diseases, some of which are preventable by vaccination.[1,2] Risk for infection is heightened by the immunosuppressive effects of chemotherapy, with some agents, such as rituximab being particularly powerful at diminishing vaccine response.[3]

Although immunization appears to be an obvious way to prevent infection, many patients with impaired immunity are unable to mount a protective immune response to active vaccination. Furthermore, studies demonstrating efficacy of vaccines in patients with cancer are insufficient to provide formal evidence-based guidelines for the prevention of vaccine-preventable infections in oncology patients (excluding those who undergo hematopoietic cell transplantation). Nonetheless, immunization recommendations for immunocompromised patients in the United States have been developed by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC). In general, immunocompromised patients, such as those with cancer, should receive only inactivated vaccines (such as influenza and pneumococcal vaccines) and not live virus vaccines, such as the zoster vaccine.[4]

Influenza vaccine. Influenza-related hospitalization is 3-5 times higher in cancer patients than the general

population and the mortality rate is 9% (relative risk 4, compared with the general population).[5] Accordingly, annual vaccination is strongly recommended for those with cancer.[6] Furthermore, antiviral prophylaxis should be considered for those undergoing the most intense chemotherapy under certain circumstances, such as following an exposure. As mentioned, certain systemic anticancer agents have profound effects on immunity. A recent study aimed to determine whether lymphoma patients receiving rituximab-containing treatment regimens during or within the prior 6 months were able to mount protective antibody responses to the influenza A (H1N1) 2009 virus. The investigators found that contrary to age-matched controls without lymphoma in whom 82% responded adequately to the vaccine, none of the 67 patients achieved protective antibody titers.[3] In earlier studies, the same group reported adequate influenza vaccine responses among non-Hodgkin lymphoma patients receiving combination chemotherapy without rituximab.[7,8] Thus, rituximab appears particularly suppressive with regard to vaccine response — an observation that warrants recognition by clinicians in formulating vaccine schedules and considering use of antivirals.

It makes sense that the optimal time to receive a vaccine is before the initiation of chemotherapy. However, due to the seasonal nature of influenza vaccination programs, such timing often is not feasible. The optimal time for vaccination in patients already receiving chemotherapy is not established. In a recent report of breast cancer patients receiving FEC (5-fluorouracil, epirubicin, and cyclophosphamide)-containing chemotherapy regimens, patients were randomized to receive influenza vaccine early in the cycle (day 4) or at mid-cycle (day 16). As expected, the overall patient group had significantly lower responses to the vaccine compared with healthy controls. However, patients vaccinated at day 4 tended to have higher antibody titers compared to patients vaccinated at day 16. Thus, at least for breast cancer patients on combination chemotherapy, vaccination early during the chemotherapy cycle induces better responses than does vaccination at day 16. Whether this finding can be generalized to patients receiving other chemotherapies for other tumors remains to be studied.

Pneumococcal vaccine. Infections due to *Streptococcus pneumoniae* are an important cause of morbidity and mortality in oncology patients. Cancer patients are known to respond variably to the 23-valent pneumococcal polysaccharide vaccine, although responses are almost comparable to age-matched controls if the vaccine is given prior to chemotherapy.[9] However, responses after chemotherapy, even years later, have been shown to be suboptimal.[10]

Although a novel protein conjugated pneumococcal vaccine (Prevnar-13) currently has been approved for use in the United States, its efficacy in patients who are immunocompromised has yet to be established. It is expected that vaccine schedules including both the conjugate and polysaccharide vaccines will be developed for immunocompromised patients, but these have yet to be provided.

Zoster vaccine. Although patients with malignancy are at increased risk for shingles, the zoster vaccine (Zostavax) is a live-attenuated virus and its use is contraindicated in cancer patients. Nonetheless, the CDC suggests that patients with hematological cancers in remission and off chemotherapy (and radiotherapy) for 3 or more months may receive zoster vaccine.[4]

RECOMMENDATION

For the patient presented, both influenza and pneumococcal vaccines would be recommended. Timing of the vaccines might prove critical, and based on the limited data available, the influenza vaccine might best be given shortly after the initiation of the next cycle of chemotherapy. However, because of the inclusion of rituximab in the treatment program, a suboptimal response might be expected. Thus, the patient should be informed that infection with influenza remains a concern despite the vaccine and that she would be a candidate for antiviral medications shortly after symptoms of influenza are noticed. Similarly, the published experience suggests a suboptimal response to the polysaccharide pneumococcal vaccine would be expected. In this regard, new recommendations about the use of the pneumococcal conjugated vaccine either alone or in sequence with the polysaccharide vaccine will be of great value. ■

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SPECIAL FEATURE

Stress and Poor Cancer Outcomes: It's More Than Psychological

By Robert L. Coleman, MD
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Dr. Coleman reports no finanical relationships relevant to this field of study.
This article originally appeared in the November 2012 issue of *OB/GYN Clinical Alert*.

SYNOPSIS: **Chronic stress has been associated with development of several diseases and the release of several cytokines and growth factors known to support cancer growth and metastases. Pharmacological agents targeting the stress response, such as beta-blockers and prostaglandin inhibitors, have been associated with improved survivorship in patients with several solid tumors, including ovarian cancer. The relationship supports prospective clinical investigation, already underway.**

SOURCE: Diaz ES, et al. Impact of beta-blockers on epithelial ovarian cancer survival. *Gynecol Oncol* 2012; doi;10.1016/j.ygyno.2012.07.102.

Mediators of the autonomic response to stress, such as the catecholamines norepinephrine and epinephrine, promote cancer growth, metastasis, and progression in preclinical models. Pharmacological intervention with beta-blockers can abrogate this effect leading to improved patient outcomes. Further, retrospective data from studies of patients with non-ovarian tumors support this hypothesis. The authors of the current study set out to evaluate the effect in patients with ovarian cancer. Patients were collected retrospectively from an institutional database of primary ovarian cancer patients treated over a 10-year period with a minimum of 5 years of follow-up. Patients were considered beta-blocker users if there were documentation of agent use over two visits a minimum of 6 months apart. Standard intravenous paclitaxel and carboplatin was used in all recruited patients to minimize the impact of therapy on the primary endpoints of overall survival (OS) and progression-free survival (PFS). In all, 248 patients were identified; 68 (27%) were patients in whom anti-hypertensive agents were used. Of these, 23 (9%) of the total sample were taking beta-blockers, both selective beta and nonselective beta (and or alpha) agents. The cohorts were defined as beta-blocker users and other. The two cohorts were well matched for age, proportion of stage IV disease, grade 3 histology, percentage of non-serous histology, and optimal cytoreduction rates (which were near 90% for tumor residual < 1 cm). When compared to the non-beta-blocker group, those taking any form of a beta-blocker had a prolonged PFS (27 months vs 17 months, $P = 0.05$) and prolonged OS (56 months vs 48 months, $P = 0.02$, hazard ratio 0.56). This effect held true even when the beta-blocker users were compared to the other hypertensive non-beta blocker users and those whom were not hypertensive. In a multivariate analysis including known prognostic factors, beta-blocker use was the only independently associated factor to PFS and OS. The authors conclude beta blockade for the management of hypertension is associated with improved survivorship and supports the prospective investigation of beta-blocker therapy in ovarian cancer patients.

COMMENTARY

The study presented appears to support the hypothesis that stress response mediation in ovarian cancer patients can have an impact on long-term outcomes, such as PFS and OS. The study also supports others done under similar pretenses demonstrating remarkably consistent results despite including diseases that arise from complex and divergent pathways.[1,2] These observations suggest that central mechanisms for tumor invasion, spread, and progression exist and are mediated, in part, by effector factors from the autonomic nervous system. While the relationship of stress to cancer prognosis has been known for years, the mechanism through which this occurs and thus, the potential opportunities to interact with these response elements, is largely unknown. However, clues recently have come to light.

Perioperative Events Impact Long-term Outcomes

Four decades ago, an observation in preclinical cancer models suggested that removal of the primary tumor led to rapid growth of subclinical and known distant metastatic disease.[3] In this body of work, an antiangiogenesis growth factor secreted by the primary tumor was discovered (endostatin), which led to the development of the field of biologically targeted antiangiogenesis therapeutic agents. Indeed, surgery is known to not only shift the angiogenic balance toward proangiogenesis, but also increase tumor cell shedding and increase the production of stimulatory growth factors. The latter, which includes catecholamines, prostaglandins, glucocorticoids, and opioids, have been extensively interrogated in preclinical models documenting their critical role in tumor cell proliferation, adhesion, locomotion, extracellular matrix invasion capacity, resistance to apoptosis with loss of cell-cell contact (a process termed anoikis), and secretion of pro-angiogenic factors.[4,5] These factors also have significant impact on suppression of anti-metastatic cell-mediated immunity (CMI). Of particular relevance in the context of surgery is that these processes occur simultaneously and may leverage their effect on long-term outcomes by promoting initiation of the angiogenic switch, which could recruit dormant metastatic lesions to initial growth. In the clinic, should this hypothesis be true, it would suggest that brief interaction of the perioperative cascade could lead to long-term beneficial effects.

The Players and How they Work

Catecholamine and prostaglandin release are a common response to stress and tissue injury, both induced in operative/perioperative settings. Catecholamines act on beta-adrenoceptors, which have been identified to be present on tumor cells, inducing the release of several pro-angiogenic and pro-metastatic factors like VEGF, matrix metallopreteinases (MMP-2, MMP-9), and interleukins (IL-6, IL-8). Relatively recently it was discovered that this cascade appears to be driven through the beta-2 adrenergic receptor, which stimulates the cyclic AMP-protein kinase A pathway and leads to src-mediated focal adhesion kinase phosphorylation — all important (and targetable) processes driving the malignant phenotype. What was striking in these experiments was the efficacy of beta-2 blockade by commonly available antihypertensive agents in orthotopic ovarian cancer models.[6,7] In the latter murine model, stress was induced not by surgery or tissue injury but by chronic stress induced by a claustrophobia-inducing, non-restraint enclosure device. In these experiments, tumor growth, enhanced under a constrained environment, was associated with massive release of catecholamines, whose effect was abrogated by treatment of beta-2 blockade.

Similarly, prostaglandins, particularly prostaglandin-E2, facilitate macrophage differentiation in the tumor microenvironment toward the M2 phenotype. This differentiation promotes tumor cell survival by modulating CMI and enhancing angiogenesis. In colon cancer for instance, COX-2 expression is associated with tumor size, stage, vascular density, depth of invasion, lymph node metastasis, recurrence, and overall survival. Both classes of compounds appear to work in concert to promote tumorigenesis; fortunately, both axes can be easily targeted clinically.

The Evidence

Currently, there are no prospective randomized, clinical trials addressing the effects of beta blockade perioperatively in cancer patients, but the retrospective evidence for its efficacy is interesting. The largest study reported on the effects of beta-blocker use and cancer survival was in breast cancer. In this registry study of women with stage I-IV invasive breast cancer diagnosed between 2001 and 2006 who were taking propranolol (n = 70) or atenolol (n = 525), patients were matched 1:2 to women not taking a beta-blocker (n = 4738).[8] The primary outcome variables were of tumor invasion at diagnosis (T4), nodal/metastatic spread at diagnosis, and time to breast cancer-specific mortality. Propranolol users were significantly less likely to present with T4 lesions at diagnosis (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.07-0.85) or nodal/metastatic spread (OR, 0.2; 95% CI, 0.04-0.88) compared to matched nonusers. The cumulative probability of breast cancer-specific mortality was significantly lower for propranolol users compared with matched nonusers (HR, 0.2-0.6; 95% CI, 0.06-0.6). Interestingly, there was no difference in T4 or nodal/metastatic disease or mortality between atenolol users and matched nonusers. This trial supports the beta-adrenergic pathway's importance in tumorigenesis as well as the differential effect of beta-2 blockade.

The experience with anti-prostaglandin therapy is more diverse and has been the subject of randomized clinical trials in several tumor types. A trial of low-dose aspirin for 1 year postoperatively in patients with gastric or esophageal cancer demonstrated a significantly improved 5-year survival rate (51% vs 41%) in low-stage, non-disseminated cases. In addition, three randomized trials of celecoxib (a COX-2 inhibitor) demonstrated significant tumor-specific effects in early breast cancer, transitional cell cancer of the bladder, and prostate cancer. In

the former two sites, there was significant increase in tumor cell apoptosis, and in the latter, there was reduced tumor cell proliferation, vessel density, angiogenesis, and hypoxia inducing factor 1-alpha expression with a short (2-4 week) presurgical exposure.[9,10] This further supports the hypothesis that specific tumor effects can be enabled by brief exposures of these compounds around the time of greatest expression of these pathways.

Where Do We Go from Here?

The study featured at the introduction identified that use of beta-blockers in women with newly diagnosed ovarian cancer was associated with prolonged survival. There are many questions not addressed in that report such as: Were these patients stressed? Did they take their antihypertensive agent around the time of surgery? Was a COX-2 inhibitor given in the perioperative period? Were epidurals used (reduces opioid and glucocorticoid secretion)? Would there be a difference in beta-2 blockade vs beta-1 blockade with a larger sample? Evidence presented would suggest that both beta-2 and prostaglandin blockade would have the greatest benefit to long-term outcomes if it could be safely administered. One significant question to address is safety of normotensive patients taking therapeutic beta-blockade in the perioperative setting. For ovarian cancer patients, the potential impact on long-term survival is not trivial. Fortunately, such a trial is already underway and should help to answer the feasibility of a larger randomized trial in women with ovarian cancer, the deadliest of all gynecologic cancers. ■

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Continuing Education Questions

1. Which of the following comments by Memon K, et al regarding the use of Yttrium-90 radiomicrospheres in metastatic carcinoid to the liver is false?

a. Of 25 patients symptomatic at baseline, only five patients reported subjective improvement after treatment.
b. Median time to response was 4 and 4.9 months by lesion and patient, respectively.
c. Median overall survival time was 34 months.
d. Sixty-four percent of lesions treated with 90Y microspheres showed > 50% reduction in size.

2. Evaluation of the SEER-Medicare data indicates that older patients with chronic fatigue syndrome have an increased incidence of each of the following *except*:

a. breast cancer.
b. non-Hodgkin lymphoma.
c. renal cancer.
d. pancreatic cancer.

3. Which of the following vaccines would *not* be recommended in cancer patients receiving chemotherapy?

a. Pneumococcal polysaccharide vaccine
b. Pneumococcal conjugated polysaccharide vaccine
c. Influenza hemagluttinin vaccine
d. Zoster (shingles) vaccine

4. What is the principal effect of beta-blockade on tumor cells that express the beta-2 adrenergic receptor?

a. M2 macrophage differentiation
b. Alteration in cell-mediated immunity
c. Increased focal adhesion kinase expression
d. Anti-angiogenesis

[IN FUTURE ISSUES]

HIV-related anal cancer:
Incidence rising despite effective antiretroviral treatment

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.*

Zolpidem and Risk of Falls in Hospitalized Patients

In this issue: Zolpidem and risk of falls; AVR and anticoagulation; statins in cancer patients; and FDA actions.

Zolpidem and risk of falls

Zolpidem (Ambien) increases the risk of falls in inpatients, according to a new study from the Mayo Clinic. The records of hospitalized patients who were not in the intensive care unit were reviewed in this retrospective cohort study. The rate of falls was compared in those who were administered zolpidem vs those for whom it was prescribed but not administered. After controlling for age, gender, insomnia, delirium, dose of zolpidem, Charlson comorbidity index, Hendrich's fall risk score, length of stay, visual impairment, gait abnormality, dementia/cognitive impairment, and concomitantly administered meds, the rate of falls was four times higher in those administered zolpidem (n = 4962) vs those who were prescribed but did not receive zolpidem (adjusted odds ratio 4.37, 95% confidence interval [CI], 3.34-5.76; $P < 0.001$). The authors conclude that zolpidem was a strong, independent, and potentially modifiable risk factor for inpatient falls. The authors suggest that changing order sets so that zolpidem use is not encouraged could potentially reduce fall rates in hospitalized patients. They also suggest that there is limited evidence to recommend other hypnotic agents as safer alternatives (*J Hosp Med* published online Nov. 19, 2012. doi: 10.1002/jhm.1985). ■

Anticoagulation and AVR

Bioprosthetic valves are preferred to mechanical valves for aortic valve replacement (AVR) in the elderly because of lack of need for anticoagulation in the long-term, but short-term anticoagulation is required. The duration of anticoagulation after valve replacement has been unclear. Now, a new study from Denmark suggests 6 months is optimal. Using the Danish National Patient Registry, more than 4000 patients who had a bioprosthetic AVR between 1997 and 2009 were identified. Rates of stroke, thromboembolic events, cardiovascular death, and bleeding were assessed along with warfarin treatment duration. Rates of events per 100 person-years in patients not treated vs those treated with warfarin for 3 months were 7 vs 2.7 for stroke, 13 vs 4 for thromboembolic events, 11.7 vs 5.4 for bleeding, and 32 vs 3.8 for cardiovascular death. The rate of cardiovascular death was 6.5 vs 2.0, favoring warfarin from 90 days to 179 days. The authors conclude that stopping warfarin within 6 months of bioprosthetic AVR surgery was associated with increased cardiovascular death. These findings challenge the current guidelines that recommend 3 months of antithrombotic treatment after AVR surgery suggesting that "patients will gain from an additional 3 months of warfarin treatment in terms of reduced cardiovascular death without risking significant increase in bleeding events" (*JAMA* 2012;308:2118-2125). An accompanying editorial states that this study provides important information to help clinicians understand the benefits and risks of warfarin use after bioprosthetic aortic valve implantation, but it

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

does not address the issue of adjunctive aspirin or the role of new novel oral anticoagulants (*JAMA* 2012;308:2147-2148). ■

Statins in patients with cancer

Patients taking a statin when diagnosed with cancer have a better prognosis than patients who are not taking statins, according to a new study. This study also used the Danish Registry in which all patients with a cancer diagnosis between 1995 and 2007 were evaluated. Roughly 19,000 patients were on a statin prior to diagnosis and 277,000 were not. Those taking statins were 15% less likely to die of any cause and 15% less likely to die of cancer (hazard ratio 0.85, 95% CI, 0.82-0.87 for cancer). The benefit was present regardless of statin dose or cancer type. The authors suggest that this is biologically plausible since cholesterol is needed for cell proliferation. They suggest "a need for trials of statins in patients with cancer" (*N Engl J Med* 2012;367:1792-1802). Previous studies have suggested reduced cancer mortality with statins in patients with prostate cancer and reduced recurrence rates in breast cancer patients. ■

FDA actions

The FDA has concluded a safety review of dabigatran (Pradaxa) and found that the drug is not associated with more serious bleeding events than warfarin. The review was done using insurance claims and data from the FDA's Sentinel Initiative. According to the FDA, the bleeding rates are consistent with the observations from large clinical trials, including RE-LY, which showed that bleeding rates in patients newly started on dabigatran were similar to rates associated with new use of warfarin. Therefore, the FDA has not changed its recommendation regarding dabigatran (FDA Drug Safety Communication, Nov. 2, 2012). The next day, *The New York Times* published an article reporting that dabigatran has been associated with more than 500 deaths in the United States since it was introduced. It also detailed several tragic cases of bleeding deaths associated with the drug. The article indicts the FDA stating "… the approval process was not sufficiently rigorous because it allowed a potentially dangerous drug to be sold without an option for reversing its effects." The article also mentions more than 100 lawsuits that have been filed in federal courts "…and thousands more are expected" (*The New York Times* Nov. 3, 2012:B1).

The FDA has expanded the approval of rivaroxaban (Xarelto) to include treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), both for acute treatment and prevention of recurrence. The drug is already approved for prevention of DVT and PE after knee and hip replacement surgery and for prevention of stroke in patients with non-valvular atrial fibrillation. It is the first oral drug approved to treat DVT and PE since warfarin was approved 60 years ago; but unlike warfarin, rivaroxaban can be used as monotherapy from diagnosis until treatment is discontinued. Approval was based on three studies of nearly 9500 patients with DVT or PE randomized to rivaroxaban, enoxaparin/vitamin K antagonist, or placebo. Rivaroxaban was equivalent to enoxaparin/vitamin K antagonist and superior to placebo for preventing recurrent DVT or PE.

The FDA has approved a new egg-free flu vaccine for adults. The vaccine is manufactured using cultured mammalian cells instead of fertilized chicken eggs. The manufacturer claims that the cell culture technology enables a rapid response to public health needs, such as a pandemic, since cell culture technology allows vaccines to be manufactured within weeks as opposed to traditional flu vaccines that depend on a large number of fertilized chicken eggs to grow the virus. Cell culture technology is used for several other vaccines including polio, rubella, and hepatitis A vaccines. Approval was based on a randomized, controlled clinical study of 7700 adults ages 18-49. The new vaccine was 83.8% effective in preventing influenza when compared to placebo. Injection site reactions are the most common side effects. The new vaccine is marketed as Flucelvax by Novartis.

The FDA has approved the first Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib, dosed orally twice a day, is approved for RA patients who have failed methotrexate. The drug will compete with the parenteral RA drugs adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). Tofacitinib carries a boxed warning regarding the increased risk of opportunistic infections, tuberculosis, cancers, and lymphoma; increases in cholesterol and liver enzymes; and decreases in blood counts. Approval was based on seven clinical trials in which the drug showed improvements in clinical response and physical function compared to placebo in patients with moderate-to-severe RA. Tofacitinib will be marketed by Pfizer as Xeljanz. The cost is projected to be just over $2000 per month, similar to other non-methotrexate biologic treatment options. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

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Gabapentin for Chronic Cough

Source: Ryan NM, et al. Gabapentin for refractory chronic cough: A randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380:1583-1589.

CHRONIC UNDIFFERENTIATED COUGH — that is, cough without any readily visible explanation such as upper respiratory infection, lower respiratory infection, pulmonary lesion, heart failure, etc. — usually turns out to be one of three entities: post-nasal drip, asthma, or acid reflux. Indeed, empirically trying meds for such maladies usually resolves the cough. Nonetheless, despite exhaustive investigation, some patients remain with cough of undetermined etiology, at which point the treatment is problematic.

It has been suggested that chronic cough might reflect a central neural sensitization process that has some pathologic similarities to neuropathic pain. Since gabapentin works well for neuropathic pain, could it also have a positive effect on chronic cough?

Ryan et al studied a population of patients with chronic cough (n = 62) in whom secondary causes (e.g., infection, reflux, asthma) had been eliminated. Study subjects were randomized to gabapentin (up to 1800 mg/d) or placebo for 10 weeks.

At the end of the trial, gabapentin improved cough-related quality of life more than placebo and was well tolerated. Considering that in neuropathic pain trials the dose of gabapentin has been up to twice as high (3600 mg/d), it is reassuring to note that moderate gabapentin doses provide clinically relevant cough improvements. In an era of closer scrutiny applied to use of opioids, another alternative for chronic undifferentiated cough is welcome. ■

Can Statins Reduce Cancer-Related Mortality?

Source: Nielsen SF, et al. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;367:1792-1802.

IT IS GENERALLY BELIEVED THAT THE PRIMARY mechanism of statin-related cardiovascular (CV) risk reduction is achieved through reductions in LDL. That statins might have other pleiotropic actions, such as plaque stabilization, is the subject of much controversy. Recently, recognition of the impact of statins on new-onset diabetes (a relative 9% greater risk than non-statin users) has given reason for pause. For secondary prevention, the risk-benefit ratio is prominently positive for statin therapy, but much less convincing for primary prevention. A similar picture is emerging in reference to aspirin in CV prophylaxis.

Reminiscent of the aspirin story (i.e., even though primary prevention with aspirin has never been shown to reduce mortality, the favorable effects on CV events — when combined with recently recognized cancer risk reduction — sweetens the deal), we are presented now with the suggestion that statins also reduce cancer-related mortality.

Nielsen et al report on a large dataset of Danish patients who had a diagnosis of cancer (n = 295,925) over the 1995-2007 interval. A comparison was made between statin never users (n = 277,204) and statin users (n = 18,721) with respect to overall and cancer-related mortality.

Statin users had a 15% relative risk reduction for cancer-related death when compared to non-users. Thirteen different cancer types were specified, each of which demonstrated similar benefit. The authors suggest that the cholesterol synthesis-limiting effects of statins may disrupt cancer cell membrane stability and cellular processes, leading to the beneficial observed effects. ■

Are All of Those Multivitamin Dollars Well Spent?

Source: Sesso HD, et al. Multivitamins in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. *JAMA* 2012; 308:1751-1760.

AMERICANS HAVE BEEN DEPICTED AS AN overly pill-happy lot, much more motivated to take a statin than incorporate dietary change for cholesterol, or take a sulfonylurea rather than exercise and lose weight to improve their diabetes, etc. For a while, the idea of multivitamins seemed like a no-lose proposition; after all, few of us were keeping track of the amounts of essential nutrients we ingest, so multivitamins appeared to provide, at worst, an innocent and inexpensive nutrient insurance policy.

In an era in which essential nutrient deficiency is a stark rarity, the use of vitamin and nutrient supplements is increasingly called into question.

The Physicians' Health Study II is a controlled trial of adult (age > 50 years) male U.S. physicians (n = 14,641) randomized to a daily multivitamin or placebo.

Over a follow-up period of (median) 11.2 years, there was no discernible difference between placebo and a daily multivitamin on CV events, stroke, or mortality.

A parallel "sister study" from the Physicians' Health Study reported a week later in *JAMA* had slightly more encouraging news: Within the same population as mentioned above, the risk of total cancer was reduced by 8% in multivitamin users. Although the risk reduction for cancer was small, and the *P* value only marginally significant, for clinicians who would advocate for multivitamins in the face of failed CV data, the cancer outcomes are modestly more sanguine. ■

Relapsing Lyme Disease: Fact or Fiction?

Source: Nadelman RB, et al. Differentiation of reinfection from relapse in recurrent Lyme disease. *N Engl J Med* 2012;367:1883-1890.

A CHARACTERISTIC DERMATOLOGIC MANIfestation of the acute phase of Lyme disease (LYME) is erythema migrans. With appropriate antibacterial treatment of LYME, the etiologic bacterium *Borrelia burgdorferi* is typically eradicated, and further disease progression is prevented. Untreated LYME can induce repetitive episodes of erythema migrans, as can LYME treated with antibiotics to which *B. burgdorferi* is not susceptible. In an individual patient, it may be difficult to differentiate disease relapse from new infection with a different strain of *B. burgdorferi*.

Genotyping of *B. burgdorferi* surface proteins allows determination of specific bacterial subtypes. Nadelman et al performed such analysis on patients (n = 17) who had experienced two episodes of erythema migrans. Each of the patients had received appropriate antibacterial treatment.

The second episode of erythema migrans was not caused by the same strain of *B. burgdorferi* in any of the patients, indicating that in each circumstance the patient had suffered reinfection rather than relapse. Whereas clinicians may have suspected relapse in patients with repeated episodes of LYME, it appears that reinfection with a new strain is more likely to be responsible. ■

Hypertension and Gout

Source: McAdams-DeMarco MA, et al. Hypertension and the risk of incident gout in a population-based study: The atherosclerosis risk in communities cohort. *J Clin Hypertens* 2012;14:675-679.

GOUT AND HYPERTENSION ARE OFTEN SEEN together. Indeed, there has been a substantial degree of discussion about the potential for elevated levels of uric acid to cause hypertension. The "storyline" remains incomplete, however, because of the observational nature of the data, confounders like thiazide diuretics (which of course elevate uric acid in treated hypertensives), and renal insufficiency, which is common in hypertension and is also associated with elevated uric acid. If uric acid is ultimately proven to increase the incidence of hypertension, it will still remain to be determined whether lowering urate can reduce hypertension safely and effectively.

The Atherosclerosis Risk in Communities study (ARIC) study population provides a dataset for evaluating the association between gout and hypertension. Adults (n = 15,792) from four different metropolitan areas were followed for approximately 10 years.

There was a strong relationship between gout and hypertension. Participants with hypertension were almost two to three times as likely to develop gout, even after adjustment for confounders. For instance, when results were evaluated only among persons not taking thiazide diuretics, a positive association between hypertension and gout was still found. The authors posit that the relationship between hypertension and gout is mediated through blood pressure-induced renal damage that leads to increased levels of uric acid. ■

Zoledronic Acid Treatment of Osteoporosis in Men

Source: Boonen S, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *N Engl J Med* 2012;367:1714-1723.

WHEN HEARING THE WORD OSTEOPOROsis, most clinicians think "pink," as if the disorder only affected women. To the contrary, 30% of hip fractures occur in men, and the post hip-fracture mortality in men is higher than women. Although the dataset about preferred treatments is less robust for men than women, trials of oral bisphosphonates have been shown to provide meaningful fracture risk reduction for men and women.

Zoledronic acid (ZOL) is a parenterally administered bisphosphonate that has been previously demonstrated to provide significant reduction in osteoporotic fractures in women. For treatment of osteoporosis, ZOL is administered as a single intravenous dose, repeated in 1 year.

Boonen et al performed a placebo-controlled randomized trial in osteoporotic men (n = 1199). As in most osteoporosis trials, calcium (1000-1500 mg/d) and vitamin D (800-1200 IU/d) supplements were administered in both the treatment and placebo arms of the study. The primary outcome variable of the study was new vertebral fractures.

At the end of the 2-year study, men who had received ZOL enjoyed a 67% relative risk reduction in new vertebral fractures (1.6% vs 4.9%), as well as improved bone mineral density. There were no serious drug-related adverse events. Risk for osteoporotic vertebral fracture in men is promptly and effectively reduced by zoledronic acid. ■

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