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A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Toward a Better Understanding of Aromatase Inhibitor-associated Musculoskeletal Symptoms

By Jerome W. Yates, MD

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

SYNOPSIS: Arthralgias and associated symptoms are common among postmenopausal breast cancer patients treated with aromatase inhibitors. Prior work from this group demonstrated anatomic correlates, including tenovial thickening and fluid accumulation present after 6 months of treatment. The current report demonstrated that these same (and other) findings are not transient but remain after 24 months on the drug. In fact, tenosynovial thickening appeared to increase from 6 to 24 months of treatment and this correlated with reduced grip strength.

SOURCE: Lintermans A, et al. Prospective study to assess fluid accumulation and tenosynovial changes in the aromatase inhibitor-induced musculoskeletal syndrome: 2-year follow-up data. *Ann Oncol* 2013;24:350-355.

Musculoskeletal symptoms including arthralgias, joint stiffness, myalgia, and carpal tunnel syndrome are the most commonly observed adverse effects of aromatase inhibitors (AIs) and occur in up to 50% of treated patients.[1] The symptoms are severe enough to account for a good share of the approximate 25% of patients who discontinue therapy.[2] To gain an anatomic explanation of AI-induced musculoskeletal syndrome (AIMSS), prior work employing MRI imaging and careful physical examination demonstrated thickening of tendon sheaths, intra-articular fluid (IAF) accumulation, and demonstrable loss of grip strength when assessed after 6 months of AI therapy.[3] The current report reflects an extension of this study to 24 months.

The study cohort included 33 postmenopausal breast cancer patients who received adjuvant endocrine therapy; 27 received an AI and 6 received tamoxifen. At baseline, 6, and 24 months patients had a rheumatologic examination, including a grip strength test and magnetic resonance imaging of both hands and wrists. The primary endpoint was tenosynovial changes; secondary endpoints were changes in morning stiffness, grip strength, and IAF. Of these, 23 AI-treated and 5 tamoxifen-treated patients completed all investigations. Between months 6 and 24, IAF further increased in AI users ($P = 0.04$) but

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not in tamoxifen users, and grip strength further decreased in both groups. The worsened tenosynovial changes were strongly correlated with a decrease in grip strength. At 24 months, morning stiffness continued to be present in more than a third of AI users. The authors concluded that AIMSS is associated with tenosynovial changes, IAF retention, joint stiffness, and loss of grip strength and that these findings do not improve with prolonged use.[4]

COMMENTARY

The paper by Lintermans and colleagues provides an explanation for the changes responsible for arthralgias in patients treated with aromatase inhibitors (AI) and adds the disappointing finding of the persistence of these adverse findings. The carefully conducted study included magnetic resonance imaging and a rheumatologic examination, including self-reported morning stiffness and grip strength measurements. The study size was too small to define differences between the various AIs that were used. At baseline, 8/23 treated with AI had morning stiffness compared with 0/5 for the tamoxifen group. Yet, all of the latter group had evidence of osteoarthritis at baseline compared with 78% of the AI group. Patients with "evidence of severe osteoporosis" were excluded from the original study.[5]

Others have demonstrated fewer musculoskeletal symptoms in patients receiving AI treatment in combination with calcium/biphosphanate.[6] In the Muslimani study, which was a large retrospective review of a single institution's (Cleveland Clinic) experience, AI-induced musculoskeletal symptoms correlated with lower bone mineral density (DEXA). Further, AI-treated patients receiving bisphosphonate and calcium were less likely to have musculoskeletal symptoms (including fracture). And, with reference to the specific type of AI prescribed, the group receiving steroidal AIs compared with nonsteroidal AIs had arthralgia, generalized bone pain and/or myalgia, and bone fractures ($P < 0.001$).

These observations suggest that musculoskeletal symptoms associated with AI treatment may involve more than tenosynovial changes alone and may also relate to preexisting or developing osteopenia/osteoporosis. To this extent, AI-treated patients should be evaluated for coexisting osteoporosis and treated accordingly, if present. ■

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ABSTRACT & COMMENTARY

Aspirin and Melanoma Prevention: Data from the Women's Health Initiative

By William B. Ershler, MD

SYNOPSIS: In a large population of Caucasian women participating in the Women's Health Initiative Observational Study, those who used aspirin had a significantly lower risk of melanoma and increased duration of use was associated with incrementally greater protection.

SOURCE: Gamba CA, et al. Aspirin is associated with lower melanoma risk among postmenopausal Caucasian women: The Women's Health Initiative. *Cancer* 2013;119:1562-1569.

The incidence of melanoma has been rising[1] and in light of marginally effective treatments for advanced disease, early recognition and prevention strategies are increasingly important. Of these, there has been much recent attention for the role of aspirin in the prevention of a broad range of cancers including breast, colon, and gastric.[2-4] There is reason to expect aspirin might be beneficial in melanoma prevention as well, in that human melanoma cells over-express cyclooxygenase-2 (COX-2)[5] and high COX-2 levels are associated with melanoma progression.[6] Indeed, case-control analyses have indicated a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs),[7,8] but the results from other analyses have been negative. A randomized trial of alternate-day, low-dose (100 mg) aspirin[9] and two additional cohort studies[10,11] have failed to demonstrate melanoma prevention for those treated with NSAIDs.

Capitalizing on the well-characterized population participating in the Women's Health Initiative (WHI) Observational Study, Gamba and colleagues evaluated the association between NSAID use (including aspirin) and cutaneous melanoma risk.

At study entry, use of aspirin and non-aspirin NSAIDs was assessed among 59,806 postmenopausal Caucasian women ages 50-79 years. Cox proportional hazards models were constructed after adjusting for participant skin type, sun exposure history, and medical indications for NSAID use among other confounders.

During a median follow-up of 12 years, 548 incident melanomas were confirmed by medical review. Women who used aspirin had a 21% lower risk of melanoma (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.63-0.98) relative to nonusers. Increased duration of aspirin use (< 1 year, 1-4 years, and ≥ 5 years) was associated with an 11% lower risk of melanoma for each categorical increase (*P* trend = 0.01), and women with ≥ 5 years of use had a 30% lower melanoma risk (HR, 0.70; 95% CI, 0.55-0.94). In contrast, use of non-aspirin NSAIDs and acetaminophen were not associated with melanoma risk.

COMMENTARY

Postmenopausal women who used aspirin had a significantly lower risk of melanoma, and longer duration of aspirin use was associated with greater protection. The observed benefit with aspirin but not NSAIDs is curious and suggests the mechanism of protection might be through pathways other than COX inhibition. However, as the authors point out, women who were using non-aspirin NSAIDS were more likely to have intermittent rather than continuous use. Indeed, the fact that the protective effect increased with duration of aspirin treatment suggests that such might be the case. Still, although large, carefully conducted and analyzed, the study was observational in design and relied on self-report of medication use and sun exposure.

The data, particularly with regard to duration of aspirin use, are reminiscent of what has been observed for aspirin prevention of colon cancer[12] and quite possibly other malignancies as well. Randomized, prospective trials are warranted, with a specific focus on those at high risk for melanoma in a manner analgous to those demonstrating colon cancer reduction in patients with Lynch syndrome.[12] ■

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ABSTRACT & COMMENTARY

Targeted Therapy for Low-grade Serous Ovarian Cancer Shows Promise

By Robert L. Coleman, MD

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

SYNOPSIS: Selumetinib, a selective MEK1/2 inhibitor, achieved objective responses in 15% of patients with recurrent low-grade serous ovarian cancer. The data are relevant as this uncommon tumor type is associated with general chemoresistance, frequent aberration in the MAPK pathway, and prolonged overall survival compared with its more common high-grade variant. Phase 3 trials are planned.

SOURCE: Farley J, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: An open-label, single-arm, phase 2 study. *Lancet Oncol* 2013;14:134-140.

Low-grade serous carcinoma of the ovary (LGSOC) is a distinct histological variant characterized by chemoresistance, frequent mutations in the MAPK pathway, and prolonged overall survival. Based on its molecular characterization, a Phase 2, open-label, single-arm trial was conducted by the Gynecologic Oncology Group using selumetinib, an oral, selective inhibitor of MEK1/2. This gene is a downstream target of many growth factors for which the *ras* and *raf* oncogenes serve as important substrates. In this trial, women (aged ≥ 18 years) with recurrent low-grade serous ovarian or peritoneal carcinoma were given selumetinib (oral 50 mg twice daily) until progression. The primary endpoint was the proportion of patients who had an objective tumor response. Secondary endpoints were progression-free survival (PFS), duration of response, overall survival (OS), toxicity and tolerance of therapy, and an exploratory analysis of K-*ras* and B-*raf* mutation was made to response. In all, 52 patients were enrolled in this flexible, two-stage Phase 2 trial over a 2-year period. All patients were eligible for analyses. Eight (15%) patients had an objective response to treatment — one patient had a complete response and seven had partial responses. The median time to response was 4.8 months and the median duration of response was 10.5 months. Thirty-four (65%) patients had stable disease. The median PFS was 11 months and the median OS has not been reached. Thirty-three (63%) patients had non-progressive disease at 6 months. There were no treatment-related deaths. Grade 4 toxicities were cardiac (1), pain (1), and pulmonary events (1). Grade 3 toxicities that occurred in more than one patient were gastrointestinal (13), dermatological (9), metabolic (7), fatigue (6), anemia (4), pain (4), constitutional (3), and cardiac events (2). No correlation to response based on K-*ras*/B-*raf* mutation was seen among the 34 patients who had enough genomic DNA for this analysis. The authors concluded that selumetinib is well tolerated and is active in the treatment of recurrent LGSOC; further investigation is warranted in these patients.

COMMENTARY

LGSOC is a distinct subset of serous ovarian cancer characterized morphologically by low-grade nuclear atypia and infrequent mitotic counts.[1] Unlike other histologies classified by the World Health Organization, serous cancer is now considered in two tiers: low grade and high grade. These categories do not strictly follow Grade 1 vs Grade 2/3; in fact, a retrospective review of serous histology in a large Phase 3 chemotherapy adjuvant trial demonstrated that 8 of 21 (38%) low-grade ovarian tumors were initially classified as FIGO grade 2/3.[2] This grading scheme has shown strong intra- and inter-pathological validity and was a strength of the current study, as all pathology was reviewed and confirmed on potential participants before registration.[3] Genomically, LGSOC is more closely aligned with serous tumors of low malignant potential (borderline tumors) than to high-grade serous ovarian cancer, despite the two histology types demonstrating invasion and metastatic and recurrence potential.[4] And, like platinum-resistant high-grade serous cancer, LGSOC is dramatically chemoresistant, demonstrating 4% or less objective response to a number of commonly used, FDA-approved cytotoxic agents for ovarian cancer management.[5] Further, it was the identification of mutations in the MAPK pathway (rare in high-grade serous ovarian cancer) that provided the rationale for using a MEK inhibitor in this disease.[6] MEK is a downstream target of a series of growth factor activation (e.g., IGF1-R, EGFR, VEGFR, etc.) that govern important cellular characteristics such as growth, proliferation, and metastases. As was observed in the trial, mutations in the immediate substrates such as *ras* and *raf* are frequent and can

lead to MEK activation. The observed response rate of 15% is impressive in the patient population given the low likelihood of objective response based on historical data with chemotherapy and hormonal therapy. Although it was disappointing to not see a direct relationship between mutation in these upstream effectors and objective response, there are several caveats to consider: 1) the test samples were from initial diagnosis in most cases (the median number of chemotherapy regimens before trial entry was three), 2) only the most common K-*ras* and B-*raf* mutations were studied, 3) only a proportion of the original population was tested, and 4) there is likely tumor heterogeneity between the primary and metastatic sites. The trial is important because it provides a clear path to potential registration in randomized trials. In these efforts, physician's choice of therapy can be used as a control arm and toxicity profiles can be extremely relevant, even if there are no response or survival differences. Currently, two randomized trials of a MEK inhibitor vs physician's choice are set to open this year. It is a unique opportunity to demonstrate targeted therapy in a subset of ovarian cancer patients where effective options, other than more surgery, are limited. ■

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ABSTRACT & COMMENTARY

Improving Transplant Outcomes for Patients without a Match

By William B. Ershler, MD

SYNOPSIS: In a retrospective review of consecutive patients treated at a single institution, recipients of cells from haploidentical donors were compared to those receiving cells from matched related or matched unrelated donors. All patients, including, those with haploidentical match, received non-T-cell depleted infusions. Haploidentical recipients did receive post-transplant cyclophosphamide. Results were comparable in terms of non-relapse mortality, relapse, and the occurrence and severity of graft-versus-host disease.

SOURCE: Bashey A, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. *J Clin Oncol* 2013,31:1310-1316.

For patients requiring allogeneic hematopoietic cell transplantation (HCT), it is commonly understood that HLA-matched siblings or HLA-matched unrelated donors (MUDs) are optimal donors. However, there remain a substantial number of patients for whom a matched donor is not available. Current research at a number of transplant centers has focused on this issue and there have developed a number of strategies in which haploidentical marrow is used. Recognizing that severe graft-versus-host disease (GVHD) would be unacceptable, methods of depleting donor T cells from the infused stem cell preparation have been tested but, unfortunately, such approaches have been associated with slow immune reconstitution and a high rate of nonrelapse mortality (NRM).[1,2] Recently, an alternative approach to haploidentical allogeneic HCT was developed, in which T cells were not removed or altered from the donor sample but immune reactivity was regulated post-transplant with cyclophosphamide.[3] This approach has demonstrated promising results in Phase 2 trials,[4-6] but a direct comparison with fully HLA matched donations had not been reported.

To address this question, Bashey and colleagues from Northside Hospital in Atlanta provide a retrospective review of their single institution experience in which consecutive patients received first transplantation for hematologic malignancy with either matched (related or unrelated) or haploidentical marrow. There were 271 patients, all with hematologic malignancy presenting between February 2005 and October 2010, included in this analysis and all underwent T-cell–replete allogeneic hematopoietic

cell transplantation. Of the 271 patients, 117 had matched related donors (MRD), 101 had MUD, and 53 had haploidentical donors.

Patients receiving MRD or MUD were treated by institutional protocols, either myeloablative, reduced-intensity conditioning, or nonmyeloablative stem cell transplantation. The 53 patients using haploidentical donors received one of two regimens. Thirty-five patients received a nonmyeloablative regimen consisting of fludarabine 30 mg/m^2 intravenously (IV) once per day on days -6 to -2; total-body irradiation (TBI) 2 Gy on day -1, and cyclophosphamide 14.5 mg/kg IV once per day on days -6 and -5 and 50 mg/kg once per day on days 3 and 4 with a bone marrow graft. Eighteen patients were treated on an institutionally developed myeloablative protocol using fludarabine 25 mg/m^2 IV once per day on days -6 to -2, busulfan 110 to 130 mg/m^2 IV once per day on days -7 to -4, and cyclophosphamide 14.5 mg/kg IV once per day on days -3 and -2 and 50 mg/kg once per day on days 3 and 4, with granulocyte, colony-stimulating, factor-mobilized peripheral blood stem cells (PBSCs; target CD34-cell count, 5-106/kg) as the graft. No pharmacokinetic adjustment of busulfan dose was performed. All patients received tacrolimus from days 5 to 180, with a target level of 5 to 15 ng/mL, and mycophenolate mofetil (maximum dose, 3 g per day in divided doses) on days 5 to 35. Filgrastim 5 mcg/kg was administered from day 5 until neutrophil recovery. Overall and disease-free survival (DFS) were adjusted for effects of significant patient-, disease-, and transplantation-related covariates using a stratified Cox model.

Patient characteristics were similar between the three donor groups. For patients undergoing MRD, MUD, and haploidentical transplantation, 24-month cumulative incidences of nonrelapse mortality were 13%, 16%, and 7%, and of relapse were 34%, 34%, and 33%, respectively (*P* not significant [NS]). Cumulative incidences of grades 3 to 4 acute GVHD at 6 months were 8%, 11%, and 11%, respectively (*P* NS); extensive chronic GVHD occurred in 54%, 54%, and 38% of patients, respectively ($P < 0.05$ for those undergoing haploidentical donor vs MRD or MUD transplantation). Adjusted 24-month probabilities of survival were 76%, 67%, and 64%, and of DFS were 53%, 52%, and 60%, respectively; these were not significantly different among the three donor groups.

COMMENTARY

Haploidentical hematopoietic stem cell transplantation is an alternative transplant strategy for patients without an HLA-matched donor. Currently, as many as half of all patients who might benefit from transplantation are unable to find an HLA-matched related or unrelated donor. Yet, for many in this situation a haploidentical donor is readily available. Early studies of haploidentical transplantation resulted in intolerable GVHD, high rejection rate, and transplant-related mortality. In recent years, there have been important advances including partial ex vivo or in vivo alloreactive T cell depletion and post-transplant cell therapy resulting in improved immune reconstitution in recipients of haploidentical transplants (for review, see reference 7). Further, results of unmanipulated stem-cell transplantation using ATG and combined immunosuppression in haploidentical transplant settings are promising. The current encouraging report indicates that post-transplantation cyclophosphamide also may be effective in this regard.

An alternative for patients without a match is transplantation of hematopoietic stem cells prepared from umbilical cord blood (e.g., double umbilical cord blood [dUCB]). In a Phase 2 study, dUCB transplantation in a similar setting (matched marrow not available) gave results comparable to haploidentical marrow.[4] A future prospective randomized trial comparing modern haploidentical HCT with dUCB would seem a reasonable next step in the promotion of effective management of selective hematological malignancies. ■

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ABSTRACT & COMMENTARY

Finding the Right Dose of Carboplatin/Pemetrexed for Elderly Lung Cancer Patients

By William B. Ershler, MD

SYNOPSIS: Carboplatin-pemetrexed doublet chemotherapy is effective primary treatment for patients with nonsquamous non-small cell lung cancer, but the applicability of standard dosing to older or more frail patients was uncertain. This current dose-escalation study in such patients aged 75 years and older finds that a carboplatin dose of AUC5 with pemetrexed at 500 mg/m^2 was both efficacious and well tolerated, but a carboplatin dose of AUC6 resulted in unacceptable toxicity.

SOURCE: Tamiya A, et al. Dose escalation study of carboplatin-pemetrexed followed by maintenance pemetrexed for elderly patients with advanced nonsquamous non-small-cell lung cancer. *Ann Oncol* 2013;24:980-985.

Non-small cell lung cancer (NSCLC) is primarily a disease of older people and its occurrence is increasing with the aging of our population. Whereas combined modality therapy is often considered the standard approach for patients who present with advanced disease, such an aggressive approach is unlikely to be tolerated by very old or frail patients. However, single agent[1-4] and doublet[5] chemotherapy strategies have been shown to be efficacious in elderly-specific chemotherapy trials. The antifol pemetrexed has demonstrable efficacy in combination with cisplatin for patients with NSCLC, particularly for those with non-squamous histopathology.[6] In light of reduced toxicity and increased convenience, carboplatin has gained widespread use as a substitute for cisplatin and may be particularly favored for older, more frail patients.

The current study was designed to determine the recommended dose of carboplatin-pemetrexed in elderly (≥ 75 years old), chemotherapy-naive patients with advanced nonsquamous NSCLC.

Patients received escalated doses of carboplatin (AUC of 4, 5, or 6) and pemetrexed (500 mg/m^2) every 3 weeks for four cycles. Patients with an objective response and stable disease continued pemetrexed therapy until disease progression or unacceptable toxicity was observed.

The combination of carboplatin at an area under the concentration-time curve (AUC) of 5 and 500 mg/m^2 pemetrexed was determined to be the recommended dose for elderly patients with advanced nonsquamous NSCLC. Of 17 patients, 10 received a median of five cycles of pemetrexed maintenance therapy without unexpected or cumulative toxic effects. The study had an overall response rate of 47.1%. The median progression-free survival time was 142 days (95% confidence interval [CI], 68-216 days) and the median overall survival time was 461 days (95% CI, 168-754 days).

COMMENTARY

Recommended chemotherapy approaches are often derived from clinical studies that include disproportionately few older patients. Further, those elderly patients who are included on trial may not be representative since they met eligibility criteria that might otherwise exclude the typical patient in this age group. Thus, age-specific inclusive clinical trials are called for, with the goal of establishing reasonable standards of care for typical and frail elderly patients. In such trials, response rates and overall survival might assume lesser importance than quality of life and independence.

In a previous clinical trial with similar methodology from Japan,[7] the carboplatin-pemetrexed doublet was examined in nonsquamous NSCLC patients younger than 75 years and the recommended carboplatin dose was an AUC of 6 and pemetrexed was 500 mg/m^2. The current study modifies that recommendation for carboplatin at an AUC of 5 for patients over the age of 75. The investigators are to be credited for addressing this important issue and their research concept will hopefully serve as a prototype for the development of standards of care for all tumor types commonly observed in frail elderly patients. ■

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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.

Continuing Education Questions

1. The appearance of which of the following findings was associated with aromatase inhibitor treatment in postmenopausal breast cancer patients?

a. Intrarticular fluid accumulation
b. Tenosynovial thickening
c. Decreased grip strentgth
d. All of the above

2. In the Women's Health Initiative Observational Study, the risk of developing melanoma in women taking aspirin daily compared to non-users was approximately:

a. 10%.
b. 20%.
c. 40%.
d. 60%.

3. In which of the following ways are LGSOC and high-grade ovarian cancer similar?

a. Ability to invade and metastasize
b. High rate of P53 mutation
c. Short overall survival
d. High rate of initial chemosensitivity
e. Frequent mitotic figures

4. In the bone marrow transplant series from Atlanta, the intervention considered most likely to minimize the development of GVHD after receiving haploidentical bone marrow or peripheral blood stem cells was:

a. ex vivo T-cell depletion prior to infusion.
b. post-transplant infusion of donor T-cells.
c. post-transplant treatment with cyclophosphamide.
d. post-transplant treatment with anti-thymocyte globulin.

5. For advanced-stage nonsquamous NSCLC patients for whom the doublet carboplatin/pemetrexed is considered, the current Japanese experience would indicate that dose modification of which drug(s) is warranted?

a. Carboplatin
b. Pemetrexed
c. Both
d. Neither

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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Extended Treatment of VTE with Dabigatran vs Warfarin

Source: Schulman S, et al. *N Engl J Med* 2013;368:709-718.

Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a "traditional" course of warfarin. ■

Selection Criteria for Lung Cancer Screening

Source: Tammemagi M, et al. *N Engl J Med* 2013;368:728-736.

The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer. ■

Special Subgroups in Hypertension: Obese Hypertensives

Source: Weber MA, et al. *Lancet* 2013; 381:537-545.

The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with *existing* CV disease), subjects with *normal* body weight bear a disproportionately *greater* risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most

frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination. ■

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

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Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. *Lancet* 2013; 381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. *JAMA* 2013;309: 578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

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.*

New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, 2 × 2 factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (*JAMA* 2013;309:1241-1250). Editorialists in the same issue of *JAMA* immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The *JAMA* editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that "these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease." (*JAMA* 2013;309:1291-1292.) Another editorialist, however, suggests that "limitations in the design and execution" of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of "softer" endpoints such as coronary revascularization and hospitalization for angina.

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.

Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, "including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy." (*JAMA* 2013;309:1293-1294.) ■

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (*BMJ* 2013;346:f880). ■

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥ 66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (*Ann Intern Med* 2013;158:447-455). ■

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in *The New England Journal of Medicine* last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug's effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget's disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee's recommendations. ■