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

ABSTRACT & COMMENTARY

Sunitinib Disappoints in First-line Phase 3 Trial in Advanced Breast Cancer

By William B. Ershler, MD

SYNOPSIS: Preclinical studies provide a rationale for examining a role for sunitinib in the treatment of breast cancer. However, in this large, multicenter trial, the combination of sunitinib with docetaxel did not prolong progression-free or overall survival when compared to docetaxel alone, and it appeared to be less well tolerated. The role for sunitinib remains to be established for the treatment of breast cancer.

SOURCE: Berg J, et al. First-line treatment of advanced breast cancer with sunitinib in combination with docetaxel versus doctaxel alone: Results of a prospective, randomized phase III study. *J Clin Oncol* 2012;30:921-929.

In laboratory and early clinical trials, sunitinib, an oral inhibitor of receptor tyrosine kinases including vascular endothelial growth factor (VEGF) receptors,[1] platelet-derived growth factor (PDGF) receptors,[1,2] stem cell factor receptor,[2] and colony-stimulating factor-1 (CSF-1) receptor[3,4] has demonstrable activity against breast cancer,[4] either when used alone,[5] or in combination with cytotoxic chemotherapy.[6] Thus, a rationale was established for examining sunitinib in a larger Phase 3 setting. The Pfizer-sponsored trial conducted throughout Europe was presented in early form at ASCO 2010 and in more detail in this manuscript.

The underlying hypothesis was that the combination of sunitinib with docetaxel would be superior to docetaxel alone in prolonging progression-free survival (PFS) as first-line therapy for women with advanced breast cancer. This was a multi-institutional study enrolling 593 patients from 127 sites in 27 countries. Patients were randomly assigned to open-label combination therapy (sunitinib 37.5 mg/d, days 2 to 15, every 3 weeks; and docetaxel 75 mg/m^2, day 1, every 3 weeks) or monotherapy (docetaxel 100 mg/m^2, every 3 weeks). PFS was the primary endpoint.

Patients were randomly assigned to combination therapy (n = 296) or monotherapy (n = 297). Median PFS times were 8.6 and 8.3 months with combination therapy and monotherapy, respectively (hazard ratio, 0.92; one-sided P = 0.265). The objective response rate was significantly higher with the combination (55%) than with monotherapy (42%; one-sided P = 0.001). Duration of response was similar in both arms (7.5 months with

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the combination vs 7.2 months with monotherapy). Median overall survival (OS) times were 24.8 and 25.5 months with combination therapy and monotherapy, respectively (one-sided $P = 0.904$). There were 107 deaths with the combination and 91 deaths with monotherapy. The frequency of common adverse events (AEs) was higher with the combination, as were treatment discontinuations caused by AEs.

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This was a large and very well coordinated clinical trial. Because of the varying doses of docetaxel used in the two different arms, the study was conducted open-label, and methodologically this could introduce some bias. Acknowledging this, all responses and endpoints were confirmed by a central committee and compared with the clinical responses recorded at each center. In general, there was agreement, and where there was some discordance, it was of little consequence to the overall study results and conclusions. Curiously, responses early-on were more apparent in the combination group, but this better response rate did not translate to improvements in either PFS or OS.

Furthermore, despite the lower dose of docetaxel used in the combination, adverse events were, if anything, greater with the combination group, as was the death rate (107 in the combination group and 91 in the docetaxel alone group), including those patients who died during the treatment phase (12 in the combination and four in the docetaxel alone group). The range of toxicities was comparable in both groups except for the appearance of hand-foot syndrome, which was greater in the combination (17% vs 1%).

Two other Phase 3 studies have been reported in which sunitinib has been combined with cytotoxic chemotherapy. The Robert study[7] also compared first-line treatment for advanced breast cancer using either sunitinib or bevacizumab in combination with paclitaxel, and the authors concluded that the bevacizumab combination was superior in that response duration was longer and the combination better tolerated. In an additional Phase 3 study in pre-treated advanced breast cancer patients and published in abstract form,[8] capecitabine plus sunitinib was not superior and had greater toxicity than capecitabine alone.

Thus, despite the encouraging preclinical results, the use of sunitinib for patients with advanced breast cancer is not recommended. Its role in this disease either in combination with other drugs or at different doses remains to be established. ■

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ABSTRACT & COMMENTARY

Moderate Alcohol Consumption: Protective Effect on Renal Cell Cancer Development

By William B. Ershler, MD

SYNOPSIS: There has been much written about the salutary effects of moderate alcohol consumption in reference to a number of non-malignant chronic diseases. The effects on cancer in general are less compelling. However, in the current meta-analysis examining alcohol consumption and the development of renal cell carcinoma, a protective effect for light and moderate drinkers is clearly demonstrated. This protective effect is in the 10-20% range.

SOURCE: Bellocco R, et al. Alcohol drinking and risk of renal cell carcinoma: Results of a meta-analysis. *Ann Oncology* 2012;23:2235-2244.

There has been a gradual increase in renal cell carcinoma (RCC) in the United States and slightly improved survival, both of which may relate to earlier detection.[1,2] There are well-established risk factors for RCC including tobacco smoking,[3] obesity,[4] and hypertension,[5] but there remains some controversy over the role of moderate or excessive alcohol intake in this context. In fact, in a pooled analysis on alcohol intake and RCC based on 12 cohort studies, moderate consumption of alcohol was inversely related to the risk of RCC, and such protection did not seem to be modified by age, body mass index, hypertension, or smoking.[6] That analysis, however, did not address the issue of high levels of alcohol intake. To address this, Bellocco and colleagues conducted a comprehensive meta-analysis of published studies on this topic.

The investigators were able to find 20 observational studies (four cohort, one pooled, and 15 case-control) published up to November 2010 that reported results on at least three levels of alcohol consumption in the context of RCC incidence. Overall relative risks (RRs) and 95% confidence intervals (CIs) were estimated using random-effects models, and both second-order fractional polynomials and random effect meta-regression models were implemented for the study of dose-risk relation.

They found the estimated RRs were 0.85 (95% CI, 0.80-0.92) for any alcohol drinking, 0.90 (95% CI, 0.83-0.97) for light drinking (0.01-12.49 g/day), 0.79 (95% CI, 0.71-0.88) for moderate drinking (12.5-49.9 g/day), and 0.89 (95% CI, 0.58-1.39) for heavy drinking (≥ 50 g/day), respectively.

COMMENTARY

Thus, the current meta-analysis supports the hypothesis of a negative effect of moderate alcohol consumption on the risk of renal cell cancer. In this analysis, special efforts were undertaken to address the interactions of smoking and obesity, both of which are highly associated with excessive alcohol intake. Thus, the protective effect of alcohol on RCC development might be countered by associated factors. Furthermore, heavy drinkers are more likely to have a poor diet, and this too would favor RCC development.[7] As such, this report provides epidemiological evidence that light or moderate alcohol consumption is associated with a reduced risk (10-20%) of RCC, and that such is observed independent of tobacco use, body mass index, or presence of hypertension.

The mechanism whereby alcohol would confer such an effect is conjectural at this time but, at least for red wine, may relate to the beneficial metabolic effects conferred by resveratrol.[8] However, there is now a growing literature supporting the positive effects of low or moderate alcohol intake on such diverse processes as diabetes,[9] cardiac disease,[10] and Alzheimer's,[11] as well as normal aging and overall mortality.[12,13] ■

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ABSTRACT & COMMENTARY

Outcomes of Stereotactic Ablative Radiotherapy in Patients With Potentially Operable Stage I Non-Small Cell Lung Cancer

By Samir P. Kanani, MD

Associate Clinical Professor of Neurosurgery and Radiation Oncology, George Washington University, Radiation Oncology, Inova Fairfax Hospital, Falls Church, VA

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

SYNOPSIS: Potentially operable patients with Stage I non-small cell lung cancer who were treated with stereotactic ablative radiotherapy (SABR) between 1993-2010 were retrospectively identified in a prospectively collected database. Despite the median age of 76 years and the median comorbidity score of 2 in these 177 potentially operable patients, the 3-year survival was 85%. Post-SABR 30-day mortality was 0%, while predicted 30-day mortality for a lobectomy, derived using the Thoracoscore predictive model, would have been 2.6%. Local control at 3 years was 93%. Regional and distant failure rates at 3 years were each 9.7%. Toxicity was mild, with grade ≥ 3 radiation pneumonitis and rib fractures in 2% and 3%, respectively. The outcomes in this SABR population compare well with previously reported surgical series.

SOURCE: Lagerwaard FJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable Stage I non-small cell lung cancer. *Int J Radiation Oncol Biol Phys* 2012; 83:348-353.

While an anatomical surgical resection is considered the gold standard for patients with early-stage lung cancer, between one-third and two-thirds will not undergo a resection because of comorbid medical conditions and patient preference. Traditionally, these patients were treated with conventional fractionated radiotherapy alone to doses between 6000 and 7000 cGy. Many of these patients passed away within 3 years of their other medical problems; however, many suffered from symptomatic local recurrences. The use of conventionally fractionated radiotherapy for this medically inoperable group of patients has largely been replaced by stereotactic ablative radiotherapy (SABR). Local control rates of approximately 90% for Stage I non-small cell lung cancer are routinely reported in single and multicenter trials.[1] These encouraging results in inoperable patients have led to at least two ongoing prospective, randomized trials evaluating SABR in operable patients as well as two single-arm Phase 2 trials that have yet to be reported. This series is a retrospective study of patients who were potentially resectable and who declined surgery at the VU medical center in the Netherlands.

The study cohort consisted of 706 patients who underwent SABR between 2003 and 2010 at the VU medical center for Stage IA-IB NSCLC who were entered into a prospective database. The database was retrospectively analyzed to determine a cohort of 177 patients who were potentially resectable with good pulmonary function (FEV1 > 50% predicted and DLCO > 50% predicted), WHO performance status 1 or 2, and lack of serious comorbidities precluding surgery such as recent myocardial infarction or renal failure. SABR was delivered as an outpatient in three (non-central and non-peripheral), five (peripheral adjacent to chest wall), or eight (central) fractions to a total dose of 60 Gy prescribed to the 80% isodose line depending on tumor size and location.

The majority of patients were Stage IA (60%). Two-thirds of patients did not have a biopsy, but nearly every patient had a positive PET scan. The patients who were treated without a biopsy had > 90% probability of malignancy based on a previously validated Dutch model. With a median follow-up of 31.5 months, the median overall survival (OS) for all patients was 61.5 months, with OS rates at 1 and 3 years of 94.7% and 84.7%, respectively. The actuarial local control rates at 1 and 3 years were 98% and 93%, respectively. In total, a relapse at any location (local, regional, or distant) was observed in 25 patients (14.1%) and was locoregional in nine patients. Three of those nine patients underwent lobectomy as salvage treatment, and another two patients received high-dose radiotherapy. Four patients received no salvage treatment. Freedom from any progression at 3 years was 81% both for patients with and without pathological verification.

No early side effects were reported by 42% of patients, and Grade 1 to 2 early side effects reported were fatigue (25%), cough (14%), local chest wall pain (11%), and dyspnea (10%), with some patients reporting more than one side effect. Severe late toxicity was uncommon, with Grade 3

radiation pneumonitis seen in four patients (2%). Rib fractures developed in five patients (3%). A total of 34 patients have died, and the cause of death could be determined in 29 patients. Of those patients, 14 patients died from disseminated lung cancer, six patients from cardiovascular events, four patients from other primary malignancies diagnosed after SABR, two patients from unrelated pulmonary hemorrhage, and two patients from renal failure. The 30-day mortality rate observed in the SABR cohort of 177 patients was 0%. In contrast, in these patients, the calculated 30-day mortality after lobectomy would have been 2.6% according to the Thoracoscore.[2] The Thoracoscore is a validated prognostic model derived from an analysis of 10,122 patients undergoing thoracic surgery that estimates early mortality based on a number of clinical factors.

COMMENTARY

The authors conclude that SABR results in local control and survival comparable to surgery and justify the current ongoing randomized trials comparing surgery to SABR. The results from this trial are on par with other reports from the literature demonstrating 3-year survival rates of 70-86%.[3,4] The observed 3-year survival rate of 84.7% following SABR is comparable to that reported after surgery.[5]

One criticism of the series is that two-thirds of the patients were treated without a biopsy. The authors highlight surgical series where operations are done in Western European countries without a biopsy that demonstrate a low 4% rate of finding benign lesions. In addition, the current series found no difference in local control or survival in patients who were treated with or without pathologic confirmation. The authors should be lauded for this retrospective review and their conclusions. Clearly, the authors are not recommending SABR in potentially operable patients, but they are adding to the growing body of literature regarding the use of SABR. It is likely that surgery will "cure" more patients than non-invasive radiotherapy when compared in randomized trials, but at what price? It is clear from the Thoracoscore model that some patients will suffer mortality and serious morbidity from surgery. Borderline resected patients should ideally be jointly evaluated by thoracic surgery and radiation oncology and the alternatives of surgery and SABR should be candidly discussed with patients. This will be even more salient as lung cancer screening becomes more widely accepted and early-stage lung cancers grow in prevalence. The results of ongoing Phase 2 and Phase 3 studies evaluating SABR and surgery are eagerly anticipated. ■

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ILLUSTRATIVE CASE SERIES

Management of Smoldering Myeloma

By William B. Ershler, MD

An 84-year-old community-dwelling retired physician who maintains an active lifestyle and regularly attends community hospital meetings and lectures is seen for advice regarding management. He has a longstanding history of mild hypertension currently controlled by diet and hydrochlorothiazide. He has had a total left knee replacement and cataract surgery bilaterally. Otherwise, he has been well and other than minor, stable arthritic symptoms, he has no physical complaints. When he was seen in his primary care physician's office for an annual physical exam, a chemistry survey revealed a total serum protein of 9.2 g/dL, with a globulin fraction of 4.8 g/dL. Total serum protein the year before was 7.9 g/dL. His physician requested serum protein electrophoresis and this revealed a monoclonal spike.

Immunofixation identified the spike to be IgGk and quantitative immunoglobulin measurement revealed 4.2 g/dL IgG, with low normal levels of IgA and IgM. Beta-2 microglobulin was 4.0 mg/L. The remainder of his chemistries were normal, including a creatinine of 0.9 mg/dL. Hemoglobin was 12.5 g/dL, white blood count was 4,500/cu mm with a normal appearing differential, and the platelet count was 215,000/cu mm. A full-bone radiographic survey revealed arthritic changes without evident lytic disease. A bone marrow aspirate and biopsy

was slightly hypercellular (for age) with normal trilinear hematopoiesis but with increased numbers of normal appearing plasma cells (14%).

Smoldering Myeloma — Criteria for Diagnosis

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic disorder characterized by the presence of serum M-protein of < 3 g/dL with fewer than 10% monoclonal plasma cells in the bone marrow.[1] Under normal circumstances, post-germinal center B cells, having undergone several rounds of somatic hypermutation and antigen selection in germinal centers and then immunoglobulin heavy chain (IgH) recombination, finally differentiate into plasmablasts, and these typically migrate back to the bone marrow and become terminally differentiated long-lived plasma cells.[2] Originally considered a benign reflection of age-associated immune dysregulation (hence the term "benign monoclonal gammopathy"), it is now believed that MGUS is a clonal disorder derived from those terminally differentiated plasma cells and is a precursor to multiple myeloma (MM). This is supported by large cohort observational studies in which stored serum from those individuals who developed myeloma was found to be positive for monoclonal protein many years in advance of the myeloma diagnosis.

As mentioned, the rate of progression to myeloma is approximately 1-2% per year, but there are some features of MGUS that would indicate a greater likelihood of more rapid progression, including a higher M protein level, IgA rather than IgG paraprotein, a higher percentage of marrow plasma cells (e.g., > 10%), unbalanced serum light chain ratio, or a beta-2 microglobulin level of greater than 3.5 mg/L. The diagnosis of MM hinges on these criteria, but also includes the presence of end organ damage (e.g., lytic bone disease, anemia, hypercalcemia, renal failure). In asymptomatic patients who meet criteria for MM but without these clinical manifestations, an intermediate category of smoldering multiple myeloma (SMM) has gained clinical recognition.[3] Although the prevalence of SMM is not yet established, progression to overt myeloma has been estimated to be on the order of 10% per year or more.[4]

Treatment Considerations

SMM is thus a premalignant condition with a very high likelihood of progression to clinically important and debilitating disease. As such, despite the asymptomatic nature of the disorder, rationale has been forwarded for therapeutic intervention and several trials have been completed or are underway. The reports to date have been mixed.

For example, a trial published in 1993 comparing early treatment with melphalan/prednisone vs treatment at the time of progression to clinical myeloma demonstrated no difference in response rates or overall survival.[5] More recent studies have included the use of immunomodulatory drugs such as thalidomide and lenalidomide or drugs targeting the bone microenvironment, such as pamidronate.[6,7] On a positive note, the PETHEMA Phase 3 trial is currently investigating treatment with lenalidomide/dexamethasone vs surveillance in high-risk SMM patients. An interim analysis showed that at 19 months of follow-up, about 50% of patients in the surveillance arm progressed to MM whereas no treated patients progressed.[8] Yet, as pointed out by Korde in a review of this topic,[4] it remains unknown whether treating SMM patients improves overall survival or quality of life, as such data are not yet available.

Recommendations

Accordingly, the current standard of care for patients with SMM is either enrollment on clinical trial or careful surveillance, with the introduction of appropriate myeloma treatment once the diagnosis is apparent. The recommended surveillance includes a serum protein electrophoresis test and physician visit every 2-3 months for the first year, followed by gradual extension of visit intervals if all remains stable.[1] Furthermore, guidelines currently recommend an MRI of the spine and pelvis as this may detect occult lesions and, if present, predict for a more rapid progression to multiple myeloma.[9]

For the patient referred to above, a thoughtful discussion about the disorder and likelihood of progression to overt myeloma is warranted. As a physician himself, he may recognize the value of participating on a clinical trial, and indeed he would be an excellent candidate. ■

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ABSTRACT & COMMENTARY

Endometriosis Is Implicated Again in Histological Variants of Ovarian Cancer

By Robert L. Coleman, MD

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

SYNOPSIS: Self-reported personal history of endometriosis was associated with an increased risk of ovarian cancer. Further, it was differentially associated with clear cell, endometrioid, and low-grade serous ovarian carcinoma in this pooled analysis. No relationship appeared between endometriosis and high-grade serous or mucinous ovarian cancer, or borderline variants of these two histologies. The results suggest further work is necessary to understand whether endometriosis plays a strategic precursor role in certain ovarian cancer histological subtypes.

SOURCE: Pearce CL, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: A pooled analysis of case-control studies. *Lancet Oncol* 2012;13:385-394.

Several studies have implicated endometriosis as a risk factor for the subsequent development of invasive epithelial ovarian cancer. However, while some histological subtypes, such as clear cell and endometrioid, have been associated, little is known of the other subtypes (e.g., serous and mucinous). To address the hypothesis, members of the Ovarian Cancer Association Consortium (OCAC) pooled data from 13 predominately population-based case-control studies conducted in Australia (1), Europe (3), and the United States (9), assessing risk factors for the development of ovarian malignancy. The data cohort included 23,144 women; 7911 (34%) with invasive epithelial ovarian cancer, 1907 (8%) with borderline tumors, and 13,326 (58%) controls. Controlled confounding variables were age, ethnic origin, oral contraceptive use, parity, breastfeeding, weight, height, body mass index, tubal ligation, and family history. Serous histology was re-classified by WHO grade with grade I representing "low-grade" serous (LGSOC) and all others as "high-grade" serous (HGSOC). A history of endometriosis was found in 9.3% of women diagnosed with invasive ovarian cancer compared to 6.2% of controls (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.31-1.63); in addition, among the five histological subtypes considered, the association was strongest for clear cell carcinoma (OR 3.05, 95% CI 2.43-3.84), compared to endometrioid (OR 2.04, 95% CI 1.67-2.48) or LGSOC (OR 2.11, 95% CI 1.39-3.20). No relationship was observed between endometriosis and invasive HGSOC or mucinous cancer, or of borderline serous and mucinous histology. The effects were upheld in a sensitivity analysis, which considered the time between endometriosis diagnosis and the diagnosis of cancer. The authors conclude that the association should raise awareness in treating clinicians and spark investigation into mechanistic processes driving malignant progression.

COMMENTARY

This article is by far the largest collection of retrospective data to address the relationship between endometriosis and ovarian cancer. The strength of the pooled analysis is that it provides the ability to delve further into histological association, which has been done only to a limited degree and for only certain subtypes.[1] The provocative data do raise the hypothesis that, albeit uncommon, a malignant ovarian phenotype occurs to a greater degree in women with a personal history of endometriosis than those without, particularly for clear cell and endometrioid tumors (previously known) and LGSOC (previously unknown). The relationships are compelling, but as is the case with retrospective studies, cannot be inferred as causal, and must consider several confounding issues and procedural assumptions that could affect the strength of association.

First, all the data regarding the diagnosis of endometriosis in this study is self-reported. There

was no attempt to confirm that, indeed, patients had the disease (e.g., a site audit). In two sites where central registries are maintained, the diagnosis was confirmed by review of discharge summaries, but even in these cases it is unknown if these are histologically based or an inferred diagnosis for pelvic symptoms. The authors acknowledge this limitation but state it would unlikely affect the differential association among the subtypes. However, it is plausible that since women with clear cell, endometrioid, and LGSOC are diagnosed at a younger age, bona fide endometriosis may be differentially recognized by a higher frequency of surgical procedures and confirmatory histology. Second, the histological criteria by which clear cell carcinoma and LGSOC is made are not clearly provided. This has been a significant issue in treatment studies where adjudication of the pathology must be made prior to registration. For instance, it is unclear how cases of mixed clear cell and serous carcinoma were handled. Third, ethnic differences were considered in the confounding variables, which is appropriate given the substantially higher frequency of clear cell carcinoma in Asian-Pacific Islanders; however, it is not clear that endometriosis is similarly increased in this cohort.[2] The higher prevalence of clear cell cancer in this population could significantly attenuate the association. Fourth, the one truly novel finding of the study, the association of endometriosis to LGSOC, was based on reclassification of the WHO grading criteria and not on pathological review. A recent study has found that this methodology misclassifies about 5% of cases, predominately WHO grade 2 (HGSOC) patients being more appropriately identified with LGSOC.[3] Since the frequency of each WHO grade was not given and pathology not reviewed for consistency, it is difficult to know how to interpret this association.

Nevertheless, the recent discovery of ARID1A mutations in clear cell and endometrioid cancers and the association of these tumors to endometriosis provide sufficient rationale to investigate the underlying biology. In addition, microarray interrogation of HGSOC has identified an inflammatory-like signature for some cases.[4] It would be of interest to know if these cases too had an association with endometriosis, which is well recognized to induce stromal alterations and an inflammatory response. ■

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CME Questions

1. In a Phase 3 trial, sunitinib was associated with:
a. a better early response rate.
b. a prolonged progression-free survival.
c. a prolonged overall survival.
d. All of the above
e. None of the above

2. In the meta-analysis conducted by Bellocco and colleagues of renal cell cancer and alcohol consumption, a protective effect was apparent for which groups?
a. Light drinkers
b. Moderate drinkers
c. Heavy drinkers
d. Both a and b
e. All of the above

3. The reported 3-year survival in a cohort of potentially operable patients with early-stage lung cancer treated with stereotactic ablative radiotherapy instead of surgery reviewed by Lagerwaard et al was:
a. 0%, significantly worse than surgical series.
b. 75%, slightly inferior to surgical series.
c. 85%, comparable to surgical series.
d. 95%, superior to surgical series.

4. Which of the following features would *not* be present in a patient considered to have smoldering multiple myeloma?
a. Beta-2 microglobulin of 4.2 mg/L
b. Serum calcium of 12.5 mg/dL
c. 14% presence of plasma cells within a bone marrow aspirate
d. Monoclonal IgA of 3.5 g/dL

[IN FUTURE ISSUES]

Adjuvant FOLFOX for elderly Stage II colon cancer

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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Refining the Relationship Between Thyroid Hormones and Left Ventricular Mass

Source: Iida M, et al. *J Am Soc Hypertens* 2012;6:261-269.

Animal studies have shown that thyroid hormones (T3 and T4) induce hypertrophy of cardiac myocytes through stimulation of both structural and regulatory myocyte genes, which can be prevented by ACE inhibitors or beta-blockers. Such observations have led to the question of whether there might be a relationship between cardiac mass and thyroid hormones, even within the range currently defined as normal.

Hypothyroidism and hyperthyroidism are each considered a potential secondary cause of hypertension: the former through endothelial dysfunction that leads to vasoconstrictor hyperresponsiveness and subsequent increased peripheral resistance, and the latter through increased sympathetic tone. Iida et al investigated hypertensive subjects (n = 293) who had no known thyroid disease and whose thyroid function tests (T3, T4, and TSH) were within normal limits.

Among these euthyroid hypertensive study subjects, multiple linear regression found a positive relationship between T3 and T4 and ventricular mass (the higher the thyroid hormones, the greater the ventricular mass), and an inverse relationship between TSH and ventricular mass. When compared with normotensive controls, no such relationship could be identified. This would lead to consideration that in persons with hypertension, higher levels of thyroid hormone — even within the normal range — may be related to the development of left ventricular hypertrophy. ■

The ORIGIN Trial: Basal Insulin vs Standard Care for Early Type 2 Diabetes

Source: The ORIGIN Trial Investigators. *N Engl J Med* 2012;367:319-328.

Type 2 diabetes reflects insulin insufficiency. Early in the disease process, plasma insulin levels may actually be higher than normal, but insufficient to maintain euglycemia. By the time of formal diagnosis, approximately half of beta cell mass has been lost, and as the disease progresses, insulin levels continue to fall.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomized subjects with prediabetes or early diabetes (n = 12,537) to insulin glargine (GLAR) or standard treatment (STND) for 6.2 years (mean). The objective of the trial was to determine whether early institution of basal insulin, as compared to STND, improves cardiovascular outcomes. Standard treatment was simply treatment of diabetes as per the treating clinician's choice; by the end of the trial, only 11% of the STND group was receiving insulin. Eighty percent of the GLAR group was on insulin at the end of the trial.

There was no difference in cardiovascular outcomes between the two treatment groups. One notable difference between treatments was the likelihood of progression from prediabetes to diabetes. The GLAR group was 28% less likely to progress than the STND group; however, there was also more hypoglycemia and weight gain in the GLAR group.

Increased incidence of cancer — a concern generated by earlier insulin trial data — was *not* seen in this large trial, and hence should be very reassuring. ■

Bronchodilators in COPD and Arrhythmias

Source: Wilchesky M, et al. *Chest* 2012; 142:298-304.

For chronic obstructive pulmonary disease (COPD), except for the provision of oxygen in late-stage disease, no pharmacologic intervention has been confirmed to save lives. Nonetheless, since bronchodilators improve symptoms, quality of life, and exercise capacity, and reduce acute exacerbations of COPD, they play an important role in routine care. Concerns about the potential capacity for arrhythmogenicity of bronchodilators has arisen from clinical COPD trials such as the Lung Health Study (n = 5887), in which short-acting ipratropium bromide was associated with a three-fold greater incidence of arrhythmia than comparator groups. Other smaller trials have not confirmed these findings, hence clarification is needed.

Wilchesky et al analyzed data from the province of Saskatchewan, Canada, to identify COPD subjects (n = 6018) and compare the incidence of arrhythmia in new users of ipratropium, beta-agonists (short- and long-acting), and methyhlxanthines to non-users.

Short-acting anticholinergics were

associated with a 2.4 relative risk of arrhythmia, and long-acting beta-agonists with a 4.5 relative risk. No statistically significant increased risk was seen with short-acting beta-agonists or methylxanthines. Despite these concerns, the authors remind us that the absolute risk increase was very small, and "in most cases would be outweighed by the therapeutic benefit accrued through symptomatic relief and consequent improvements to quality of life." ■

Reversible Dementia from Corticosteroid Therapy

Source: Cipriani G, et al. *Clin Geriatrics* 2012;20:38-41.

Although there are many clinical situations in which corticosteroids (CTS) are disease modifying and life saving, one aspect of CTS that has not received much attention is the potential for central nervous system (CNS) adverse effects. CTS may be largely subgrouped into mineralocorticoids exemplified by aldosterone, and glucocorticoids (GLC) like prednisone, the latter of which is the object of this case report.

There are at least two types of CTS receptors in the brain: type I (mineralocorticoid receptors) and type II (glucocorticoid receptors). Type II receptors are found in the hippocampus as well as diffuse other sites throughout the brain. The hippocampus is required for voluntary recollection of learned information, such as recalling what you had for dinner last night. Even low doses of GLC have been shown to impair hippocampal function, despite being used for short time periods: doses of prednisone of 80 mg/day have been shown to alter cognitive function within 4-5 days.

The authors include discussion of a report detailing six cases of dementia-like cognitive decline (distinct from steroid psychosis) in patients whose cognitive function was restored upon GLC discontinuation.

Clinicians should be vigilant for decline in cognitive function in persons receiving GLC treatment, even over the short-term. ■

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Could Thinner be Worse for Newly Diagnosed Diabetics?

Source: Carnethon MR, et al. *JAMA* 2012;308:581-590.

Usually, we anticipate a direct relationship between overweight and cardiovascular adversity, attributed to increases in blood pressure, lipids, glucose, insulin resistance, and sympathetic tone that are associated with obesity. There appears to be some exception to this general rule in reference to diabetes. For instance, in the TRIAD study, diabetics who were normal weight at entry to the study had a *higher* mortality than overweight/obese study subjects; similarly, in the PROactive trial, normal weight subjects or those who lost weight had *higher* mortality than overweight subjects. Because these two studies included confounding issues such as diabetes of varying duration and pre-existing cardiovascular disease, a more clear-cut relationship between body mass index (BMI) and outcome in diabetes could be discerned by selecting newly diagnosed diabetics.

Carnethon et al performed a pooled analysis of five longitudinal cohort studies (n = 2625) to examine the relationship between mortality and BMI for persons with newly diagnosed diabetes. Overall, only 12% of study subjects had a BMI < 25 at the time of diagnosis, but the relative risk for total mortality during follow-up (up to 15 years) was essentially doubled in this population compared to overweight individuals.

The mechanism(s) by which lower BMI increases mortality risk are unknown. Clinicians must not be falsely reassured that this lower-BMI phenotype, which is commonly seen in Asian-Americans, portends a favorable future. ■

The Impact of Exercise on Depression in Heart Failure

Source: Blumenthal JA, et al. *JAMA* 2012;308:465-474.

It is estimated that 5 million Americans have chronic heart failure (CHF), and almost half of these patients fulfill diagnostic criteria for depression. Subsyndromal depression is present in as many as 75%. Notwithstanding the burden of depression on quality of life, a direct impact on mortality has been shown in post-myocardial infarction patients, and even in patients with hypertension in the Systolic Hypertension in the Elderly Program. Unfortunately, to date the information on the impact of treating depression is both limited and generally disappointing. For instance, a clinical trial of sertraline in depressed patients with CHF found no cardiovascular event outcomes benefit.

Exercise is a treatment for depression, and exercise has been shown to provide event reduction in CHF patients. Whether it might improve depression and cardiovascular events in CHF patients was the object of the HF-ACTION trial (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise Training).

More than 2000 patients with stable CHF were randomized to an aerobic exercise program. The exercise subjects enjoyed a statistically significant 11% reduction in mortality over the next 30 months. Although the mean score on the Beck Depression Inventory was statistically significantly lower in the exercise group, the improvement was sufficiently modest to be of uncertain clinical impact. Exercise in CHF reduces mortality and may have a modest effect on depression. ■

PHARMACOLOGY WATCH

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

Statins and Cognition — More to the Story?

In this issue: Side effects of statins; effects of cannabis use; antihypertensives and lip cancer; and FDA actions.

Review challenges FDA warning

Do statins cause changes in cognition? In February, the FDA added warnings to statin labels regarding the risk of reversible memory loss and confusion. But a new review from the *Journal of the American College of Cardiology* reviews the evidence given to the FDA and concludes "that there is no increased risk of cognitive decline" with statin use. The State-of-the-Art Paper was a comprehensive review of case reports, observational research, and randomized, controlled trials of statins and cognitive change, as well as risk of cancer and diabetes. Most of the evidence for cognitive changes came from individual case reports, many of which were self-reported by consumers to the FDA. Observational studies gave mixed results on cognition with four of nine studies showing statins improved cognition, while three showed no change, and two studies found an increased risk of cognitive impairment. The authors suggest that these studies are inconclusive and prone to selection bias. Two large, randomized, controlled clinical trials specifically looked at the effect of statins on cognitive function as the major secondary endpoint. In both, no significant differences were seen between the study and control groups with regard to cognitive decline. Twelve smaller studies showed mixed results with the majority showing no change and only one in 12 showing a detrimental effect of statins on cognitive function, while two studies showed a benefit. Along with lack of evidence to suggest statins lead to cognitive decline, the authors also found no evidence that statins increase the risk of cancer. They did, however, find a small risk for development of diabetes, which they felt was "outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended" (*J Am Coll Cardiol* published online August 15, 2012). ■

Cannabis use and cognitive decline

Persistent cannabis use — particularly in adolescence — may lead to permanent cognitive decline, according to a new study. Researchers looked at a birth cohort of 1037 healthy individuals in New Zealand who underwent neuropsychological testing in the mid 1980s before the onset of cannabis use, and then again in 2010-2012 after some had developed a persistent pattern of cannabis use. Persistent cannabis use over 20 years (at least 4 days per week) was associated with neuropsychological decline, with greater decline evidence for more persistent users. This effect was only seen in adolescent-onset cannabis users and was associated with an average 8 point loss in IQ by age 38. The effect persisted after controlling for education, other drugs, or tobacco. The effects were not seen among adult-onset cannabis users. The authors conclude that increasing efforts should be directed toward delaying the onset of cannabis use by young people, "particularly given the recent trend of younger ages of cannabis use initiation in the United States and

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evidence that fewer adolescents believe that cannabis use is associated with serious health risk." (*Proc Natl Acad Sci U S A* published online August 27, 2012). This study and others are increasingly important as cannabis, the most widely used illicit drug in the world, is being considered for more medicinal uses as well as legalization. ■

Antihypertensives and lip cancer

Two photosensitizing antihypertensives, hydrochlorothiazide and nifedipine, may increase the risk for lip cancer in non-Hispanic white patients, according to a new study from Kaiser Permanente in California. From a large cohort of patients, 712 were identified with lip cancer along with nearly 23,000 matched controls. At least a 5-year supply of the drug resulted in the following odds ratios for lip cancer (95% confidence intervals) — hydrochlorothiazide 4.22 (2.82-6.31), hydrochlorothiazide-triamterene 2.82 (1.74-4.55), nifedipine 2.50 (1.29-4.84), and lisinopril 1.42 (0.95-2.13). When atenolol was given without other hypertensives, the odds ratio for lip cancer was 0.54 (0.07-4.08). The authors suggest that while antihypertensive therapy outweighs the risk of lip cancer, preventive measures should be taken for those at increased risk because of fair skin and long-term sun exposure (*Arch Intern Med* published online August 06, 2012). ■

FDA actions

The FDA has approved a delayed-release form of prednisone for the treatment of endocrine, inflammatory, and neoplastic conditions. Delayed-release prednisone should be taken once a day with timing to be determined by the disease being treated. For example, 10 p.m. dosing is recommended for rheumatoid arthritis, as it is more effective than immediate-release prednisone taken in the morning for treating morning stiffness associated with the disease. Dosing is based on the theory that both cytokines and endogenous cortisol follow a circadian rhythm, and that dosing the drug based on the condition being treated may afford more effective treatment than immediate-release prednisone. The new product delays the release of prednisone by approximately 4 hours. Side effects are the same as short-acting prednisone. Delayed-release prednisone will be marketed as RAYOS by Horizon Pharma.

The FDA has approved a new chlorofluorocarbon (CFC)-free, over-the-counter inhaled racepinephrine product for the treatment of asthma. The new product takes the place of the banned Primatene Mist, which was taken off the market at the end of 2011 because it contained CFCs. Inhaled epinephrine has been used for the treatment of asthma for more than 100 years. Marketed as Asthmanefrin, the new product will be sold as a starter kit and refill package. The starter kit will include 10 vials of racepinephrine along with the EZ Breathe Atomizer. The refill kit will include 30 vials of the drug. The drug is not without controversy, however, with many asthma experts feeling that the side effects of epinephrine are serious and well-documented, and over-the-counter use goes against published guidelines for treating asthma. Asthmanefrin will be marketed by Nephron Pharmaceuticals.

The FDA has approved linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. The drug is the first guanylate cyclase (GC-C) agonist that acts locally in the gut with minimal systemic exposure. The drug is taken once daily on an empty stomach at least 30 minutes before the first meal of the day. Safety and efficacy in the management of irritable bowel syndrome with constipation was established in two double-blind studies of nearly 1300 patients who were randomly assigned to linaclotide or placebo for 12 weeks. Patients taking the drug experienced more complete spontaneous bowel movements than those taking placebo. The drug should not be used in patients 17 years or younger. Linaclotide will be jointly marketed by Ironwood Pharmaceuticals and Forest Pharmaceuticals as Linzess.

Montelukast (Singulair), Merck's popular asthma and allergy medication, will soon be available as a generic. The leukotriene receptor antagonist will be manufactured by 10 generic companies in tablet form, oral granules, and chewable tablets. The FDA warns that montelukast should not be used for relief of sudden asthma attacks and further warns that patients should contact a clinic immediately if they are experiencing behavior and mood-related changes such as aggression, depression, or hallucinations.

The FDA has approved the first generic version of pioglitazone (Actos). The drug is approved along with diet and exercise to improve blood sugar control in adults with type 2 diabetes. This happens as thiazolidinediones have generally fallen out of favor for use in type 2 diabetes due to side effects including worsening heart failure and edema. The FDA also recently issued a warning for pioglitazone regarding increased risk of bladder cancer if the drug is taken for more than 1 year. The first generic pioglitazone will be manufactured by Mylan Pharmaceuticals. ■