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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Trastuzumab and the Risk of Congestive Heart Failure

By Gary R. Shapiro, MD

Medical Director, Cancer Center of Western Wisconsin, New Richmond, Wisconsin

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

SYNOPSIS: This retrospective cohort study of 12,500 women with breast cancer, treated in the community, compared the incidence of congestive heart failure in those who received trastuzumab-containing adjuvant chemotherapy regimens with those who did not. There was a four-fold increase in the risk of heart failure in women who received trastuzumab alone and a seven-fold increase in those who received anthracycline plus trastuzumab.

SOURCE: Bowles EJ, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: A retrospective cohort study. *J Natl Cancer Inst* 2012;104:1293-1305.

The Cancer Research Network (CRN), a consortium of nonprofit research centers based in integrated health care delivery organizations, used administrative procedure and pharmacy codes to identify heart failure and/or cardiomyopathy (HF/CM) in women with breast cancer at eight CRN sites who received adjuvant anthracycline, trastuzumab, and other chemotherapy. Of the 12,500 women (mean age, 60 years; range, 22-99 years) in this population-based, retrospective cohort study, 29.6% received anthracycline alone, 0.9% received trastuzumab alone, 3.5% received anthracycline plus trastuzumab, 19.5% received other chemotherapy, and 46.5% received no chemotherapy.

Compared to those who did not receive adjuvant chemotherapy, multivariable Cox proportional hazards regression analysis determined the risk of HF/CM was higher in patients treated with anthracycline alone (adjusted hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.11-1.76), though this increased risk was similar to that of other chemotherapy (adjusted HR, 1.49; 95% CI, 1.25-1.77). On the other hand, the risk of HF/CM was decidedly increased in patients treated with trastuzumab alone (adjusted HR, 4.12; 95% CI, 2.30-7.42) or anthracycline plus trastuzumab (adjusted HR, 7.19; 95% CI, 5.00-10.35).

COMMENTARY

Although the relationship between trastuzumab-based adjuvant chemotherapy and HF/CM is well known, this is the first study to examine the "real world" of community-dwelling breast cancer patients. Older women and women with major

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comorbidities are underrepresented in formal clinical trials, and observational studies using Surveillance, Epidemiology, and End Results (SEER)-linked Medicare data do not include the broader group of women with breast cancer.[1]

As one might expect, women who received anthracycline alone or anthracycline plus trastuzumab in the CRN analysis were younger (age < 65 years, 86.4% and 89.6%, respectively) and had fewer comorbidities (Charlson score ≥ 2, 10.0% and 7.7%, respectively) than recipients of other or no adjuvant chemotherapy.

The median follow-up time for the analysis was 4.4 years, but it is important to note that the cumulative incidence of HF/CM in those who received anthracycline plus trastuzumab increased from 6.2% after 1 year of follow-up to 20.1% by 5 years. The 5-year cumulative incidence of HF/CM was 12.1% in those who got trastuzumab alone but only 4.3% in those who received anthracycline alone. These compare to a 5-year cumulative incidence of HF/CM of 4.5% in those who received other types of adjuvant chemotherapy and 3.1% in those who did not receive any adjuvant chemotherapy.

The 5-year cumulative incidence of trastuzumab-related HF/CM was most striking in the older age groups: 35.6% of those aged 65-74 and 40.7% of those 75 years of age and older who received anthracycline plus trastuzumab. These compare to 6.2% in those aged 65-74, and 10.6% in those 75 years and older who received anthracycline alone, and 8.7% of those age 65-74 years and 18.7% of those 75 years or older who received other forms of adjuvant chemotherapy.

Although the risk of anthracycline-associated HF/CM in younger women was similar to that reported from randomized clinical trials, the CRN analysis revealed a greater risk of trastuzumab-associated HF/CM in both younger and older women than previously reported (whether the trastuzumab was administered alone or following anthracycline).[2] The study's median 4.4 years of follow-up is longer than that reported by other investigators, and it highlights the heretofore underappreciated ongoing long-term risk of trastuzumab-related HF/CM. Indeed, there appears to be no leveling off of this risk, and until more long-term data are accumulated, clinicians would be wise to provide ongoing surveillance for HF/CM in their patients who have received trastuzumab-containing adjuvant chemotherapy regimens. ■

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ABSTRACT & COMMENTARY

PET/CT SUV of Prognostic Value in Metastatic Breast Cancer

By William B. Ershler, MD

SYNOPSIS: By examining a large series of patients who had PET/CT scans obtained within 2 months of diagnosis of metastatic breast cancer, it was discovered that site-specific SUV correlated with survival. This was most apparent and statistically significant when comparing survival for patients with bone metastases, although similar but not statistically significant data also were presented for patients with liver, lung, or lymph node involvement.

SOURCE: Morris PG, et al. Standardized uptake value by positron emission tomography/computed tomography as a prognostic variable in metastatic breast cancer. *Cancer* 2012;118:5454-5462.

Metastatic breast cancer (MBC) remains a challenge. Approximately 20% of patients present with metastatic disease and one-third or more of those treated initially with local or regional disease will relapse at distant sites.[1] The goal of cure remains elusive for patients with MBC and median overall survival (OS), although highly variable, is between 24 and 36 months.[2]

Although a number of factors have proven useful in estimating prognosis for those with metastatic disease, including patient age, disease-free interval, and site of recurrence, clinical course remains highly variable. In this context, investigators at Memorial Sloan Kettering Cancer Center in New York explored the hypothesis that data from positron emission tomography/computed tomography (PET/CT) could further refine prognostic capabilities for patients with MBC.

The authors performed a retrospective analysis examining the PET/CT-derived maximum standardized uptake value (SUV_{max}) obtained on newly diagnosed MBC patients. For inclusion in this analysis, PET/CT images had to be available within 60 days of diagnosis of MBC and the patients included were those evaluated at their institution over an 8-year period (2001-2008). Patients were excluded if they had received chemotherapy in the 30-day period before the PET/CT images were obtained. OS was determined by accessing medical records. Since there was variability within individuals in the SUV by site of metastatic disease, separate analyses were conducted by site (e.g., bone, lymph node, liver, lung). Patients were classified into tertiles (highest, intermediate, and lowest) based on SUV_{max} at each site. Thus, some patients who had lesions at multiple sites contributed to the analysis for each site. The relationship between SUV_{max} and OS were assessed using Cox regression analysis.

In total, 253 patients were identified, and their median age was 57 years (range, 27-90 years). Of these, 152 patients (60%) died, and the median follow-up for the entire group was 40 months. On univariate analysis, SUV_{max} tertile was strongly associated with overall survival in patients who had bone metastases (n = 141; hazard ratio [HR], 3.13; 95% confidence interval [CI], 1.79-5.48; $P < 0.001$). This effect was maintained on multivariate analysis (HR = 3.19; 95% CI, 1.64-6.20, $P = 0.002$) after correcting for known prognostic variables including tumor histology and grade, ER/PR/EGFR status, prior therapy, and disease-free interval.

A greater risk of death was associated with SUV_{max} tertile in patients who had metastases to the liver (n = 46; HR, 2.07; 95% CI, 0.90-4.76), lymph nodes (n = 149; HR, 1.1; 95% CI, 0.69-1.88), and lung (n = 62; HR, 2.2; 95% CI, 0.97-4.95), although these results were not significant ($P = 0.18$, $P = 0.31$, and $P = 0.095$, respectively).

COMMENTARY

PET/CT imaging has evolved to become an essential tool in cancer medicine, but its role in staging and management of breast cancer remains to be established. Although not commonly recommended in the staging of early breast cancer,[3] PET/CT has been helpful when standard imaging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

In the current study performed exclusively in the metastatic diseases setting, it was found that the FDG PET/CT-derived SUV offered prognostic information; those with high levels of FDG uptake (i.e., high SUV) had shorter survival than those with low levels. This was particularly true when comparing patients with bone metastatic lesions for which the observation reached statistical significance, even when controlling for other prognostic factors. When comparing SUV for patients with liver and/or lung lesions, the correlation was present, but not quite to the level of statistical significance. Thus,

[Clinicians should be aware that the level of SUV within bone MBC lesions may be an indicator of more agressive disease.]

clinicians should be aware that the level of SUV within bone MBC lesions may be an indicator of more aggressive disease, although there is insufficient evidence to date to base treatment decisions on this alone. This was a large, carefully conducted study including a broad array of MBC patients and sufficient time to determine median survival, yet conclusions should be tempered by acknowledging that it was a retrospective observational analysis from a single institution. Nonetheless, in light of these data, we can hope that investigators will incorporate SUV_{max} in future randomized interventional studies to confirm the prognostic value of this measure and, of equal or even greater importance, to determine if a decline in SUV_{max} is a reliable biomarker for treatment response and improved progression-free and overall survival. ■

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ILLUSTRATIVE CASE SERIES

Postoperative Management of GIST

By William B. Ershler, MD

A 61-year-old nuclear engineer with a past history of hypertension was admitted through the emergency department because of persistent lower abdominal pain. Clinical picture and imaging studies initially pointed to pelvic abscess. Computerized tomography (CT) had revealed a large (14 x 14 x 14 cm) fluid collection most consistent with that diagnosis. He was treated with antibiotics including Flagyl, vancomycin, and Zosyn and underwent percutaneous drainage. Repeat CT (post drainage) demonstrated residual fluid and an adjacent solid mass. Subsequently, he underwent a CT-guided biopsy revealing a spindle cell tumor strongly positive for CD117 and negative for CD34, S100, CD68, and pancytokeratin. The findings were more consistent with gastrointestinal stromal tumor (GIST). The patient was readmitted and underwent surgical resection at which time a 12 cm tumor was removed intact. Histologic evaluation once again revealed a high-grade spindle-cell tumor with a high mitotic index (12 mitoses per 50 high power fields) and extensive necrosis.

[A recent panel of experts concluded that adjuvant imatinib should be considered the standard treatment in all patients with significant recurrence following resection of primary gastrointestinal stromal tumors.]

The postoperative course was marked by gradually diminishing abdominal pain and was otherwise uneventful. Two weeks after discharge he was seen in the office for discussion regarding adjuvant therapy.

His prior medical history was significant only for hypertension, which was controlled with metoprolol 25 mg daily.

On physical exam he appeared thin and somewhat pale. His blood pressure was 120/70 and pulse was 84 and regular. The abdominal exam revealed the surgical site to be well healed with slight tenderness but no palpable mass. CBC and chemistries revealed a mild microcytic anemia but without other abnormalities.

Future management recommendations were solicited.

DISCUSSION

GISTs are mesenchymal in origin, most commonly arise from the stomach or small intestine, and frequently have demonstrable mutation in the KIT (approximately 75%) and/or PDGFRA (approximately 10%) gene.[1,2] Complete surgical excision offers the best chance for cure, yet up to 50% of patients relapse within 5 years.[3,4] For patients with advanced disease, imatinib has proved to be effective in reducing tumor burden, but eventually disease progression occurs.[5,6]

Predictive models have been developed to assess risk for disease recurrence after primary GIST resection.[7,8] Risk factors include mitotic index and tumor size. The commonly used NIH Consensus Criteria for high risk include the presence of one of the following: 1) tumor diameter greater than 10 cm, 2) mitototic count greater than 10 per 50 high power fields (hpf), 3) tumor diameter greater than 5 cm AND mitototic count greater than 5/ 50 hpf, or 4) tumor rupture before or during surgery.[7,8]

For patients at high risk for recurrence, there have been two large trials that support the role for adjuvant imatinib by demonstrating both improved relapse-free and overall survival.[9,10] From these and other supporting data, a recent panel of experts concluded that adjuvant imatinib should be considered the standard treatment in all patients with significant risk of recurrence following resection of primary GISTs.[11] What remains to be answered is the length of therapy. Although 1 year of treatment had been common practice, the Scandinavian Sarcoma Group SSGXVIII trial[10] clearly demonstrated that 3 years of treatment of 400 mg of imatinib per day for high-risk GIST was superior to 1 year in terms of both relapse-free and overall survival, and the FDA has now recommended the extended treatment for such patients.

Accordingly, as the patient presented above met

criteria for high-risk for recurrence (based on both size and mitotic index), a minimum of 3 years of imatinib therapy would be recommended. The question would be whether the drug should be discontinued after 3 years if he remains relapse free. Inasmuch as the specific mutations that drive this neoplastic proliferation are directly inhibited by imatinib, it would be tempting to continue indefinitely. On the other hand, it is notable that patients who present with metastatic disease are known to become imatinib-resistant over time. Hopefully, additional research will address whether there is an advantage to continue patients indefinitely on imatinib or stop at a defined time, such as 3 years. ■

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ABSTRACT & COMMENTARY

Watchful Waiting for Patients with Follicular Lymphoma: Even in the Rituximab Era

By William B. Ershler, MD

SYNOPSIS: In an analysis of a well-characterized dataset capturing outcomes for patients with asymptomatic, low-burden follicular lymphoma, those managed by initial watchful waiting had outcomes similar to comparable patients who were treated at the time of diagnosis with regimens including rituximab. Thus, delayed initial therapy remains a reasonable approach for selected follicular lymphoma patients.

SOURCE: Solal-Celigny P, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: Results of an F2-study database. *J Clin Oncol* 2012;30:3848-3853.

It has long been held that follicular lymphoma (FL) is typically indolent but incurable. However, it's not indolent for every patient. Progression, either shortly after diagnosis or months to years later, is observed in most patients and transformation to a more malignant variant with all the features of aggressive lymphoma occurs in a small subset. Furthermore, with the advent of new and targeted therapies, the "incurable" moniker also may be challenged. It has been speculated that therapies such as rituximab may change the natural history of this disease, and, if not resulting in cure, at least prolonging survival beyond that seen for patients treated with chemotherapy alone.

Accordingly, the practice of delaying initial treatment (watch and wait, W&W) for those with low-burden FL needs careful reexamination. The premise for such an approach has been based on studies initially published from Stanford in which a W&W approach was compared with chemotherapy demonstrating no significant differences in terms of overall survival.[1-3] These conclusions have been confirmed in additional studies in which selected FL patients were randomized to observation (W&W) or treatment with chemotherapy (either single or multiple agents) or interferon with no significant difference in overall survival observed.[4-6] Yet, the question is whether early treatment with rituximab would provide results that would change the current sentiment or whether there is no disadvantage to delaying initial therapy.

To address this, investigators participating in the International Follicular Lymphoma Prognostic Factor Project examined data derived from more current FL patients (i.e., in the rituximab era) registered in the F2-study and initially managed without treatment to

describe the presentation and outcome of a W&W strategy. The goal was to identify parameters for initiating treatment and to evaluate whether initial W&W could have deleterious effects on treatment efficacy after progression or relapse when compared to those receiving current management including rituximab.

Between 2003 and 2005, 120 patients selected from the 1093 treatment-naive patients with FL in the F2-study cohort initially were managed expectantly (W&W), and 107 patients were assessed. Most of these patients (80%) had disseminated disease with a low tumor burden, according to Groupe d'Etudes des Lymphomes Folliculaires criteria.[5] After a median follow-up of 64 months, treatment was initiated in 54 patients (50%), with a median delay of 55 months for the entire cohort. In a univariate analysis, involvement of more than four nodal areas (hazard ratio [HR], 2.26) and serum albumin < 3.5 g/dL (HR, 3.51) were predictive of a shorter time to lymphoma treatment initiation. In a multivariate analysis, only involvement of more than four nodal areas remained significant (HR, 2.32). The 4-year freedom from treatment failure (FFTF) rate of W&W patients (79%; 95% CI, 69% to 85%) was not inferior to that of a subgroup of 242 patients from the F2-study cohort with good prognosis characteristics who were initially treated with a rituximab-based regimen (69%; 95% CI, 61%-76%; $P = 0.103$).

COMMENTARY

Clinical oncologists (like me) may not be too familiar with the FFTF endpoint, but it is indeed an outcome of relevance when comparing delayed vs initial therapy. The issue is best exemplified by the intriguing findings presented at the American Society of Hematology annual meeting in 2010 by Ardeshna and colleagues.[7] They presented preliminary results from a trial in which 450 asymptomatic FL patients were randomly assigned to either W&W or to four weekly doses of rituximab followed either by observation or by 2 years of maintenance rituximab. They found the time to initiation of chemotherapy or radiotherapy was significantly prolonged in the early intervention arms — findings that would argue against delaying treatment, even in asymptomatic low-burden patients. That conclusion, however, has raised some controversy as articulated both by the authors of the current study and by Dr. Cheson who provided the accompanying editorial.[8] They emphasized that rather than compare the time to initial treatment for the W&W patients with the time to second-line therapy for the treated patients, it would be more appropriate to compare the FFTF or the time to second lymphoma therapy and, of course, when the data are sufficiently mature, the overall survival for each of the cohorts.

The currently presented careful analysis of a well-constructed dataset would suggest patients with asymptomatic, low-burden FL can still be managed safely with W&W as such an approach, even in the rituximab era, does not have apparent detrimental effects on FFTF and overall survival rates. ■

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ABSTRACT & COMMENTARY

Clinical Considerations for Uterine Serous Cancer

By Robert L. Coleman, MD

Professor, University of Texas; M.D. Anderson Cancer Center, Houston

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

This article originally appeared in the December 2012 issue of OB/GYN Clinical Alert.

SYNOPSIS: Uterine (papillary) serous cancer is a genomically unstable cancer associated with poor survival even in stage I. It is also frequently associated with a secondary malignancy, particularly breast cancer. Comprehensive

surgical staging is recommended since extrauterine disease can be present without other high-risk uterine features, like myometrial invasion. However, an optimal adjuvant treatment protocol remains to be defined.

SOURCE: Growdon WB, et al. Prognostic determinants in patients with stage I uterine papillary serous carcinoma: A 15-year multi-institutional review. *Int J Gynecol Cancer* 2012;22:417-424.

To evaluate the impact of surgical staging on survival of women with early stage (Stage IA and Stage IB) uterine papillary serous cancer (USC), a retrospective analysis was undertaken on patients treated over a 15-year period at two institutions. Over this time period, 84 cases of early stage cancer were identified. The diagnosis was based on histologic features, including papillary architecture with tuft stratification, marked nuclear pleomorphism, high nuclear-to-cytoplasmic ratio, and a high mitotic count. Of the 84 identified cases, the majority were stage IA (n = 71); 37 patients (44%) had a history of a second cancer (22 breast tumors, 9 synchronous müllerian cancers). Surgical staging with at least hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic lymph node dissection was performed in 60 (71%) of 84 patients. The median survival for all patients was 10 years. Univariate analysis revealed that surgical staging ($P < 0.001$), normal preoperative CA-125 ($P < 0.001$), and absence of a secondary malignancy ($P < 0.01$) were associated with improved survival. Age-adjusted multivariate analysis incorporating these factors revealed that surgical staging (hazard ratio, 0.18; $P < 0.001$), substage (hazard ratio, 4.59; $P < 0.05$), and history of a second malignancy (hazard ratio, 2.75; $P < 0.04$) were independent factors associated with reduced overall survival. The former two remained independent factors if secondary malignancy was excluded. Treatment approach (observation, radiation, chemotherapy, or both) did not impact survival. It was concluded that independent of adjuvant therapy, early substage of disease, comprehensive surgical staging, and the presence of a second malignancy significantly impacted overall survival.

COMMENTARY

Uterine papillary serous, now termed uterine serous cancer, is widely recognized as unique histology, distinguished from "common" type or endometrioid adenocarcinoma by its frequent metastatic disease at presentation, frequent recurrence, and poor overall survival. Classically, it has underscored the two-class nomenclature frequently seen in textbooks, which highlight a disease (type II) that is associated with older age at presentation, absence of obesity, disassociation from estrogen use, and deep myometrial invasion.[1] USC accounts for just 10% of all primary uterine cancers but is responsible for 40% of the cancer-related deaths. The rarity of presentation has hindered clear treatment guidelines, particularly from Phase 3 adjuvant trials. This has led to a series of reports, like the current, which are retrospective in nature, generally with small patient cohorts, and gathered over long periods of time. However, from these types of studies, hypotheses can be generated which, until better information is available, can help foster rational treatment approaches. For most gynecologic oncologists, the most significant is recognition that uterine factors, such as size, location, and depth of myometrial invasion, are poorly associated with the probability of extrauterine spread. This is common practice for endometrioid, particularly early-stage, low-grade tumors where the risk of extrauterine spread is < 5% and formal staging may be overtreatment and unnecessary. In USC, even tumors confined to a polyp are associated with extrauterine or peritoneal dissemination (particularly the omentum) in one-third of patients.[2] The Society of Gynecologic Oncology and the National Comprehensive Cancer Network both have issued guidelines recommending surgical staging in all such cases if medically feasible.

[The uterine serous cancer population represents an important and distinct entity of disease challenged by much of the same clinicopathological features seen in ovarian malignancy.]

The high rate of secondary tumors, particularly breast cancer, is curious but consistent across USC studies. The Cancer Genome Atlas (TCGA) has characterized USC to be not only distinct from its endometrioid counterpart, but in many ways, similar to high-grade serous ovarian cancer, with frequent P53 mutation and E-cadherin loss. The relationship between breast and ovarian cancer is well documented, but the association of BRCA germline mutation carrier status and USC is much less clear. Although more investigation is needed, the frequency of USC and breast cancer does raise

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the question of hysterectomy at the time of risk-reducing ovarian/tubal surgery for high-risk individuals.

In all, the USC population represents an important and distinct entity of disease challenged by much of the same clinicopathological features seen in ovarian malignancy. It is hoped that information emerging from the TCGA and other genomic interrogation efforts will help identify novel targets for future intervention.[3] ■

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Objectives

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

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

CME Questions

1. Women with breast cancer who receive trastuzumab-containing adjuvant chemotherapy regimens:

a. need to be followed for treatment-related congestive heart failure for only 1 year after their last trastuzumab infusion.
b. are at risk for treatment-related congestive heart failure only if they also received an anthracycline.
c. are at risk for treatment-related congestive heart failure at any age.
d. None of the above

2. For which of the following sites of newly diagnosed metastatic breast cancer would a PET/CT SUV level offer significant prognostic information?

a. Bone
b. Liver
c. Lung
d. Lymph node

3. Current recommendations for adjuvant therapy for patients at high risk for relapse include:

a. imatinib 400 mg/day for 1 year.
b. imatinib 800 mg/day for 1 year.
c. imatinib 400 mg/day for 3 years.
d. imatinib 400 mg/day indefinitely.

4. When comparing delayed intervention (i.e., watchful waiting) vs immediate therapy for patients with low-burden follicular lymphoma, which outcome is likely to be most instructive?

a. Response rate
b. Freedom from treatment failure
c. Time to lymphoma treatment
d. First remission duration

5. Which of the following features was not used to establish the diagnosis of uterine papillary serous cancer?

a. High nuclear-to-cytoplasmic ratio
b. Nuclear atypia
c. High proliferation
d. P53 protein loss

[IN FUTURE ISSUES]

Stress and poor cancer outcomes:
It's more than psychological

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

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The essential monthly primary care update

By Louis Kuritzky, MD

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Beta-Blocker Use in Situations Other than Just Post-MI

Source: Bangalore S, et al. *JAMA* 2012; 308:1340-1349.

Current standard-of-care management of post-myocardial infarction (MI) patients includes long-term use of a beta-blocker, unless otherwise contraindicated. The length of the leash on this concept is not long, however, as prospective data confirming benefits of beta-blockers post-MI are limited to just a few years. Since clinicians have not been given concrete advice about when to *stop* beta-blockers, most patients are kept on beta-blockers indefinitely. Perhaps our indecisiveness is bolstered by anxieties related to the potential consequences of beta-blocker withdrawal in persons with known coronary artery disease (CAD).

In the absence of data from a randomized, prospective, long-term trial, observational data may provide some clues about the relative benefit (or lack thereof) of beta-blockers in at-risk populations. To that end, Bangalore et al report on the outcomes of three different at-risk populations from a CAD registry: post-MI patients (n = 14,043), CAD patients without history of MI (n = 12,012), and patients with CAD risk factors but no known CAD (n = 18,653). Study subjects were enrolled in 2003-2004, and followed for approximately 4 years.

Beta-blocker use was not associated with improved outcomes in *any* of the three subgroups, even the one group we take for granted that there will be beneficial effects: the post-MI group. In the 1990s, the term "cardioprotective" was sometimes used in reference to beta-blockers. Although this may be true for the few short years immediately after an MI where older clinical trials have found a benefit, whether such benefits persist, or extend to other at-risk groups, remains to be determined. ■

Long-Term Sexual and Psychological Adverse Effects of Finasteride

Source: Irwig MS. *J Clin Psychiatry* 2012;73:1220-1223.

Cutaneous dihydrotestosterone is etiologically involved in the development of male pattern baldness. Since finasteride blocks the conversion from testosterone to dihydrotestosterone, it is commonly used to treat the disorder. Systemic alpha-reductase inhibitors like finasteride are occasionally associated with sexual side effects, but only recently has there been the suggestion that finasteride-associated sexual side effects might persist beyond the time treatment is administered. Additionally, recent FDA labeling changes have added depression as a recognized adverse effect of finasteride treatment. Although mechanisms to explain persistent adverse sexual effects are unclear, some animal data suggest persistent diminution in penile relaxation and contraction subsequent to finasteride.

From a population of young men (mean age 31 years) with male pattern baldness (n = 91), Irwig compared men who reported sexual dysfunction for at least 3 months after finasteride cessation to men with male pattern baldness who had not used finasteride. Outcomes of interest were depression scores and suicidal thoughts.

Depression, depressive symptoms, and suicidal thoughts were all substantially more common in the former finasteride users than controls. For example, 75% of former users had a Beck Depression Inventory Score of at least 14 (confirming depression) as opposed to 10% of controls. It is important that clinicians recognize the potential for enduring adverse sexual and psychological symptoms associated with finasteride. ■

Novel CV Risk Markers: How Much Cluck for the Buck?

Source: The Emerging Risk Factors Collaboration. *N Engl J Med* 2012;367:14: 1310-1320.

The c-reactive protein (CRP) debate has no end in sight. While traditional risk stratification tools like the Framingham Risk Score remain well established to distinguish high- and low-risk groups, the intermediate-risk group is the population in which further refinement in risk score might be helpful. Tools like CRP and fibrinogen, when applied to persons of intermediate Framingham risk, might help identify a subgroup that merits consideration for interventions like statins.

The Emerging Risk Factors Collaboration analyzed data from prospective cohort studies (n = 246,669) that included persons free of CV disease at baseline in whom CRP, fibrinogen, and components of Framingham risk score were available. Among persons with an intermediate Framingham risk score (10-20% risk of CV event over the next 10 years), the ad-

dition of either CRP or fibrinogen to risk assessment would result in reclassification of approximately 5% from intermediate to high risk. Such risk status elevation would justify statin treatment. According to current outcomes data, statin intervention in this population would prevent one CV event for every 440 intermediate-risk persons screened. Results were similar for fibrinogen.

The results obtained are "modeled" results rather than actual outcomes. CRP and fibrinogen testing are readily available. Yet, the number needed to test for avoidance of one CV event — more than 400 — is substantial. The authors do not offer an opinion on the *propriety* of such an investigation as CRP or fibrinogen; rather, they simply provide a metric to help quantify how much cluck for the buck one might anticipate. ■

Antidepressants and Auto Accidents

Source: Orriols L, et al. *J Clin Psychiatry* 2012;73:1088-1094.

DRIVING SIMULATION TESTS PERFORMED with *healthy, non-depressed volunteers* indicate varying degrees of deleterious effect on driving skills with tricyclics (TCA) and mirtazapine, but less so with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine. In direct contrast, but perhaps more pertinent to clinical medicine, trials of driving performance in *depressed patients* on antidepressants suggest better driving skills on SSRIs or mirtazapine than TCAs or venlafaxine. To gain more insight into the effects of antidepressant treatments on auto crashes, Orriols et al reviewed the database of accidents accrued by the French police force from 2005-2008 (n = 210,818).

Being on an antidepressant increased the odds ratio of being the at-fault driver by 34% compared with persons not on antidepressants. The immediate time period around initiation or change of treatment was particularly high risk. Subgroup analysis found the greatest risk among persons receiving serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) and the least risk among TCA recipients (e.g., amitriptyline). Even though driving simulation tests suggest that depressed patients who are being treated perform better than untreated patients, clinicians must still exercise vigilance and should consider informing patients — especially upon initiation of or change in treatment — about driving risks. ■

A Different Kind of Fish Story

Source: Rizos EC, et al. *JAMA* 2012;308:1024-1033.

THE IDEA THAT OMEGA-3 POLYUNSATURATED fatty acids — a.k.a. fish oil — are beneficial stems from *some* positive randomized clinical trials. But the word "some" is limiting in the previous sentence, since some other trials do not report benefit. Rizos et al performed a systematic review and meta-analysis based on 28 studies (n = 68,680) in which adults were treated with omega-3 fatty acids for primary or secondary prevention of cardiovascular disease.

Studies were reported between 1999-2010, and averaged 2 years of follow-up, although some data went as long as 6.2 years. The majority of trials were secondary prevention trials, which — because they represent a higher risk group — might be anticipated to more readily demonstrate risk reduction.

Contrary to popular opinion, this meta-analysis was unable to confirm any positive effects of omega-3 fatty acids, whether the metric was all-cause mortality, cardiac death, sudden death, MI, or stroke. Most of the trials used combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), leaving open the possibility that an EPA or DHA individually might have produced different results. The authors conclude that their data support neither the routine inclusion of omega-3 fatty acids in clinical practice nor guideline recommendations that advocate their use. ■

Risk of Cancer in RA Patients Treated with Disease-Modifying Drugs

Source: Lopez-Olivo MA, et al. *JAMA* 2012;308:898-908.

IN THE EARLY YEARS OF TREATMENT EXPERIence with biologic response modifiers (BRMs) for rheumatoid arthritis (RA), concern was raised that the immune-modulating effects responsible for dramatic symptomatic improvement might also lead to increased risk for cancer. Indeed, based on excess cases of lymphoma reported in the Adverse Event Reporting System database among children and adolescents treated with BRMs, the FDA recommended a warning label for all TNF-inhibitors. Should we be worried about cancer risk in patients treated with BRMs?

Lopez-Olivo et al performed a data analysis on randomized, controlled trials (n = 63 trials) of BRM treatment in RA patients in which a BRM was compared with placebo or another traditional therapy such as methotrexate (n = 29,423). A wide variety of BRMs was included in the analysis (e.g., abatacept, adalimumab, anakinra).

This dataset was restricted to trials with at least 6 months' duration. No signal for increased risk of cancer was discerned. Although a trend for increased risk of lymphoma was found, the numbers did not achieve statistical significance. It is not possible to determine whether longer-term outcomes in relation to BRMs will be impacted by cancer risk, since this dataset is comprised of studies of 3 years' duration or less. Additionally, whether RA patients who have already suffered a cancer are at greater risk of recurrence subsequent to BRM treatment is unknown. The dramatic RA disease remission we have come to commonly see thanks to treatment with BRMs appears to be safe from an increased risk for cancer. ■

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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.*

Menopausal Hormone Therapy and the Risk for VTE, AD

In this issue: Menopausal hormone therapy and risk of VTE and AD; patients' understanding of chemotherapy benefits; and FDA actions.

Hormone therapy and VTE risk

The different drug formulations of menopausal hormone therapy (HT) may determine the risk of venous thromboembolism (VTE), according to a new study. It is known that combined estrogen-progesterone therapy has a higher risk of VTE than estrogen-only therapy, and oral therapy has a higher risk than transdermal therapy. Now, a follow-up study from the Million Women Study with more than 3.3 million patient-years of follow-up looks at the varying risks of different HT combinations. The risk of VTE was again found to be significantly higher for combination estrogen-progesterone therapy compared to estrogen-only therapy (relative risks [RR] = 2.07 [95% confidence intervals (CI) 1.86-2.31] vs 1.42 [1.21-1.66]). Transdermal estrogen-only therapy resulted in no excess risk for VTE (RR 0.82 [0.64-1.06]). Among users of combination estrogen-progesterone, the risk of VTE varied by progestin type with significantly greater risk for preparations containing medroxyprogesterone compared to other progestins (2.67 [2.25-3.16] vs 1.91 [1.69-2.17]; *P* heterogeneity = 0.0007). The risk of VTE was significantly higher (2 times the risk) in the first 2 years after starting combination HT than later years. Five-year risks for pulmonary embolism (PE), both fatal and nonfatal, were calculated as: 1 in 664 for never users of hormone therapy, 1 in 475 for current users of oral estrogen-only, 1 in 390 for users of estrogen-progesterone containing norethisterone/norgestrel, and 1 in 250 for users of estrogen-progestin therapy containing medroxyprogesterone. The authors conclude that VTE risk varies considerably by HT formulation and is greatest in users of oral estrogen-progesterone therapy containing medroxyprogesterone. One case of PE could be avoided for every 1295 current users of oral HT if estrogen-only rather than estrogen-progesterone was used. Among combined HT users, one PE in 700 women could be avoided by use of a progestin other than medroxyprogesterone (*J Thromb Haemost* published online Sept. 10, 2012. doi: 10.1111/j.1538-7836.2012.04919.x). These data follow on the Women's Health Initiative, which also showed a higher risk of breast cancer for combination hormone replacement therapy vs estrogen-only therapy, but this risk is offset by the risk of endometrial cancer in women with an intact uterus on unopposed estrogen. ■

Hormone therapy and AD risk

Does the timing of menopausal HT affect the risk of Alzheimer's disease (AD)? Several studies have suggested the timing of postmenopausal HT is critical, especially during the first 5 years after menopause when hormones appear to be somewhat neuroprotective. The Women's Health Initiative (WHI) study clearly showed that starting HT after age 65 had no effect on cognition and in fact may be harmful. Now a new study confirms that starting HT immediately after menopause may have neuroprotective benefits. In a follow-up from the Cache

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County study, 1768 women provided a detailed history on age at menopause and use of HT between 1995 and 2006. During this interval, 176 women developed AD. Women who used any type of HT within 5 years of menopause were at 30% less risk of AD (95% CI, 0.49-0.99), especially if they used it for 10 years or more. By contrast, woman who started HT 5 or more years after menopause did not have a decreased rate of AD. Confirming the WHI findings, rates of dementia were nearly doubled among those who began combination estrogen-progesterone compounds later in life. The authors conclude that the association of HT and the risk of AD may depend on the timing of use. HT appears to be beneficial during the critical window near menopause, but may be associated with an increased risk if initiated later in life. (*Neurology* 2012;79:1846-1852). An accompanying editorial suggests that AD and coronary heart disease share common risk factors. WHI data show that women assigned to HT close to menopause had a reduction in the risk of coronary heart disease, whereas women given HT later in life had increased risk. The same seems to be true for the risk of AD. Two soon-to-be published studies will provide evidence regarding hormone effects on cognition in younger postmenopausal women (*Neurology* 2012;79:1840-1841). The decision to initiate HT in postmenopausal women is generally based on severity of symptoms, risk of breast cancer, risk of venous thromboembolic disease, and other factors. Benefits on cognition and potential protection against AD may now need to be added to the equation. ■

Chemotherapy often misunderstood

Chemotherapy for metastatic lung or colon cancer may provide palliation and prolongation of life by weeks or months, but a new study shows that most patients with these diseases erroneously think that chemotherapy is curative. Researchers studied nearly 2000 patients in the Cancer Care Outcomes Research and Surveillance study who were alive 4 months after diagnosis of stage IV lung cancer or colorectal cancer. All patients received chemotherapy. Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy "was not at all likely to cure their cancer." This misunderstanding about the benefits of chemotherapy was more prevalent among nonwhite and Hispanic patients as compared to non-Hispanic white patients (odds ratio [OR] for Hispanic patients 2.82, 95% CI, 1.51-5.25; OR black patients 2.93, 95% CI, 1.80-4.78). Patients who rated communication with their physician favorably also had a higher OR (1.90; 95% CI, 1.33-2.72). Educational level, functional status, and the patient's role in decision making were not associated with inaccurate beliefs about chemotherapy. The authors conclude that "many patients receiving chemotherapy for incurable cancers may not understand that chemotherapy is unlikely to be curative." This misunderstanding suggests that patients "have not met the standard for true ongoing informed consent" and may not accept toxic treatment with no reasonable hope of cure. The data also suggest that patients rate their doctors as better communicators if they are more optimistic. The authors suggest that honest communication is "a marker of quality of care" but may cause lower patient ratings (*N Engl J Med* 2012;367:1616-1625). ■

FDA actions

The FDA has approved a new drug for the treatment of chronic myelogenous leukemia (CML). Omacetaxine mepesuccinate is a protein translation inhibitor that was originally identified in the 1970s as a potential treatment for CML as well as other hematologic conditions and even solid tumors. It was eventually dropped from development as the tyrosine kinase inhibitors (TKIs) became the mainstay of therapy. Emerging resistance to imatinib and other TKIs has led to renewed interest in the drug. It was recently approved for chronic, accelerated, or blast-phase Philadelphia-chromosome-positive CML that is resistant or in patients who are intolerant of other therapies including TKIs. Approval was based on a study of patients in chronic or accelerated-phase CML who had been treated with two or more TKIs. Omacetaxine is administered by subcutaneous injection. It is marketed by Teva Pharmaceuticals as Synribo. It joins Pfizer's bosutinib (Bosulif), which also was recently approved for the same indication.

The FDA has approved perampanel as adjunctive treatment for partial onset seizures in patients 12 years of age and older. The drug is the first in its class of noncompetitive AMPA receptor antagonists that are taken orally once daily. Approval was based on data from three Phase 3 studies of nearly 1500 patients with partial-onset seizures which found that perampanel, when used as an adjunctive therapy with other anti-seizure medications, significantly reduced seizure frequency. The drug comes with a boxed warning regarding serious neuropsychiatric events including agitation, aggression, anxiety, paranoia, euphoria, anger, and irritably. Perampanel is marketed by Eisai Inc. as Fycompa. ■