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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Early Baldness is Associated with Prostate Cancer Development

By William B. Ershler, MD

SYNOPSIS: In a case-control study, patients with prostate cancer and matched controls were asked to recall whether they experienced male-pattern baldness by 20, 30, or 40 years of age. Prostate cancer patients were twice as likely to have alopecia at age 20 than controls. Early-age alopecia was not associated with early diagnosis of prostate cancer or with markers of disease aggressiveness. Thus, men with male-pattern baldness at age 20 may be at higher risk for the development of prostate cancer and perhaps more aggressive screening or other disease preventing interventions might prove beneficial for this population.

SOURCE: Yassa M, et al. Male pattern baldness and the risk of prostate cancer. *Ann Oncol* 2011;22:1824-1827.

Intuitively, one might expect an increased incidence of cancer among men with alopecia. Androgens, critical to the pathogenesis and progression of prostatic cancer, also are known to play a role in the development of male-pattern baldness.[1,2] Furthermore, finasteride, a type II 5-alpha reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone is used in the treatment of male-pattern baldness and has been shown to reduce the incidence of prostate cancer.[3,4] Nonetheless, the demonstration of an association of baldness with prostate cancer has been inconclusive. Some studies examined baldness at the time of diagnosis, and these generally were negative.[5,6] However, the onset of early-onset baldness might well be different. In one prospective study over approximately 20 years, men with male-pattern baldness had a 50% greater risk for developing prostate cancer.[7] In still another study, men who developed baldness by age 30 had close to a two-fold increase in the risk of cancer.[8] But in a more recent epidemiological study, Wright and colleagues found that subject recollection of baldness at the age of 30 was actually associated with reduced incidence of prostate cancer.[9]

In an effort to clarify this issue, Yassa and colleagues conducted a case-control study enrolling patients and matched controls, all of whom were asked to recall the presence or absence of hair loss

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Clinical Oncology [ALERT]

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at 20, 30, and 40 years of age. They were guided in their responses by pictures of various characteristic balding patterns.

The study revealed that patients with prostate cancer were twice as likely to have androgenic alopecia at age 20 (odds ratio [OR] 2.01, $P = 0.0285$). No specific pattern of hair loss was predictive for the development of cancer. There was no association between early-onset alopecia and an earlier diagnosis of prostate cancer or with the development of more aggressive tumors.

COMMENTARY

This was a well-conducted retrospective case-control study that relied heavily on patients' recollection of the onset of hair loss. The mean age of both subjects and controls was greater than 65 years, and for some, the accuracy of assessing their own hair loss at ages more than 4 decades earlier might be tenuous. That stated, prostate cancer patients had twice the risk of having shown evidence for male-pattern baldness at age 20 than did controls. Baldness first recognized at age 30 or beyond was not significantly associated with developing prostate cancer.

These days there is increased interest in disease prevention, and thus establishing risk factors is of more than passing interest. The data, and that accumulated from prior studies, support the conclusion that early-age male-pattern baldness is associated with later in life prostate cancer. Perhaps, as the authors suggest, this population might benefit from routine prostate cancer screening or systematic use of 5-alpha reductase inhibitors as primary prevention strategies. Such might be the subject of a valuable, but long-term, interventional trial. ■

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ABSTRACT & COMMENTARY

Bortezomib, Rituximab, and Dexamethasone for Relapsed Mantle Cell Lymphoma

By Andrew S. Artz, MD, MS
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Dr. Artz reports no financial relationships relevant to this field of study.

SYNOPSIS: Preclinical data suggest bortezomib and rituximab have synergy for mantle cell lymphoma (MCL). The authors studied bortezomib, rituximab, and dexamethasone in relapsed and refractory MCL using 1.3 mg/m^2 of bortezomib on days 1, 4, 8, and 11 with rituximab on day 1 and 40 mg of dexamethasone on days 1-4. Among 16 patients enrolled, 81% achieved a response for an overall survival (OS) of 12.1 months and progression-free survival (PFS) of 38.6 months. Seven (43.8%) reached complete response for whom median PFS and OS have not been reached. Grade 3 toxicity included thrombocytopenia (37.5%), fatigue (18.8%), and

peripheral neuropathy (12.5%). This combination has considerable activity in relapsed MCL and those reaching complete remission (CR) have prolonged disease control.

SOURCE: Lamm W, et al. Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma. *Haematologica* 2011;96:1008-1014.

Mantle cell lymphoma is an uncommon B-cell non-Hodgkin's lymphoma for which historical survival with cytotoxic chemotherapy alone (e.g., CHOP) has been poor. Prognosis can be stratified with the mantle cell index or follicular lymphoma international prognostic index (FLIPI).[1] Half of the patients fall into the high-risk FLIPI category for which 5-year survival is only 8%. Intensive therapy incorporating rituximab and high-dose chemotherapy followed by autologous stem cell rescue appears to enhance survival.[2] Still, many patients relapse and many other patients have health limitations or advanced age that precludes high-dose chemotherapy approaches.[3]

Bortezomib, a proteasome inhibitor, has been approved by the FDA for relapsed myeloma and relapsed MCL. Inhibition of transcription factor nuclear factor kappa–B (NF-KB) is a downstream consequence from proteasome inhibition and may reverse chemoresistance.[4] Preclinical data suggest bortezomib, rituximab, and dexamethasone may be a synergistic combination for MCL.[5] Thus, investigators explored the combination for bortezomib, rituximab, and dexamethasone (BORID) for relapsed MCL.

Inclusion criteria for this single-center Phase 2 study required patients to have relapsed MCL after at least one line of conventional chemotherapy. Bortezomib was given at 1.3 mg/m^2 on days 1, 4, 8, and 11 every 21 days. Rituximab at 375 mg/m^2 was administered on day 1 and oral dexamethasone at 40 mg on days 1 through 4 of each cycle. The median age of the 16 patients enrolled was 69 years. All patients had failed at least CHOP-based chemotherapy, 88% had received rituximab, and 33% had received a prior autologous transplant. Patients received a median of 4.4 cycles enabling an overall response in 13 of 16 (81%). Seven (43.8%) of these reached CR of whom six underwent PET scanning, which confirmed absence of metabolic activity in all. For five of seven reaching CR, the response has been maintained for more than 48 months.

The median PFS and OS were 12.1 months and 38.7 months. As expected, those who achieved a CR had substantially prolonged PFS and OS relative to those reaching only a partial remission (PR). The most common serious hematologic toxicity was grade 3 thrombocytopenia in 6 (37%). Other grade 3 and 4 toxicities included fatigue (18.8%), peripheral neuropathy (12.5%), and hypnonatremia (12.5%). Common grade 1 and 2 toxicities were infections (43.8%), peripheral neuropathy (43.8%), fatigue (25%), diarrhea (25%), and skin toxicity (18.8%).

COMMENTARY

This study showed a high overall response rate of 81% to bortezomib, rituximab, and dexamethasone for relapsed and/or refractory MCL in a single-center study of 16 patients. The overall rate of CR was 43.8%. Prior data suggest a CR rate of 8% to bortezomib alone and only partial responses to rituximab monotherapy.[4,6] Therefore, the CR rate appears promising. The longer PFS and OS for those achieving CR is expected; the observation that five of seven patients achieving CR maintained response after 48 months provides additional support for this being a highly active regimen. Other trials have also shown high response rates to bortezomib combinations for MCL.[7] As a consequence, bortezomib is now being studied in upfront trials for MCL.

[Preclinical data suggest bortezomib, rituximab, and dexamethasone may be a synergystic combination for MCL.]

The toxicities of the regimen were expected for a bortezomib-based regimen and primarily consisted of thrombocytopenia, fatigue, and neuropathy. A recent trial of bortezomib and rituximab for follicular and MCL reported 52% with grade 3 neurotoxicity but the bortezomib dose was higher at 1.5 mg/m^2.[8]

The limitations are as expected from a small Phase 2 trial. As relapsed MCL is not common, any single-center study will be limited by small sample size. Of note, only one-third underwent an autologous transplant. The median age was 69 years and it is likely that some of the candidates

for this trial could have proceeded to autologous transplant if not allogeneic transplant. One cannot confidently establish the true response rate or toxicity profile in a small Phase 2 study.
In summary, bortezomib, rituximab, and dexamethasone is an active combination for relapsed or refractory MCL. Bortezomib-based combination therapy continues to be explored at relapse and as initial therapy. ■

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ILLUSTRATIVE CASE SERIES

Ductal Carcinoma in Situ

By Jerome Yates, MD

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

A 57-year-old, postmenopausal African American schoolteacher was found by annual screening mammogram to have a suspicious irregularity. Follow-up ultrasound did not reveal cystic disease so a repeat "spot" mammogram-assisted biopsy was obtained and a grade 1 invasive ductal carcinoma with tubular elements was found. A lumpectomy was performed confirming these results, but in addition there were elements consistent with non-contiguous ductal carcinoma in situ (DCIS). The carcinoma was 0.7 x 1 cm in size and surgical margins were > 1 cm. A sentinel node biopsy was negative and the tumor was ER+, PR+, and Her2Neu-. Subsequent discussions included the rationale for different treatment options, including bilateral mastectomy with reconstruction, whole breast radiation to the involved breast, and adjuvant chemotherapy and/or anti-estrogen therapy. The most critical issue discussed was the question of bilateral mastectomy or whole breast radiation in light of the DCIS. Subsequent systemic therapy was expected.

Case Discussion

There has been a significant increase in the diagnosis of DCIS since the widespread application of screening mammography. Although this patient demonstrates the coexistence of invasive breast cancer (IBC) and DCIS, population studies have raised questions about the progression of all DCIS to IBC.[1] If a large portion of the patients with DCIS progressed to IBC in months to a few years, there would be a major increase in the incidence (new cases) of IBC. The SEER data reflect both an increase in new cases of localized IBC and DCIS since about 1985. Even though the detection and treatment of DCIS has increased dramatically since that time, there has not been a concomitant decrease in IBC, suggesting that either the progression of DCIS occurs in a small number of cases or that the time period for the evolution of IBC from DCIS is much longer than even a period of 5 or 10 years. Mortality from IBC is low among women diagnosed with DCIS with a range of 1% to 2.6% in the 10 years following diagnosis.[2] Treatment for DCIS is aggressive: surgery that often is disfiguring, radiation that carries some long-term risks, and the expense and inconvenience of adjuvant hormonal therapy. Just as the need for sub-classifying IBC is driving many laboratories and statisticians to find a molecular signature for indolent, intermediate, and aggressive disease to minimize iatrogenic treatment complications while maximizing treatment for aggressive disease, the same principle holds for the pursuit of a better understanding of the biology of DCIS.

Our understanding of the biology of breast cancer, relevant prognostic variables, and the hazards

of overtreatment took us from the Halstead era through the urban ultra-radical mastectomy period and into the subtraction (less surgery) and addition (chemotherapy) phase that we are all familiar with today. Clinical trials conducted by the NSABP, including B-17 and B-24, have provided insight into the importance of radiation and hormonal therapy following breast conserving surgery.[3] There is evidence from randomized trials that radiation following breast-conserving therapy for DCIS will reduce the local recurrence by 53% to 70%.[4,5] The absolute reduction in the local recurrence from 5 years of tamoxifen administration is in the range of 2%-4% and, considering the vagaries of DCIS progression to IBC, may not be justified or accepted by the patients.

The study of DCIS characteristics as indicators of local recurrence following therapy include comedonecrosis (cell ghosts that attract calcium producing the flecks of density on mammograms), focality, surgical margins, method of detection, and tumor grade and size.[6] These clinical indicators will be refined and supplemented with statistical precision and augmented by new molecular predictors of DCIS that will progress to IBC. The stratification of patients in studies of therapeutic approaches will improve our understanding of the merits of treatments. It is hoped this will lead to less aggressive interventions promoting quality-of-life issues in a disease that is being overtreated presently.

After discussions with her physician and her family, this patient elected not to have bilateral mastectomy followed by reconstruction, but instead whole breast radiation followed by mammograms every 6 months for the first 2 years. In light of our current understanding of DCIS, this seems like a rational approach. ■

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ABSTRACT & COMMENTARY

First-Line NSCLC with Erlotinib: Effective, but not for Everybody

By William B. Ershler, MD

SYNOPSIS: In a multicenter randomized (not blinded) Phase 3 study of erlotinib vs chemotherapy for EGFR-mutation positive non-small cell lung cancer (NSCLC), progression-free survival was both significantly greater and toxicity less for patients treated with erlotinib. The findings suggest that erlotinib should be considered first-line therapy for patients with advanced EGFR mutation-positive NSCLC.

SOURCE: Zhou C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomized, phase 3 study. *Lancet Oncol* 2011;12:735-742.

Non-small cell lung cancer (NSCLC) is the number one cause of cancer-related death worldwide.[1] The majority of patients present with advanced disease and systemic chemotherapy remains only marginally effective at prolonging life. Recently, attention has focused on targeted therapies including the tyrosine kinase inhibitors (TKI) gefitinib (Iressa®) and erlotinib (Tarceva®). It is now understood that a subset of patients with NSCLC will have tumors with activating mutations in the EGFR gene (i.e., exon 19 deletions or exon 21 L858R point mutations) and such patients are more likely to achieve benefit from treatment with TKI therapy.[2,3] Activating EGFR mutations are more commonly observed in tumors with adenocarcinoma histology, in non-smokers, in older patients, in females, and in Asians.[4,5] However, using these clinical characteristics alone as selection criteria for demonstrating improved activity has not resulted in significant improvement in outcomes.[3] Accordingly, there has been an increased emphasis on accurate EGFR testing in order to enrich the study population for demonstrating efficacy of TKI therapies. With this aim, a group of oncologists throughout China designed the OPTIMAL study

which compared the efficacy and tolerability of erlotinib vs standard chemotherapy in the first-line treatment of patients with advanced EGFR mutation-positive NSCLC.

For this, the investigators conducted an open-label, randomized, Phase 3 trial at 22 centers in which they enrolled adult patients with histologically confirmed stage IIIB or IV NSCLC and a confirmed activating mutation of EGFR (exon 19 deletion or exon 21 L858R point mutation). Such patients were randomized to receive either oral erlotinib (150 mg/day) until disease progression or unacceptable toxic effects, or up to four cycles of gemcitabine plus carboplatin, considered the standard doublet therapy for such patients throughout China. Gemcitabine was given at 1000 mg/m^2 on days 1 and 8 and carboplatin at area under the curve of 5 on day 1 of each 3-week cycle. The randomization was conducted in such a way to balance for EGFR mutation type, histological subtype (adenocarcinoma vs non-adenocarcinoma), and smoking status. The primary outcome was progression-free survival and secondary outcomes included overall survival, objective response rate, time to progression, response duration, safety, and quality of life.

Of the 165 randomized patients, 83 patients were assigned to receive erlotinib and 82 to receive gemcitabine plus carboplatin. The median progression-free survival was significantly longer in erlotinib-treated patients than in those on chemotherapy (13.1 vs 4.6 months [$P < 0.0001$]). As expected, chemotherapy was associated with more grade 3 or 4 toxic effects than was erlotinib (including neutropenia in 30 [42%] of 72 patients and thrombocytopenia in 29 [40%] patients on chemotherapy vs no patients with either event on erlotinib). The most common grade 3 or 4 toxic effects with erlotinib were increased alanine aminotransferase concentrations (three [4%] of 83 patients) and skin rash (two [2%] patients). Erlotinib appeared to demonstrate superiority over chemotherapy independent of patient age, sex, smoking history, tumor histology, or mutation type. Furthermore, patients who received erlotinib had a significant improvement in quality of life. The data from the trial were not mature enough to determine any treatment-associated improvement in overall survival.

COMMENTARY

Thus, compared with standard chemotherapy, erlotinib conferred a significant progression-free survival benefit in patients with advanced EGFR mutation-positive NSCLC and was associated with less toxicity and improved quality of life. The trial was the first Phase 3 study of erlotinib for mutation positive NSCLC and the results coupled with prior Phase 2 studies of both gefitinib and erlotinib and preliminary results from a Phase 3 trial of erlotinib vs. chemotherapy for mutation positive NSCLC should be sufficient for clinicians to take notice. It is clear now that clinicial parameters (non-smoker, female, adenocarcinoma histology) are not sufficiently reliable to support this alternative approach to chemotherapy and molecular testing is required. However, pathologists are now prepared to assess tissue for EGFR mutations and if present in the appropriate domains (e.g., exon 19 or 21) initial therapy should be with a tyrosine kinase inhibitior. The evidence is now in. Yet, the majority of NSCLC patients, even in China, are those without these mutations. Hopefully, new targets will be identified within larger subsets of NSCLC allowing for more widespread applicability of effective targeted therapy. ■

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ABSTRACT & COMMENTARY

Risk of Developing Brain Metastases in Patients with Metastatic Breast Cancer

By William B. Ershler, MD

SYNOPSIS: In a retrospective analysis of risk factors for the development of cerebral metastases in patients with known metastatic breast cancer, several factors including ER, HER-2, patient age, and site of first metastatic recurrence were found to be predicted. Using a cumulative incidence model employing competing-risk regression

analysis, small initial tumor size, and the absence of metastatic disease at the time of diagnosis appeared to be independent risk factors.

SOURCE: Heitz F, et al. Cerebral metastases in metastatic breast cancer: Disease-specific risk factors and survival. *Ann Oncol* 2011;22:1571-1581.

For patients with existing metastatic disease from primary breast cancer, the new development of cerebral metastases (CM) predicts shortened survival.[1] For all patients with newly diagnosed, operable breast cancer, the likelihood of developing CM is approximately 5%,[2] but for all those who develop metastatic disease at sites other than the brain, the subsequent development of CM is considerably higher, ranging from 10%-42%.[3,4] Thus, the identification of those at high risk for developing CM is warranted not only to adjust follow-up care but also for the investigation of preventive strategies. For example, with small cell lung cancer, a disease in which there is a high risk for the development of CM, prophylactic whole brain irradiation has been shown to reduce the occurrence of brain metastases and prolong survival.[5]

To identify risk factors associated with the development of CM in patients with metastatic breast cancer, Heitz and colleagues from Wiesbaden, Germany, performed a retrospective analysis of their institution's experience with CM occurring in patients with known metastatic disease. Their analysis, which included 668 patients with metastatic breast cancer treated between 1998 and 2008, examined cumulative incidences and employed multivariable regression analyses.

Of the 668 patients with metastatic disease, 49 were excluded for a variety of reasons but primarily because they presented with CM as their initial metastatic site. Of the remainder, 69% presented with a single metastatic site, bone being most common. The median follow-up for all patients was 10.8 years from diagnosis of breast cancer and 4.0 years from the first distant metastasis. The median distant-disease-free survival (DDFS) was 2.2 years. Of the 626 patients, 66 (11%) developed CM whereas 320 (51.1%) had died without known CM. Thus, there were 240 patients who had not developed CM and had not died.

Within this population of women with metastatic breast cancer, the estimated probability for CM was 5%, 12%, and 15% at 1, 5, and 10 years. In contrast, the probability of death without CM was 21%, 61%, and 76%, respectively at those same time points. In univariate analysis a number of factors were associated with the development of CM. These included small primary tumor size, ER and HER2 status, ductal histology, lung and lymph node metastases, younger age, and initial M0 status. Of these, only HER2, initial M0 status, and younger age proved independent predictors by multivariate analysis. As expected, for patients with metastatic breast cancer, survival was shorter for those who developed CM (24 months) compared to those with no CM (33.6 months).

COMMENTARY

This is a retrospective analysis from a single institution, subject to the usual biases of this type of review. However, the sample size is substantial and the results generally confirm earlier reports from smaller series,[4,6,7] which more or less suggested the importance of ER, HER2 status, young age, and the presence of lung metastases in predicting the occurrence of CM. The value added in the current report is by virtue of the statistical methodology undertaken including cumulative-incidence and competing risk-regression analysis.[8] This method accounts for the large portion of patients with aggressive but non-cerebral metastatic disease resulting in death before CM would have become apparent. Thus, the subset of patients who presented with smaller tumors, and particularly those who were M0 at the time of initial diagnosis, once diagnosed with distant metastases were at greater risk for developing CM.

It is by no means settled that preventive strategies to reduce CM would prolong life or even prevent the occurrence of brain metastases in high-risk breast cancer. In fact, there are at least two trials employing prophylactic whole brain irradiation in HER-2 positive patients that currently are underway. The current report would suggest that other risk factors might be examined to define those breast cancer patients who might benefit from similar intervention. ■

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CME Questions

9. Male-pattern baldness at 20 years of age was shown by Yassa and colleagues to be:

a. associated with early-onset of prostate cancer.
b. associated with more aggressive prostate cancer.
c. associated with higher incidence of prostate cancer.
d. not associated with prostate cancer development or aggressiveness.

10. What was observed for bortezomib, rituximab, and dexamethasone combination therapy for relapsed or refractory mantle cell lymphoma (MCL)?

a. Complete remission was achieved in around 43% of patients, most of whom had prolonged progression-free survival.
b. Neuropathy was limited to grade 1 or 2.
c. Only patients who underwent allogeneic hematopoietic cell transplant lived for more than 2 years.
d. Most patients could only tolerate two cycles of therapy.

11. Regarding the OPTIMAL study comparing erlotinib to gemcitabine/carboplatin as first line therapy for patients with EGFR mutation-positive non-small cell lung cancer, which of the following outcomes was NOT observed?

a. Prolonged progression-free survival for the erlotinib treated group.
b. Better quality of life for the erlotinib treated group.
c. Prolonged overall survival for the erlotinib group.
d. More treatment-related toxicity in the chemotherapy group.

12. In univariate analysis, which of the following factors was NOT associated with the development of cerebral metastases among breast cancer patients with known metastatic disease elsewhere?

a. ER negative status
b. HER-2 positive status
c. Large primary tumor
d. Younger age at diagnosis
e. Metastatic disease within the lung

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
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[IN FUTURE ISSUES]

Bendamustine as first-line lymphoma therapy

PHARMACOLOGY WATCH

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ACEIs and ARBs Help Patients with Aortic Stenosis

In this issue: ACEI/ARB therapy for AS; safety alert issued for dronedarone; statins and cancer risk; nesiritide and heart failure; and FDA actions.

ACEI/ARB therapy for aortic stenosis

Drugs that block the renin-angiotensin system are not only safe, they are beneficial in patients with aortic stenosis (AS) according to a new study. This runs counter to current recommendations that suggest that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are relatively contraindicated in patients with AS. The study looked at more than 2000 patients with AS in Scotland, of which the majority had mild-to-moderate stenosis, while about one-quarter had severe AS. Of the total number, nearly 700 were on ACEI or ARB therapy. Over a mean follow-up of 4.2 years, just over half the patients died, of which 48% died from cardiovascular (CV) deaths. Those treated with ACEIs or ARBs had a significantly lower mortality rate (adjusted hazard ratio [HR] 0.76; confidence interval [CI] 0.67-0.92; $P < 0.0001$) and fewer CV events (adjusted HR 0.77; 95% CI: 0.65-0.92; $P < 0.0001$) compared to those not on ACEIs/ARBs. The authors conclude that ACEI/ARB therapy is associated with improved survival and lower risk of CV events in patients with AS. These findings were consistent in patients with nonsevere and severe AS. The rate of valve replacement also was lower in patients treated with ACEIs/ARBs (*J Am Coll Cardiol* 2011;58:570-576). This study was a retrospective observational study and prospective, randomized, controlled trials are warranted to confirm these findings. ■

Drug safety alert issued for dronedarone

The antiarrhythmic dronedarone (Multaq) is again coming under scrutiny from the FDA after review of the company-sponsored PALLAS study of more than 3000 patients, which showed that the drug is associated with an increased mortality rate in patients with atrial fibrillation (AF). Dronedarone currently is approved for treatment of paroxysmal AF and atrial flutter. The new study investigated its use in patients with permanent AF. The study was halted early when the mortality rate in the treatment group was found to be double the rate in the placebo group (32 deaths [2%] in the dronedarone arm vs 14 [0.9%] in the placebo arm). The rate of unplanned hospitalization and stroke also was double in the dronedarone group vs the placebo group. All findings were statistically significant. These findings led the FDA to issue a drug safety alert on July 21, 2011. This follows a January 2011 drug safety alert regarding rare but severe liver injury associated with use of dronedarone. Currently, the FDA is recommending that physicians should not prescribe dronedarone to patients with permanent AF while they further evaluate the data (FDA Drug Safety Communication at www.FDA.gov/drugs/drug safety). ■

Statins do not increase risk of cancer

A new retrospective cohort analysis suggests that statins are not associated with an increased risk of cancer. Researchers used the General

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Electric Centricity electronic medical record database of more than 11 million adult Americans to match nearly 46,000 patient pairs by propensity scores receiving and not receiving statin therapy. With an average time in the database of 8 years, the incidence of cancer in patients taking a statin was 11.37% compared with 11.11% in matched patients not taking a statin (HR 1.04; 95% CI: 0.99-1.09). The authors conclude that this analysis demonstrates no statistically significant increase in cancer risk associated with statins, although they do suggest that more research is needed (*J Am Coll Cardiol* 2011;58:530-537). Lingering fears about cancer risk associated with statins was strengthened by the SEAS trial published in 2008, which showed the combination drug simvastatin/ezetimibe (Vytorin) was associated with a two-fold increase in the rate of cancer in a small group of patients. The FDA has continued to study these data along with data from other studies, but this new analysis adds significant evidence of a lack of association between statins and cancer. ■

Nesiritide and heart failure

Nesiritide can no longer be recommended for use in congestive heart failure based on the findings of a new study. The drug is a recombinant B-type naturetic peptide (BNP) that was approved in 2001 for use in patients with acute heart failure. The approval was based on small studies showing a reduction in pulmonary capillary wedge pressure and improvement in dyspnea 3 hours after administration. However, subsequent data raised questions about the drug's safety, especially with regard to worsening renal function and even increased mortality. Based on the recommendations of an independent panel, the manufacturer performed a placebo-controlled randomized trial of more than 7000 patients hospitalized with acute heart failure to assess the drug's safety and efficacy. Patients with heart failure were randomized to receive nesiritide or placebo for 24-168 hours in addition to standard care. The drug was modestly effective at reducing symptoms of dyspnea at 6 and 24 hours. More significantly, however, the rate of rehospitalization for heart failure or death from any cause within 30 days was no different. Nesiritide was not associated with a worsening of renal function but was associated with worsening hypotension. The authors conclude that on the basis of these results, "nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure" (*N Engl J Med* 2011;365:32-43). ■

FDA actions

The highly anticipated oral factor Xa inhibitor rivaroxaban has been approved by the FDA to reduce the risk of deep venous thrombosis, blood clots, and pulmonary embolism in patients undergoing knee or hip replacement. The once-a-day medication should be taken for 12 days by patients undergoing knee replacement and 35 days for patients undergoing hip replacement. The approval was based on three studies (RECORD 1, 2, and 3) which showed that rivaroxaban is superior to subcutaneous enoxaparin in this role. Bleeding, the primary side effect of the drug, was no more common with rivaroxaban than enoxaparin. Rivaroxaban also has been looked at in phase III trials for stroke prevention in patients with nonvalvular atrial fibrillation, and treatment and secondary prevention of venous thromboembolism, although the FDA has yet to act on approval for these indications. Rivaroxaban was developed by Bayer and is marketed by Janssen Pharmaceuticals as Xarelto.

The FDA has approved ticagrelor, a new antiplatelet drug for patients with acute coronary syndrome, including unstable angina and myocardial infarction (MI). The approval was based on studies that coupled ticagrelor with low-dose aspirin. The approval recommends use with aspirin although it carries a warning that aspirin doses above 100 mg per day may decrease the effectiveness of the drug. Ticagrelor requires twice a day dosing in contrast to the other drugs in this class, clopidogrel and prasugrel, which can be dosed once daily. The approval was based on the PLATO trial, a head-to-head study with clopidogrel which showed that in combination with aspirin, ticagrelor resulted in the lower composite endpoint of cardiovascular death, stroke, or MI (9.8% vs 11.7% with clopidogrel, $P < 0.001$).

The FDA has approved six manufacturers for the 2011-2012 flu vaccine. The strains included this year are A/California7/09 (H1N10), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 — the exact same components as last year's vaccine. One of the manufacturers, Sanofi Pasteur, has received permission to market Fluzone Intradermal, the first flu vaccine administered via a novel intradermal microinjection that is touted as being more comfortable than intramuscular injections. The new intradermal system in approved for adults ages 18-64 years. ■