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Clinical Oncology [ALERT]

A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Adolescent Use of Tanning Salons and Melanoma Risk

By William B. Ershler, MD

SYNOPSIS: The use of sunlamps or sunbeds for tanning purposes has grown in popularity, such that their use is very common among teenagers and young adults. In a well-conducted Australian multicenter, case-controlled study, it is clear that such use among teenagers is associated with a significantly higher risk of cutaneous melanoma. In fact, the risk is higher than it is for middle-aged sunbed users.

SOURCE: Cust AE, et al. Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. *Int J Cancer* 2011;128:2425-2435.

It previously has been reported that artificial tanning, for example by use of sunlamp or sunbed such as one might find at a tanning salon, is associated with an increased risk of melanoma. Previously, a meta-analysis of 19 studies revealed that ever-use of sunbeds was associated with 15% increased risk of melanoma compared with never having used a sunbed.[1] There has been concern about the common use of such equipment among adolescents and young adults, estimated to be 20%-40% in these age groups in the United States,[2,3] and whether this is associated with melanoma occurring in younger age groups.

To address the question of whether younger people are more susceptible to the carcinogenic effects of UV radiation, Cust and colleagues from three major centers in Australia investigated the association between sunbed use and risk of early-onset cutaneous malignant melanoma. For this study, they capitalized on data available within the Australian Melanoma Family Study, a multicenter, population-based, case-control family epidemiologic study.[4] They analyzed data from 604 cases diagnosed between ages 18 and 39 years and 479 matched controls. Data were collected by interview. Associations were estimated as odds ratios (ORs) using unconditional logistic regression, adjusting for age, sex, city, education, family history, skin color, usual skin response to sunlight, and sun exposure.

Compared with having never used a sunbed, the OR for melanoma associated with ever-use was 1.41 (95% confidence interval [CI] 1.01-1.96) and 2.01 (95% CI 1.22-3.31) for more than 10 lifetime sessions (*P* trend 0.01 with cumulative use). The association was stronger for earlier age at first use

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Clinical Oncology [ALERT]

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(*P* trend 0.02). The association also was stronger for melanoma diagnosed when aged 18-29 years (OR for more than 10 lifetime sessions = 6.57, 95% CI 1.41-30.49) than for melanoma diagnosed between the ages of 30-39 years (OR 1.60, 95% CI 0.92-2.77; *P* interaction 0.01). Among those who had ever used a sunbed and were diagnosed between 18-29 years of age, three-fourths (76%) of melanomas were attributable to sunbed use.

COMMENTARY

Melanoma occurs with increased frequency in middle-aged and older people. The median age at diagnosis is 60 years.[5] Yet, this disease remains among the leading causes of cancer deaths in young adults.[5] Although the association with UV radiation exposure has been well established, this is the first report examining the risk of early-onset melanoma with sunbed use. It was unknown whether the risks were greater for those exposed early in life compared with those with similar sunbed use in middle-age and whether early use was associated with early-onset melanoma (i.e., before the age of 40 years). The data presented demonstrate that adolescent sunbed use is associated with increased risk of early-onset melanoma and that the risk increases the earlier one starts and with greater use. Furthermore, there is greater risk of melanoma when the first use is at an earlier age and that risk increases with greater use. The popularity of tanning salons, particularly among adolescents, should raise high concerns among public health agencies and the medical community at large. ■

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ABSTRACT & COMMENTARY

The Relevance of FLT3 in APL

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

SYNOPSIS: The prognostic relevance of fms-like tyrosine kinase 3 (FLT3) internal tandem duplications and point mutations at D835 in acute promyelocytic leukemia (APL) is controversial. Among APL patients treated with ATRA and anthracycline-based regimens on serial protocols, 22% of 306 patients harbored an internal tandem duplication (ITD) mutation and 9% of 213 evaluable had a D835 mutation. FLT3 ITD mutational status was associated with higher white blood cell count, microgranular variant of APL, and high blast count. In unadjusted analysis, the presence of a FLT3 ITD mutation but not D835 mutation conferred a greater risk of induction death, and inferior relapse-free and overall survival. However, after adjusting for high white blood cell count and other traditional prognostic factors, mutational status was not statistically associated with outcomes. FLT3 mutational status does not retain independent significance for APL outcomes, although it is a rational target for future studies, particularly among the high white blood cell count APL subset.

SOURCE: Barragan E, et al. Prognostic value of FLT3 mutations in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy. *Haematologica* 2011 [Epub ahead of print].

Acute promyelocytic leukemia (APL) is a prognostically and therapeutically distinct category of acute myeloid leukemia (AML) resulting from a rearrangement of the PML and RAR-alpha genes, usually generating the

t(15;17)(q22;q12) classic breakpoints. Variant breakpoints may occur. High white blood cell count (> 10 K/uL) and thrombocytopenia (< 40 K/uL) are adverse prognostic factors. Whether additional markers can better stratify patients or suggest therapeutic targets is of considerable interest.

FLT3 (fms-like tyrosine kinase 3) mutations, particularly internal tandem duplications (ITD), confer an inferior prognosis for patients with normal karyotype AML.[1] The adverse impact of FLT3 point mutations arising from the activation loop at D835 may be less significant for outcomes. FLT3 mutations are not uncommon in acute promyelocytic leukemia (APL);[2] however, the prognostic value of FLT3 mutational status remains controversial.[3]

In this study, the authors take advantage of a large cohort of 739 APL patients enrolled in various trials employing oral ATRA and anthracyclines for remission with different combinations of anthracyclines and other drugs for maintenance. FLT3 mutational analysis was available in 306 (41%) for ITD mutations and 213 (29%) for the D835. The authors also evaluated FLT3 ITD mutation length. Among evaluable patients, 22% showed an FLT3 ITD mutation and 9% harbored the D835 mutation. Only one patient had both mutations. FLT3 ITD mutations were clinically associated with leukocytosis, high LDH, microgranular variant as well as peripheral blood and bone marrow blasts greater than 70%, whereas the point mutation was not associated with clinical characteristics.

FLT3 ITD was associated with a greater proportion suffering induction death (16% vs 7%, $P = 0.03$) and differentiation syndrome (22% vs 13%, $P = 0.05$). Multivariate analysis revealed high white count, age 60 and older, or creatinine greater than 1.4 mg/dL as risk factors for induction death. The D835 mutation did not affect induction outcomes. FLT3 ITD, but not the point mutation, showed inferior 5-year relapse-free survival (77% for ITD mutation vs 88% without, $P = 0.02$). However, in multivariable analysis, only high WBC was associated with worse RFS but not FLT3 mutational status or ITD mutation length. Overall survival was shorter for FLT3 ITD mutation patients at 5 years but not D835 mutation-carrying patients. Multivariate analysis only showed that high WBC above 10 K/uL and age older than 60 translated into worse outcomes. Thus, FLT3 mutational status was not independently significant.

COMMENTARY

APL is a relatively uncommon category of AML, but it is essential to diagnose and initiate treatment early to reduce complication rates and potentially improve curability. All oncologists must be aware of APL and be prepared for rapid diagnosis and either immediate treatment or transfer to another facility.

The need to evaluate newly diagnosed AML for molecular abnormalities has increasingly become appreciated. This has not necessarily been standard for APL, which often presents with characteristic morphology and the ability for rapid confirmation either with PCR or FISH studies. In this study, the authors were able to evaluate more than 300 APL patients for FLT3 ITD mutations and more than 200 for D835 point mutations. The incidence of FLT3 ITD mutations and D835 point mutations at 22% and 9% approximates prior studies on the prevalence of FLT3 mutations at diagnosis. Whether the mutation rate differs at relapse

[The need to evaluate newly diagnosed AML for molecular abnormalities has increasingly become appreciated.]

requires further study, as FLT3 generally is thought to be a late-acquired event in leukogenesis.[4]

The authors demonstrated nicely that FLT3 ITD mutations, but not D835 mutations, are associated with numerous clinical features, including leukocytosis, high blast count, coagulopathy, and certain immunophenotypic markers. The most noteworthy findings were that while ITD mutations were associated with greater rates of induction death, inferior relapse-free survival, and worse overall survival, FLT3 ITD mutational status did not retain significance in multivariate analysis whereas high white blood cell count did. The data contrast somewhat with prior studies, suggesting an adverse prognosis of FLT3 ITD and possibly point mutations.[2,3,5]

To the extent this series is larger and employed multivariate analyses, these data are more likely to be valid. This is an important negative study indicating we should retain leukocytosis and thrombocytopenia rather than FLT3 mutational status into prognostic assessment. Nevertheless the link between FLT3 ITD mutation and high white blood cell count, as has been seen with FLT3 mutational status in non-APL AML, suggest targeted therapy inhibiting the FLT3 tyrosine kinase

represents a rational approach, particularly among FLT3 ITD mutated patients with a high white blood cell count, as high white blood cell count results in suboptimal long-term outcomes.

In conclusion, FLT3 ITD and point mutations do not retain independent prognostic significance among APL patients treated with ATRA and anthracyclines. However, the association of FLT3 ITD mutations and high white blood cell count suggest FLT3 inhibitors could be tested in this subset. ■

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ILLUSTRATIVE CASE SERIES

Glioblastoma

By Samir Kanani, MD

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

A 78-year-old man was referred for evaluation and treatment of recently discovered glioblastoma. While dining with his children he collapsed from his chair and was observed to have a grand mal seizure. He had transiently lost consciousness and when he awoke he had weakness in both upper and lower extremities on the right side.

Past medical history is significant for long-term cigarette smoking, chronic obstructive pulmonary disease, hypertension, mild congestive heart failure, and type II diabetes mellitus.

He was taken to the emergency room where he was found to be slightly disoriented but awake. Blood pressure was 180/80, pulse 93/min, and respiratory rate 16/min. Oxygen saturation was 94% on room air. His chest was clear to auscultation and heart sounds were regular with an S4 gallop but no murmur. Neurologic exam revealed prominent right-sided weakness and slight facial asymmetry with weakness on the left. An MRI of the brain and spine revealed an enhancing solitary tumor mass of approximately 2 cm in diameter in the left prefrontal region with moderate surrounding edema. The patient was admitted and on the following day an open biopsy revealed a high-grade glioblastoma.

CASE DISCUSSION

In general, gliomas account for 60% of all central nervous system (CNS) malignancies and glioblastoma (GBM) is the most prevalent subtype of gliomas. Presenting symptoms of GBM are variable and depend on the location of the lesion. Seizures, headaches, nausea, vomiting, hemiparesis, personality change, and memory difficulties are the most common symptoms of CNS malignancies.

GBM can be classified into two general categories: primary and secondary. In this age group of patients older than 50, primary GBMs account for the vast majority of tumors. Although primary GBMs develop de novo over a few months, secondary brain tumors develop over years through malignant transformation of lower grade gliomas. Genetically, primary and secondary tumors develop from unique genetic pathways. Recent gene expression profiling has focused on identifying four subtypes of GBM: classical, mesenchymal, proneural, and neural.[1] The use of genetic profiling in clinical practice currently remains experimental and is the subject of a number of current clinical trials.

No formal staging system exists to assist in managing patients with GBM; however, well-known prognostic factors can be applied to stratify patients for prognostic purposes and to assist in treatment decisions. Through recursive partition analysis (RPA), various prognostic groups can be identified. Two well-known and widely used RPAs are the RTOG[2] and the EORTC.[3] Age, performance status, neurologic status, and extent of surgery provide the backbone for defining

RPA class. The RTOG RPA stratifies patients into prognostic groups based on studies where all patients were treated with radiation. The EORTC stratifies patients based on the landmark Stupp trial where patients received a combination of temozolomide and 6000cGy radiation followed by adjuvant temozolomide.[4] The above patient with age > 50 years, ECOG 4 (bedridden), significant neurologic symptoms (hemiplegia), and post-biopsy alone, falls in RPA class V. According to both of the well-known RPAs, class V has the most dismal prognosis of 9-10 months with or without chemotherapy. I would not recommend chemotherapy in this patient based on the lack of any significant benefit in this RPA class. Radiation therapy alone or supportive care should be discussed with the patient. If the patient agrees to radiation therapy, serious consideration should be made for a short course or hypo-fractionated course of radiation therapy rather than the standard course of 6000cGy in 30 fractions. A randomized trial comparing the standard course of radiation to 4000cGy in 15 fractions in this patient population found no difference in median survival.[5] The issues of transportation can be difficult in patients with significant neurologic complications; therefore, all patients should be given a realistic expectation of the results from radiation, and consultation with palliative care or hospice care should be initiated early in the process. ■

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ABSTRACT & COMMENTARY

Colorectal Cancer in Younger Patients: Any Difference?

By William B. Ershler, MD

SYNOPSIS: In a review of nine Phase 3 trials enrolling 6,284 patients, data from 793 who were younger than 50 years old were compared to the remainder who were older than 50 years, with attention given to progression-free survival, response rates, and overall survival. Although there was a slightly reduced progression-free survival in younger patients, response rates and overall survival were not statistically different. A failure to demonstrate altered responses in the very young may be a reflection of age-associated variability in enrollment onto clinical trials.

SOURCE: Blanke CD, et al. Impact of young age on treatment efficacy and safety in advanced colorectal cancer: A pooled analysis of patients from nine first-line phase III chemotherapy trials. *J Clin Oncol* 2011;29:2781-2786.

Colorectal cancer occurs primarily in older people. The median age at diagnosis is 72 years and more than 25% diagnosed are 80 years or older.[1] Yet, approximately 5% of patients are 50 years or younger. When colorectal cancer occurs in younger patients, it is more likely to present at a more advanced stage (III or IV).[2] The question of whether, stage for stage, younger age confers a negative prognosis remains to be conclusively established.

To address whether age at diagnosis influences treatment response and survival, Blanke and colleagues analyzed individual data on 6,284 patients from nine Phase 3 trials of advanced colorectal cancer (aCRC) that used either fluorouracil-based single-agent or combination chemotherapy. Of these, 793 patients (13%) were younger than 50 years old and 188 (3%) were younger than 40 years old. Stratified Cox and adjusted logistic-regression models were used to test for age effects and age-treatment interactions.

Grade 3 or worse nausea was statistically more common, but severe diarrhea and neutropenia were less common in younger (younger than 50 years) than in older (older than 50 years) patients. Age was prognostic for progression-free survival (PFS), with poorer outcomes occurring in those younger than 50 years (median, 6.0 vs 7.5 months; hazard ratio, 1.10; $P \leq 0.02$), but it did not affect response rate (RR) or overall survival (OS). In the subset of monotherapy vs combination chemotherapy trials, the relative benefits of multiagent chemotherapy were similar for young and older patients. Results were comparable when utilizing an age cut point of 40 years.

COMMENTARY

Clinical oncologists are familiar with the heterogeneity in tumor biology with age, and there has been a long-held notion that certain common malignancies (e.g., breast and prostate carcinomas) are less aggressive in the oldest-old. This notion has been difficult to prove by epidemiologic data, perhaps because it is confounded by special problems common to geriatric populations (e.g., comorbidity, "poly-pharmacy," physician or family bias regarding diagnosis and treatment in older patients, and age-associated life stresses) — any or all of which might negatively influence standard "aggressive" management, and thus response rates and survival. Yet, under well-controlled experimental conditions in various tumor models, it has been clearly demonstrated that tumors grow more slowly, are less invasive, and spread less frequently in older animals.[3-6] In considering explanations for observed age-associated changes in tumor biology, it is useful to consider the "seed vs. soil" hypothesis. Although the "seed" (tumor cell) may be of the same origin and inherently similar in proliferative potential, the microenvironment ("soil") that provides nutrients and growth factors for proliferating cells may be less fertile in tissues from older hosts. Accordingly, it would come as no surprise to find more aggressive tumors growing in younger patients — this without having to implicate any substantive difference in the tumor itself.

Colorectal cancer occurring in younger patients tends to present at a more advanced state and this remains to be addressed satisfactorily. Perhaps, as the authors suggest, this results from the success of large-scale screening initiatives starting at age 50. Further, a subset of younger patients carry a genetic susceptibility for the development of colorectal cancer, but such patients generally have a better prognosis, perhaps reflecting the greater likelihood of associated microsatellite instability, a known favorable prognostic factor.[7,8]

Thus, the current study in which young age was only modestly associated with poorer PFS but not OS or RR in comparably treated patients with advanced colorectal cancer was somewhat surprising. However, as the authors suggest, the study reflects patients enrolled in clinical trials and might not be representative of either typical young or old patients with advanced colorectal cancer, many of whom do not make it onto trial for any number of reasons. It is curious that younger patients experienced more nausea with therapy, but less diarrhea and neutropenia. These are findings that will come as no surprise to clinicians but are useful to remember.

The safest conclusion to remember from this report is that both young and old patients derive similar benefits from combination chemotherapy. ■

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ABSTRACT & COMMENTARY

Assessing Physical Function and QOL in Doublet-Treated Elderly Lung Cancer Patients

By William B. Ershler, MD

SYNOPSIS: In a trial of two platinum-based chemotherapy regimens for non-small-cell lung cancer in older patients, pretreatment assessment of physical function and quality of life predicted certain different adverse outcomes but neither treatment assignment was superior to the other with regard to improved "global" quality of life.

SOURCE: Biesma B, et al, on behalf of the Dutch Chest Physician Study Group. Quality of life, geriatric assessment, and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study. *Ann Oncol* 2011;22:1520-1527.

The majority of non-small-cell lung cancer (NSCLC) patients are older than age 70 years[1] and identification of treatment goals for this group is important as the maintenance of quality of life (QoL) is most frequently desired. Although single-agent treatment often is recommended for elderly NSCLC patients,[2-4] subset analysis from several platinum-based trials suggests similar efficacy in elder as younger patients without excessive toxicity.[5,6] In this regard, the second drug might be of critical importance to clinical outcomes including QoL and physical function as well as survival. Previously, there had been no prospective randomized trials with platinum-based combination regimens in elderly NSCLC patients published.

To address this, Biesma and colleagues within the Dutch Chest Physician Study Group conducted a Phase 3 randomized clinical trial of two platinum-based drug regimens administered to elderly (70 years and older) NSCLC patients. A total of 181 chemotherapy-naive patients (performance score [PS] of 0–2) with stage III–IV NSCLC received carboplatin and gemcitabine (CG) (n = 90) or carboplatin and paclitaxel (CP) (n = 91) every 3 weeks for up to four cycles. Comprehensive geriatric assessment (CGA) and measurement of QoL were determined prior to treatment and components of these analyses were measured throughout the treatment program. Carboplatin was administered at an area under the concentration–time curve of 5 mg/ml/min on day 1 and either gemcitabine 1250 mg/m^2 on days 1 and 8 or paclitaxel 175 mg/m^2 on day 1. The primary endpoint was change in global QoL from baseline compared with week 18. A "QoL responder" was defined as a patient who had improvement of 10 points or more compared to baseline on the global QoL scale. Pretreatment CGA and mini-geriatric assessment during and after treatment were undertaken. A principal component analysis was carried out to determine the underlying dimensions of CGA and QoL that subsequently related to survival.

The number of QoL responders was small and there were no significant differences by treatment allocation (CG arm, 12%; CP arm, 5%). With regard to the comprehensive geriatric assessment, findings were only significantly associated with neuropsychiatric toxicity. Quality-adjusted survival was not different between treatment arms. The principal component analysis derived from nine CGA, six QoL, and one PS score indicated only one dominant dimension. This dimension was strongly prognostic, and physical and role functioning, Groningen Frailty Indicator, and Geriatric Depression Scale were its largest contributors.

Global QoL scores were lower in patients with worse baseline PS scores. However, there were no associations between the global QoL and treatment, age, gender, pretreatment weight loss, or extent of disease. There also were no significant interactions between QoL scores and treatment.

With regard to components of the CGA, baseline deficits in emotional functioning (QLQ-C30), role functioning (QLQ-C30), or depression (GDS) scores were more likely to experience > grade 2 neuropsychiatric toxic effects. There were no significant interactions between CGA scores and treatment. Patients with better ADL, IADL, or physical functioning (QLQ-C30) scores were more likely to finish all chemotherapy cycles. Patients with worse emotional functioning (QLQ-C30), role functioning (QLQ-C30), or GDS scores were more likely to experience grade 2 or greater psychiatric toxic effects.

More myelosuppression and fatigue were observed in the CG arm. Grade 2 or greater neurological toxicity occurred more frequently in the CP than in the CG arm (neurosensory: 19% vs 5%, $P = 0.002$; neuromotor: 10% vs 2%, $P = 0.03$). In both arms, approximately 25% of the patients experienced grade 2 or greater neuropsychiatric toxicity. Alopecia grade 2 was observed in 7% and 37% of the patients in the CG and CP arms, respectively.

COMMENTARY

This was the first report of its kind — a randomized trial focusing primarily on pretreatment comprehensive assessment and measures of QoL in the context of two effective chemotherapy regimens for NSCLC. The investigators are to be commended for the design and conduct of this trial and for the thorough analysis of complex data. For the practicing clinician, the findings are interesting but are not applicable yet to day-to-day practice. Further research needs to define those components of geriatric assessment that will prove useful in prescribing optimal treatment with as little impairment on QoL and physical function as possible.

From this report, we know paclitaxel or gemcitabine added to carboplatin did not have a differential effect on global QoL. Components of the CGA were associated with certain toxic effects but only in a very limited manner. In both treatment arms, patients with better physical functioning received more chemotherapy and survived longer. ■

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CME Questions

4. From the Australian melanoma case/control study, among those who had ever-used a sunbed and were diagnosed with cutaneous melanoma between 18 and 29 years of age, approximately what percent could be attributed to sunbed use?

a. 10%
b. 25%
c. 50%
d. 75%

5. Which of the following statements is true regarding FLT3 mutational status and acute promyelocytic leukemia treated with ATRA-based therapy?

a. ITD mutations are associated with high white blood cell count at presentation.
b. Point mutations at D835 confer an independent adverse prognosis.
c. ITD and D835 point mutations occur in more than 50% of APL patients.
d. APL patients with FLT3 mutations should be referred for allogeneic transplant.

6. Which of the following is an appropriate treatment for GBM?

a. 6000cGy/30 fractions
b. 6000cGy/30 fractions with concomitant and adjuvant temozoloomide
c. 4000cGy/15 fractions
d. Supportive care
e. All of the above

7. Colorectal cancer in younger patients (50 years or younger) compared to the same disease in those older than 50 years of age:

a. is more likely to present at an earlier stage (I or II).
b. is associated with poorer responses to chemotherapy and reduced overall survival.
c. is associated with poorer progression-free survival but comparable response rates and overall survival.
d. results in greater nausea, diarrhea, and neutropenia with treatment.

8. For elderly patients receiving chemotherapy for NSCLC when considering a doublet of carboplatin with gemcitabine (CG) or carboplatin with paclitaxel (CP), which of the following statements is NOT true:

a. Those receiving CG are more likely to experience myelosuppression and fatigue.
b. Those receiving CP are more likely to experience neurotoxicity.
c. Global quality of life is more likely to improve for those who receive CG.
d. Regardless of treatment assignment, patients with better baseline ADL scores were more likely to finish all chemotherapy cycles.

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.

[IN FUTURE ISSUES]

Risk Factors for Brain Metastases in Patients with Breast Cancer

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.*

FDA issues Multiple Drug Warnings

In this issue: FDA issues multiple drug safety alerts; ARBs and cancer risk; and FDA actions.

Avoid high-dose simvastatin

The FDA is advising physicians to avoid high-dose simvastatin (Zocor) because of the risk of myopathy and rhabdomyolysis. The agency is advising that patients should not be started on the 80 mg dose and patients who already are on 80 mg should be continued only if they have been on that dose for 1 year or longer. The recommendations are based on results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocystine (SEARCH) trial — a 7-year randomized, controlled trial comparing the efficacy and safety of simvastatin 80 mg vs simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction. There was no significant difference in the incidence of major vascular events between the two doses; however, 52 patients (0.9%) in the 80-mg group developed myopathy vs one patient (0.02%) in the 20-mg group. Of the high-dose group, 22 patients (0.4%) developed rhabdomyolysis vs no patients in the 20-mg group. The risk for myopathy and rhabdomyolysis with simvastatin 80 mg was highest in the first 12 months of treatment. Of concern, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, particularly diltiazem. The majority of patients who developed myopathy also had a genetic variant that affects coding of the transporter responsible for simvastatin uptake in the liver, resulting in higher serum simvastatin levels. The FDA not only recommends against using simvastatin 80 mg, but also suggests that the drug is contraindicated for use in patients taking itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. The maximum dose of simvastatin should be only 10 mg in patients taking amiodarone, verapamil, and diltiazem while the maximum dose is 20 mg in patients taking amlodipine and ranolazine. The new guidance recommends using a different statin if the patient's LDL targets aren't met with the 40-mg simvastatin dose. The loss of high-dose simvastatin comes as a blow to cost-concious consumers who now likely will be prescribed brand name atorvastatin (Lipitor) or rosuvastatin (Crestor). Generic atorvastatin is likely to be available in late 2011. ■

Increased risk of prostate cancer

The FDA has issued a somewhat controversial warning regarding an increased risk for high-grade prostate cancer associated with the 5-alfa reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn). Ironically, the new warning stems from studies designed to evaluate whether the drugs offer protection *against* prostate cancer. Both drugs are marketed to treat benign prostate hypertrophy and both are known to significantly decrease the prostate-specific antigen levels. In separate studies, both drugs were investigated to see if they reduce the incidence of prostate cancer. FDA experts reviewed the results of the Prostate Cancer Prevention Trial (PCPT), which evalu-

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ated finasteride vs placebo for 7 years, and the Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), which compared dutasteride to placebo for 4 years. Prostate cancers were significantly reduced in both trials; however, the reduction was limited to low-grade prostate cancers with a Gleason score of 6 or lower. The rate of cancers with a Gleason score of 8-10 was increased in both studies. Previous analyses of these data have suggested that finasteride did not increase the risk of high-grade prostate cancers, but rather made them easier to diagnose by decreasing the volume of the prostate (*Clin Cancer Res* 2009;15:4694-4699; *J Natl Cancer Inst* 2007;99:1366-1374). The FDA panel, however, disagrees and feels it prudent to add a warning to labeling of both medications regarding increased risk of high-grade prostate cancer associated with use of the drugs. The guidance further recommends that prior to initiating therapy patients should be evaluated to rule out other urologic conditions, including prostate cancer, that might mimic benign prostatic hypertrophy. ■

Actos and bladder cancer risk

The diabetes drug pioglitazone (Actos) is the subject of a new warning from the FDA regarding possible bladder cancer risk associated with use of the drug. The FDA ongoing safety review suggests that use of pioglitazone for more than 1 year may be associated with increased risk of bladder cancer based on review of a 5-year interim analysis of an ongoing 10-year epidemiologic study. Patients who had been on pioglitazone the longest and who had the highest cumulative dose of the drug had a slightly increased risk of bladder cancer. This warning falls on the heels of a French study that also showed increased risk of bladder cancer. Based on these findings, France's drug regulatory agency has suspended use of the drug. While the FDA is not recommending withdrawing the drug from the market, it does recommend avoiding pioglitazone in patients with active bladder cancer and using it with caution in patients with prior history of bladder cancer. Thiazolidinediones — including pioglitazone — have also come under scrutiny in recent years because of increased risk of congestive heart failure and bone fractures in females. ■

Chantix and cardiovascular events

The FDA has issued an alert regarding varenicline (Chantix) regarding a small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The warning regarding the smoking cessation drug was the result of review of a randomized, double-blind, placebo-controlled trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. The overall rate of adverse effects was low but cardiovascular events, including heart attack, were reported more frequently in the treatment group. The warning will result in a change in labeling for the drug and the FDA is also requiring Pfizer, the drug manufacturer, to conduct an analysis of other trials to further assess the risk. Varenicline already carries a box warning regarding neuropsychiatric symptoms including suicidality. ■

ARBs and cancer risk

Finally some good news from the FDA. After a 2010 meta-analysis showed a possible link between angiotensin receptor blockers (ARBs) and cancer, the agency has completed its own review and has found no evidence of increased risk of "cancer events" including new cancers, cancer-related deaths, breast cancer, lung cancer, or prostate cancer associated with the drugs. The agency conducted a much larger meta-analysis than the original study, including more than 150,000 patients in 31 long-term, randomized, controlled clinical trials. The rate of cancer events in the ARB group was 1.82 per 100 patient years while the rate in the non-ARB group was 1.84 per 100 patient years (relative risk of incident cancer in patients taking ARBs 0.99, 95% confidence interval, 0.92 to 1.06) There was no statistically significant difference in cancer death rates or incidence of individual cancer types. The agency continues to monitor this issue but currently states that the benefits of ARBs continue to outweigh the potential risks (summary available at FDA.gov/drugs/drugsafety/). ■

FDA actions

The FDA has approved the first generic version of levofloxacin (Levaquin). The popular fluoroquinolone is commonly used for treatment of respiratory infections, sinusitis, prostatitis, pyelonephritis and skin infections. Generic forms will include tablets, oral solutions, and injectable solutions.

The FDA has approved an abuse-resistant short-acting oxycodone tablet. Pfizer Pharmaceuticals has licensed the "AVERSION Technology" from Acura Pharmaceuticals. The technology prevents dissolving and injecting tablets by creating a gel when mixed with water or other solvents that prevents snorting crushed tablets by burning nasal passages, and also prevents intentional swallowing of excess quantities by adding niacin which causes intense flushing, itching, and sweating. Long-acting oxycodone (OxyContin) was similarly reformulated in 2010 to prevent misuse and abuse. ■

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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Fracture Risk Stratification in Diabetics

Source: Schwartz AV, et al. *JAMA* 2011; 305:2184-2192.

It has recently been recognized that type 2 diabetes (DM2) increases risk for osteoporotic fracture, even though it has been demonstrated that DM2 is associated with a paradoxical increase in bone mineral density (BMD) compared to age-matched control populations. With a burgeoning prevalence of DM2 in the United States, almost 20% of the at-risk population for osteoporotic fracture has DM2, hence, clarification of risk stratification for this group is highly relevant.

The World Health Organization (WHO) and the U.S. National Osteoporosis Foundation (NOF) suggest that clinicians assess patient risk for osteoporotic fracture by means of the fracture risk algorithm (FRAX) score. FRAX, an online risk assessment tool (available free of charge at http://www.shef.ac.uk/FRAX/), allows input of patient characteristics including gender, ethnicity, body mass index, risk factors for osteoporosis, history of fracture, family history of fracture, and BMD to calculate a 10-year risk of any osteoporotic fracture as well as 10-year risk of hip fracture. Similar to the structure of the ATPIII lipid guidance, intervention is threshold-based: Anyone with a 10-year risk of hip fracture > 3%, or total fracture risk > 20%, should be considered for pharmacotherapeutics intervention.

Gathering data from three prospective observational studies (n = 9449 women, 7346 men), Schwartz et al studied the relationship between FRAX scores, BMD, and subsequent osteoporotic fractures. Of concern, for any given T-score or FRAX score, the rate of osteoporotic fractures was higher in DM2 subjects than controls. DM2 appears to be a risk factor for osteoporotic fracture, above and beyond what is predicted by BMD or FRAX. ■

Amantadine for Dysphagia in the Elderly

Source: Gokula M, et al. *Ann Long-Term Care* 2011;19:37-40.

When amantadine (AMTD) was an appropriate first-line treatment for influenza, clinicians gained familiarity with its use. In the last decade, influenza resistance to the adamantanes (i.e., AMTD, rimantadine) has essentially eliminated their utility. The safety profile of AMTD is excellent however, heightening interest in clinical use for other syndromes.

Dysphagia in the elderly can be problematic, potentially leading to feeding difficulties and aspiration pneumonia. Probably the two most common scenarios in which we encounter dysphagia are Parkinson's disease and post-stroke, each of which is associated with reduced levels of dopamine. Since AMTD is a dopamine agonist, there is putative rationale for its potential use in dysphagia.

Gokula et al report their clinical experiences with AMTD in elderly patients with dysphagia. Based on positive responses in two test cases, they performed an uncontrolled case series (n = 12) among dysphagia subjects in a long-term care facility using an AMTD dose of either 50 mg or 100 mg/d orally. By 4 weeks, 11 of the 12 subjects demonstrated better swallowing, decreased cough, and weight gain. Additionally, fewer episodes of aspiration were seen.

Because AMTD is generally well tolerated, inexpensive, and there is little other resource for addressing dysphagia, clinicians may wish to consider a clinical trial. ■

Is Homocysteine a Culprit in Aging Skin?

Source: Namazi MR, Feily A. *J Am Acad Derm* 2011;64:1175-1178.

The association of homocysteine (HCST) with atherosclerosis is as strong and consistent as cholesterol, which prompted a flurry of clinical trials in the 1990s and early 2000s attempting to improve cardiovascular outcomes by lowering HCST levels (usually with pharmacologic doses of B vitamins). Unfortunately, HCST modulation did not result in cardiovascular risk reduction, to the point that interventions aimed at HCST have been largely abandoned.

HCST might also, however, be a culprit in aging skin. Photoaging is attributed to up-regulation of cutaneous matrix metalloproteinases and down-regulation of collagen synthesis. Homocystinuria, an inborn error of metabolism characterized by marked elevation of HCST, demonstrates thin, transparent skin.

HCST negatively impacts the three primary structural elements of healthy skin: collagen, elastin, and proteoglycans. Not only does elevated HCST in-

crease degradation of these components, it also inhibits their regeneration.

There have not yet been any clinical trials to examine whether HCST reduction favorably impacts skin aging. ■

Hepatitis C Treatment by Primary Care Clinicians

Source: Arora S, et al. *N Engl J Med* 2011;364:2199-2207.

In most communities in the United States, hepatitis C (HEPc) treatment is provided by gastroenterologists. Because HEPc is now the most common cause of end-stage liver disease, and — unless trends reverse — will continue to be so for the foreseeable future, it is important that identification of HEPc infection be continued vigorously in the primary care community, since most at-risk persons see primary care clinicians as their point of initial contact with the health care system.

Treatment of HEPc offers the opportunity for cure of the disease more than 50% of the time, although persons infected with HEPc genotype I have a somewhat lower success rate. Ideally, treatment would be offered to as many infected persons as possible, yet limitations in specialist consultants who traditionally administer the treatment are an obstacle to access for some patients.

The ECHO program (Extension for Community Healthcare Outcomes) is intended to enhance opportunities for provision of health care to underserved populations through, for instance, videoconferencing technology that allows primary care clinicians to receive case-based education with specialist colleagues. Since 2003, ECHO has resulted in 800 HEPc patients being treated by primary care clinicians. The primary outcome of this ECHO-based trial was sustained virologic response, which is defined as undetectable HEPc RNA 6 months beyond the end of treatment. Encouragingly, analysis of outcomes for patients treated on-site at the University of New Mexico HEPc clinic were essentially identical with those of patients treated at distant sites by clinicians guided though case-based video conferencing. Hopefully, enlarging the spectrum of clinicians who can provide state-of-the-art care for HEPc patients will become a goal for other sites that have the capacity for video conferencing. ■

COPD Exacerbations: The EXACT Tool

Source: Jones PW, et al. *Chest* 2011;139: 1388-1394.

The impact and consequences of chronic obstructive pulmonary disease exacerbations (COPD-e) are underappreciated. This year, COPD has risen in prominence from the fourth most common cause of death to the third. COPD-e are problematic on multiple levels: as many as 10% of patients admitted for COPD-3 die in the hospital, and the mortality within the year of hospitalization is as much as 20%. Additionally, each COPD-e is associated with a further decline in FEV1 that is not restored once the exacerbation is resolved.

Jones et al have performed the first published formal analysis of COPD-e to derive an instrument known as EXACT (Exacerbations of Chronic Pulmonary Disease Tool).

Based on interviews with COPD patients (n = 410), the authors quantified items pertaining to dyspnea, cough, sputum production, chest discomfort, limitations of activity, fatigue, sleep disturbance, and anxiety associated with COPD symptoms.

Ultimately, 14 items were discerned that quantified COPD-e presence and severity. Hopefully, such a tool could be used in daily diaries of COPD patients to help identify exacerbations at the earliest possible stage so that abortive therapy could be instituted without delay. It remains to be determined whether enhanced early detection and intervention for COPD-e will favorably affect symptomatic control, hospitalizations, or mortality. ■

Are Diabetes Prevention Treatments Truly Disease Modifying?

Source: The DREAM Trial Investigators *Diabetes Care* 2011;34:1265-1269.

Prevention of type 2 diabetes (DM2) is possible by means of several different paths including diet, exercise, metformin, thiazolidinediones, orlistat, acarbose, and valsartan. Although reduced conversion from pre-diabetes to DM2 by as much as 60% has been seen in some DM2 prevention trials, critics point out that it is unclear whether any of the natural history of DM2 — that is, progressive decline in beta cell function — is impacted by currently available interventions. Animal studies have found incretin effects, such as beta cell proliferation and improved beta cell mass, but no persistence of such effects has been confirmed in humans, and most data suggest that none of these favorable effects persist once pharmacotherapy is discontinued. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Trial Investigators published an analysis of glycemic control 2-3 months after cessation of ramipril or rosiglitazone, the agents used in the DREAM trial.

Although the Heart Outcomes Prevention Evaluation trial supported a role for DM2 prevention by ramipril, this was not confirmed in the DREAM Trial, nor was there any beneficial "legacy effect." Although rosiglitazone was effective in DM2 prevention, once stopped, progression to DM2 was similar to placebo. Hence, although prevention of DM2 is achievable with thiazolidinediones, they do not appear to make a sustained impact upon underlying disease pathophysiology since drug cessation is followed by a resumption of declining beta-cell function similar to placebo. ■

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