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Evidence-based summaries on cancer treatment and research

ABSTRACT & COMMENTARY

Chemotherapy-induced Amenorrhea in Patients with Breast Cancer

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

SYNOPSIS: The frequency of chemotherapy-induced amenorrhea was found to be greater than 90% in premenopausal breast cancer patients treated with standard adjuvant chemotherapy. Of these, nearly 60% had long-term (> 12 months) amenorrhea and risk factors included age > 40 years, treatment with a taxane in addition to adriamycin/cytoxan, and exposure to tamoxifen. Chemotherapy-induced amenorrhea was associated with significant negative impact on menopause-associated quality of life, as measured by the MENQOL self-assessment questionnaire. Future studies are warranted to better understand and manage chemotherapy-induced amenorrhea.

SOURCE: Yoo C, et al. Chemotherapy-induced amenorrhea, menopause-specific quality of life, and endocrine profiles in premenopausal women with breast cancer who received adjuvant anthracycline-based chemotherapy: A prospective cohort study. *Cancer Chemother Pharmacol* 2013;72:565-575.

Advances in adjuvant therapy for premenopausal breast cancer have resulted in improved overall survival, but this often comes at the cost of ovarian failure,[1] which can be the source of both physical and emotional distress. Depending on how chemotherapy-induced amenorrhea (CIA) is defined and on what drugs are used in the adjuvant setting, its occurrence has ranged from 29-93%.[1,2] Although the development of CIA may suggest better tumor control, the adverse effects on quality of life are of considerable importance. This may be particularly true in Asia where there is a greater prevalence of premenopausal breast cancer.[3]

To examine this question further, Yoo and Korean colleagues conducted a prospective, observational study in premenopausal women with breast cancer receiving adjuvant chemotherapy. The aims of the study were to define the pattern of CIA, describe menopause-specific QOL (MENQOL) using a validated self-questionnaire,[4] evaluate endocrine profiles at baseline and following chemotherapy, and determine the predictors for CIA, MENQOL, and hormonal profiles.

For this study, 387 premenopausal women with breast cancer who underwent curative surgery from October 2003 through July 2007 were

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initially enrolled. However, 75 were later excluded because of noncompliance or disease recurrence. The inclusion criteria for the study population were as follows: age ≥ 30 years, premenopausal status with regular menstruation at diagnosis, intact ovary and uterus, and a q3 week adjuvant chemotherapy schedule. Exclusion criteria included prior treatment for ovarian suppression or ablation. Planned chemotherapy included four cycles of adriamycin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), with or without four cycles of a taxane, depending on lymph node status. The majority of patients continued treatment with tamoxifen.

Assessment of menstrual pattern, laboratory studies including measures of follicle-stimulating hormone (FSH) and estradiol, and the MENQOL self-questionnaire were obtained prior to chemotherapy and at 1, 6, and 12 months thereafter.

Data analysis was done on 312 patients. Of these, the median age was 43 years (range 30-52) and body mass index was 22.5 kg/m^2 (range 18-32). All patients received the adriamycin and cyclophosphamide, 120 patients (39%) received a taxane, and 215 (69%) received tamoxifen. The median duration of follow-up was 17.5 months (range 7.5-29.2 months).

All patients experienced some degree of variation in their normal menstrual cycles and were subsequently classified into one of three categories: 1) long-term CIA (n = 180, 57.7%), 2) temporary CIA (n = 113, 36.2%), and 3) menstrual irregularity (n = 19, 6.1%). For patients who developed temporary or long-term CIA, the median time to onset of amenorrhea was 2 months (range 0-13 months). Risk factors for long-term CIA included age ≥ 40 years ($P < 0.001$), taxane use ($P = 0.01$), and tamoxifen use ($P = 0.03$). For patients with temporary CIA, amenorrhea was significantly longer in those who received taxane therapy (mean 9.4 vs 6.2 months, $P = 0.001$).

Endocrine profiles and MENQOL scores were assessed for each group of patients. In all groups, the MENQOL scores were the worst at 1 month after completion of therapy and improved over time.

In the long-term CIA group, FSH was substantially increased after chemotherapy when compared to baseline ($P < 0.001$), and estrogen was significantly lower than baseline at all time points ($P < 0.001$). In the temporary CIA group, FSH was again significantly increased after treatment ($P < 0.001$). There was a significant difference in estrogen level at 1 month when compared to baseline ($P < 0.001$), but this difference was not sustained at additional time points. In the menstrual irregularity group, FSH was significantly increased at 1 month post-treatment ($P < 0.001$), but was not different from baseline at additional time points. For this group, there were no statistically significant differences in estrogen levels when compared to baseline.

COMMENTARY

In approximately 60% of premenopausal breast cancer patients treated with standard anthrcycline-based adjuvant chemotherapy, long-term amenorrhea occurred, and in all but a few of the rest, a temporary cessation of menses (median 7 months) occurred. Risks for long-term CIA included age > 40 years, the addition of a taxane to adriamycin and cyclophosphamide, and exposure to tamoxifen.

A strength of the current study is the valuable quality-of-life data using the MENQOL questionnaire. MENQOL was worst immediately after the completion of adjuvant chemotherapy, but tended to improve over time, especially in patients with temporary CIA and menstrual irregularity; however, this reduced MENQOL did not recover to baseline levels until 12 months after chemotherapy. As expected, the long-term CIA group experienced the most severe disturbances to their MENQOL compared with the other groups.

Considering that most premenopausal patients will experience at least temporary CIA, the findings highlight the prevalent disruption of quality of life, particularly in domains related to menopause (e.g., sexuality, vasomotor, and psychosocial). These are the expected rather than the unusual consequence of adjuvant chemotherapy. Patient education and

counseling may be of value in preparing for these changes, but the truth is we have a lot to learn about the immediate and long-term consequences and the management of rapid-onset menopause in the context of young patients receiving cancer chemotherapy. ■

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ABSTRACT & COMMENTARY

Diabetes and the Risk for Biliary Tract Cancer

By Jerome W. Yates, MD

Hematology/Immunology Unit, National Institute on Aging, National Institutes of Health

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

SYNOPSIS: There has been much written recently about the association of diabetes and cancer. In this analysis of a large European cohort, the development of biliary tract and hepatocellular cancer was increased in diabetics compared with controls. However, the data as presented, though interesting, are not conclusive and additional research is called for to establish this association with confidence.

SOURCE: Schlesinger S, et al. Diabetes mellitus, insulin treatment, diabetes duration, and risk of biliary tract cancer and hepatocellular carcinoma in a European cohort. *Ann Oncol* 2013;24:2449-2455.

Epidemiological studies suggest that individuals with diabetes mellitus (DM) are at higher risk of cancer.[1,2] Capitalizing on the large EPIC (European Prospective Investigation into Cancer and Nutrition) cohort including 363,426 participants with self-reported diabetes data, Schlesinger and coinvestigators conducted a prospective analysis to examine the risk of hepatic and biliary cancer among those with diabetes.[3] Multivariable adjusted relative risks (RR) and 95% confidence intervals (CI) were estimated from Cox regression models. In a nested, case-control subset, analyses were carried out in HCV/HBV-negative individuals.

During 8.5 years of follow-up, 204 biliary tract cancer (BTC) cases (including 75 gallbladder cancer [GBC] cases), and 176 hepatocellular cancer (HCC) cases were identified. Independent of body mass index and waist-to-height ratio, diabetes status was associated with higher risk of BTC and HCC (RR, 1.77; 95% CI, 1.00-3.13; and RR, 2.17; 95% CI, 1.36-3.47). For BTC, the risk seemed to be higher in participants with shorter diabetes duration and those not treated with insulin. Regarding cancer subsites, diabetes was only associated with GBC (RR, 2.72; 95% CI, 1.17-6.31). The risk for HCC was particularly higher in participants treated with insulin. The results were not appreciably different in HCV/HBV-negative individuals.

COMMENTARY

The authors concluded that their findings support the hypothesis that pre-existing diabetes is a risk factor for BTC (particularly GBC) and HCC, but that additional research will be essential to establish whether diabetes treatment or duration is associated with these cancers.

Indeed, multiple studies have indicated there is an association between DM and a variety of gastrointestinal cancers.[1,2] This paper focuses on the association with DM and BTC, GBC, and HCC. It reports the results of a prospective, nested, cohort study based on available data from the EPIC cohort relying on self-reported health, disease, and diet information from a large number of subjects (n = 363,426) for a mean follow-up time of 8.5 years. This study included information about general and abdominal obesity, information not available in many of the meta-analyses previously reported, and the authors felt this factor strengthened their results. They concluded that DM is a risk factor for BTC (RR, 1.77; 95% CI, 1.00-3.13), GBC (RR, 2.72; 95% CI, 1.17-6.31), and HCC (RR, 2.17; 95% CI, 1.36-3.47). The diagnosis of DM was based on self-report, which was only collected once with the initial questionnaire, and the only treatment data related to DM concerned insulin usage. BTC seemed to be more common in those with DM of short duration and HCC was increased in those treated with insulin.

Case control studies are often criticized because the cases and controls are not always selected from the same pool of subjects and unidentified confounding variables (associated both with the exposure of interest and an outcome of interest). These variables, if known, are optimally considered in the analysis. If unknown, they may obscure the study results. For this study, the authors considered factors such as obesity, gall stones, and hepatitis and controlled for these using appropriate statistical methodology.

[The highest relative risk for biliary tract cancers was found in obese diabetics, a finding that clearly warrants additional research.]

The patients with DM not treated with insulin were at an increased risk for BTC, whereas only the participants treated with insulin and younger in age were at increased risk for HCC. These somewhat unexpected outcomes are of great interest but also raise questions about result validity. The highest relative risk for BTC was found in obese diabetics, a finding that clearly warrants additional research.

A major weakness of this study is the instability based on the small number of cancers of interest. Further, the diagnosis of DM was based on patient-supplied information at the time of study entry. Although the authors support the reliability of self-reported data in patients with DM, the multicultural background of participating subjects, the variability in their awareness of the diagnosis, and their understanding of the treatment may diminish that reliability. Because DM was determined only at the baseline (prevalence) and there was no reclassification of post-entry incident cases, three types of time biases were introduced (immortal, time window, and time lag).[4] Duration and severity of the DM is not consistently available, further blurring the estimates of the relationship with these cancers depending on the magnitude of the misclassification. In addition, there is no information about medications other than insulin, including metformin. Metformin appears to have a role in preventing some cancers.[5] This could decrease the number of cancers in the study population and decrease these relative risk estimates.

Thus, the findings are of interest, but design flaws limit the absolute validity of observations. Certainly, as the authors suggest, the association is of theoretical importance, but additional research is required to establish it with confidence. ■

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ABSTRACT & COMMENTARY

Treatment of AML Based on Age

By William B. Ershler, MD

SYNOPSIS: In a retrospective review of 2276 patients with acute myeloid leukemia (AML) treated on one of three consecutive Phase 3 studies using non-age based, standard intensive chemotherapy conducted by the Japan Adult Leukemia Study Group between 1995 and 2005, there was a significant decline in overall survival in patients aged ≥ 50 years when compared to those < 50 years. However, there was no difference in survival for patients aged 50 through 64 years. Although older patients with AML are often treated with less intensive therapy than younger patients, this analysis suggests that intensive chemotherapy without dose modification based on age may be considered for otherwise healthy patients with AML up to age 64.

SOURCE: Yanada M, et al. The demarcation between younger and older acute myeloid leukemia patients. *Cancer* 2013;119:3326-3333.

Because of both biological and clinical factors, age is known to be an important prognostic factor in adult acute myeloid leukemia (AML).[1,2] With increasing age, there is a higher prevalence of adverse disease characteristics such as unfavorable cytogenetics and prior myelodysplastic syndrome (MDS).[3,4] In addition, older patients are more likely to have comorbid medical conditions

and a worse performance status. As a result, current treatment regimens are typically based on age, with older patients, frequently defined as those ≥ 55 or 60 years of age, receiving less intense treatment than younger patients. However, it remains unknown if older patients who are generally in good health require this treatment modification.

To investigate the correlation between age and outcomes in patients with AML treated with intensive chemotherapy, Yanada and colleagues reviewed data from three consecutive prospective Phase 3 studies conducted by the Japan Adult Leukemia Study Group between 1995 and 2005. In these studies, there were no dose modifications made based on age, and all patients received the standard intensive cytarabine-based chemotherapy. All of the studies had the same inclusion criteria, which were as follows: newly diagnosed AML (excluding acute promyelocytic leukemia), age 15-64 years, an ECOG performance status of ≤ 3, and adequate liver (serum bilirubin < 2.0 mg/L), renal (serum creatinine < 2.0 mg/dL), pulmonary (PaO_2 ≥ 60 Torr or SpO_2 ≥ 93%), and cardiovascular function (normal EKG and ECHO). Exclusion criteria included AML secondary to myelodysplastic syndrome or previous cytotoxic therapy. Data on 2276 patients aged < 65 years who met these criteria and were enrolled on one of these studies were retrospectively analyzed.

Initially, patients were divided into four subgroups based on age for data analysis: age 15-29, 30-39, 40-49, 50-64 years. However, because initial analysis revealed a significant difference in overall survival between patients aged 40-49 and 50-64, subsequent analyses focused on two further-defined comparisons: 1) age < 50 (n = 1339) vs ≥ 50 (n = 937) years, and 2) age 50-54 (n = 334) vs 55-59 (n = 322) vs 60-64 (n = 281) years. There were no significant differences in performance status between the groups.

There was a significant decline in overall survival in patients aged ≥ 50 years when compared to those < 50 years (37.0% and 49.6% at 5 years, $P < 0.001$). However, there were no significant differences in overall survival in patients aged 50-54, 55-59, and 60-64, with overall survival rates of 38.2%, 35.1%, and 38.0%, respectively ($P = 0.934$).

In addition, differences were noted in cytogenetic profiles and subsequent risk between the two age groups. Specifically, favorable cytogenetics including t(8;21) and inv(16)/t(16;16) occurred more frequently in patients < 50 years ($P < 0.001$ and $P = 0.043$, respectively), and less favorable cytogenetics including add(5q)/del(5q)/-5, add(7q)/del(7q)/-7, complex karyotype, and monosomal karyotype were more frequent in patients ≥ 50 years ($P = 0.002$, $P = 0.021$, $P < 0.001$, and $P < 0.001$, respectively). However, there were no significant differences in the cytogenetic profiles in patients aged 50-54, 54-59, and 60-64.

Of the 2276 patients evaluated, 1788 achieved complete remission (CR). Patients < 50 years appeared to have a higher rate of CR than those ≥ 50 years (79.8% vs 76.7%). However, this difference was not statistically significant ($P = 0.078$). There was no difference in CR rate among patients aged 50-54, 54-59, and 60-64 ($P = 0.829$). Patients ≥ 50 years were more likely to experience relapse than those < 50 years (61.1% vs 53.4%, $P = 0.008$). There was no difference in relapse rate among patients aged 50-54, 54-59, and 60-64 ($P = 0.196$). There were no significant differences in early death or non-relapsed mortality among any of the age groups.

COMMENTARY

Those of us with a focused interest on cancer in older people might understandably be drawn to the title of the current paper, only to learn that "old" was defined as 50-plus. Although we all understand that AML is different, the median age for this disease is 70 years[5] and, thus, the majority of patients with AML would not be included in an analysis that restricts discussion to those 65 years and younger. That stated, the data from Japan are both notable and interesting. There seems to be an age-associated hinge point at age 50 years with a deflection downward in treatment response and survival thereafter. What is particularly curious is that beyond age 50 through age 64 years, response rates and survival did not show incremental declines but were stable. One possible explanation is that AML when it occurs in late middle age as opposed to earlier is somewhat different, with less favorable prognostic features including cytogenetic changes and markers of drug resistance. Beyond age 65, host factors such as prevalent comorbidities and functional declines contribute to the more dismal outcomes associated with AML observed.

[There seems to be an age-associated hinge point at age 50 years with a deflection downward in treatment response and survival thereafter.]

To further explain the Japanese data, it should be remembered that these were patients enrolled on clinical trials and thus may not represent the general AML population. If data were available for all patients in the selected age groups, it is quite possible an incremental decline in response rates and survival would be observed, as described in the epidemiologic study from England[6] also reviewed in this issue of *Clinical Oncology Alert*. ■

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ABSTRACT & COMMENTARY

AML Survival: Changes over 3 Decades

By William B. Ershler, MD

SYNOPSIS: In an epidemiological evaluation of acute myeloid leukemia survival over 3.5 decades, dramatic improvement was demonstrable for younger patients, but not so for the elderly. The data are consistent with data recently published from Sweden and the United States. In this disease that occurs most frequently in geriatric populations, there is a great need for developing more effective treatment strategies.

SOURCE: Shah A, et al. Survival and cure of acute myeloid leukemia in England, 1971-2006: A population-based study. *Br J Haematol* 2013;162:509-516.

Acute myeloid leukemia (AML) accounts for approximately 80% of all acute leukemia in adults and its incidence has remained fairly stable over the past several decades except for a fairly dramatic increase in its occurrence in patients 75 years and older,[1] a finding that may reflect improved diagnostic techniques and registration. However, with the demographic changes currently upon us and with this increased recognition of AML in the elderly, the median age at diagnosis is currently 70 years.[2,3] It is estimated that 13,780 individuals were diagnosed with AML in the United States in 2012, and that 10,200 will die of the disease.[1] The incidence increased from two to three per 100,000 in young adults to 13 to 15 per 100,000 in the seventh and eighth decades of life.[4]

[There is epidemiological evidence for improvement in survival and even cures (defined epidemiologically) for acute myeloid leukemia over the past 3 decades.]

There has been a sense that the developments in AML management including standardized chemotherapeutic approach, the selective use of novel targeted agents, and improved supportive management have resulted in improved survival.[5,6] However, most reports examining survival are derived from clinical trials that include younger and functionally more capable patients, and these may not reflect the general population of AML patients.[7] To get a sense of the magnitude of improvement in treatment success for the general population of AML patients, Shah and colleagues presented epidemiological data derived from cancer registries throughout England. This population-based study estimated the 5-year relative survival and "cure" for 48,380 adult patients diagnosed with AML in England during 1971-2006. Taking a statistical perspective, "cure" was defined as when AML patients experience the same mortality as individuals without AML who have similar demographic characteristics. The authors argue that "cure" models facilitate greater insights into the outcome of patients than survival alone. The aim of this study was to evaluate trends in population-based survival (measured by 5-year relative survival), the percentage "cured," and the median survival time of the "uncured" for adult patients diagnosed with AML in England during 1971-2006.

The analysis indicated the 5-year relative survival and the percentage "cured" increased for patients aged < 70 years at diagnosis during 1971-2006, but advancing age remained associated with poorer outcome. During the study period, a dramatic

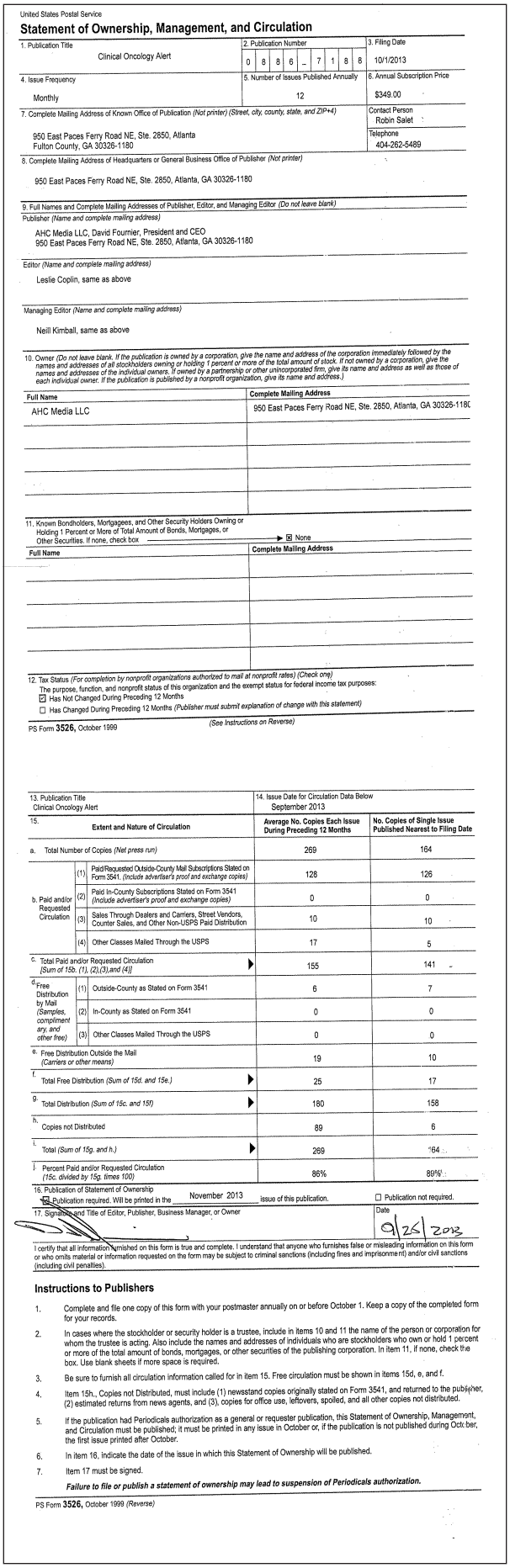
increase in 5-year relative survival occurred in those aged 15-24 years, from 7% to 53%. The percentage "cured" was < 10% for all ages in 1975, but increased to 45% for those aged 15-24 years in 2000. Cure could not be estimated for patients > 70 years, because survival was consistently low (< 5%).

COMMENTARY

As a reader unaccustomed to thinking of "cure" in an epidemiologic sense, I found the current report to be both refreshing and enlightening. Certainly, over these three and one-half decades, the long-term outcome for patients with AML has improved substantially, but notably, only for younger patients. And, even for younger patients, there remains room for improvement.

The data presented are comparable to a similar population-based analysis of AML "cure" conducted in Sweden for patients diagnosed between 1973-2001.[8] The percentage "cured" was < 7% for all patients in 1975, which increased to 68% in patients aged 19-40 years at diagnosis and to 8% in patients aged 61-70 years by 2000. Similarly, Thein and colleagues examined the NCI SEER database and examined overall AML survival by decade for different age groups.[9] In that analysis, there was modest 2-year survival improvement for those aged 65-74 years over the 3 decades (from 10% to 17%), but no survival improvement over the same period for those aged ≥ 75 years.

Thus, as anticipated by the published results from clinical trials, there is epidemiological evidence for improvement in survival and even cures (defined epidemiologically) over the past 3 decades. However, the data also highlight the discouraging lack of survival improvement for older patients. What accounts for this remains to be established, but explanations probably include the inability or reluctance to use standard chemotherapy schedules as well as tumor-related factors such as less favorable cytogenetics and prior myelodysplasia, both of which are more common in the elderly. Nonetheless, as the population ages, an increased emphasis on developing effective AML treatment for older patients is in order. Age-specific clinical trials, such as the European trial of clofarabine for elderly AML patients,[10] will hopefully result in epidemiological evidence for improved survival for the population as a whole. ■



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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%.
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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.

Continuing Education Questions

1. Risk factors for the development of long-term amenorrhea after adjuvant adriamycin and cyclophosphamide chemotherapy in women with premenopausal chemotherapy include:
a. age > 40 years.
b. additional therapy with a taxane.
c. additonal therapy with tamoxifen.
d. All of the above

2. The data presented from the EPIC cohort regarding the association of diabetes with biliary tract cancer suggests that a prior diagnosis of diabetes was associated with the development of:
a. gall bladder cancer.
b. hepatocellular cancer.
c. both a and b.
d. neither a nor b.

3. In the Japanese acute myeloid leukemia experience, a decline in overall survival for patients with AML was observed at age:
a. 40 years.
b. 50 years.
c. 55 years.
d. 65 years.

4. Five-year survival for acute myeloid leukemia patients ≥ 75 years is currently:
a. < 5%.
b. 13%.
c. 23%.
d. 40%.

[IN FUTURE ISSUES]

Bevacizumab, QOL, and survival in advanced ovarian cancer

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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.*

VOLUME 18, NUMBER 11 PAGES 21-22 NOVEMBER 2013

Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

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Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

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Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

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20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

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