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

ABSTRACT & COMMENTARY

Quality of Life to Predict Outcome for Older AML

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Dr. Artz reports no relationships relevant to this field of study.

SYNOPSIS: Investigators prospectively assessed quality of life in newly diagnosed AML patients 60 years and older using the EORTC QLC-C30 and QOL-E surveys. Among the 113 patients enrolled, 42.4% underwent intensive induction chemotherapy and 57.6% received palliative treatment. Self-rated quality of life did not correlate with physician-rated performance status or induction chemotherapy. Lower self-report functional status predicted higher mortality, even after adjusting for age, treatment, and comorbidity. Patient-reported quality of life may be an independent prognostic factor for AML outcomes.

SOURCE: Oliva E, et al. Quality of life in elderly patients with acute myeloid leukemia: Patients may be more accurate than physicians. *Haematologica* 2011;35:696-702.

Acute myeloid leukemia (AML) generally occurs in older adults, with a median age at diagnosis older than 65 years of age. Studies consistently demonstrate poor long-term outcomes even among fit elderly receiving induction chemotherapy on clinical trials or major university programs.[1] Survival deteriorates for each decade of age and for performance status limitations.[1] Elderly patients not only manifest more resistant and high-risk disease, but induction therapy exacts a greater toxicity burden related to reduced physiologic reserve. Typical health measures employed by oncologists include age, performance status, and more recently comorbidity. However, these parameters may not optimally capture health impairments that influence toxicity or survival, presenting challenges in determining prognosis and selecting treatment intensity.

The authors prospectively assessed patient-reported quality of life (QOL) using the QOL-E questionnaire, a previously validated tool for myelodysplastic syndrome.[2,3] The QOL-E scores can range from 0–100 with a score < 60 considered subjective poor health. In addition, another more widely used QOL instrument in Europe, the EORTC-QLQ, was administered.

They studied 113 patients 60 years and older diagnosed with de novo AML. The mean age was

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71.7 years and ECOG PS was good (0 or 1) in 101 (89%). At least one comorbid condition requiring treatment prior to an AML diagnosis existed in 68/113 (60.1%). As expected, hypertension, cardiac disease, and diabetes accounted for the majority of conditions. Treating physicians were unaware of the QOL scores. The majority (57.6%) were assigned palliative treatment while 42.4% received intensive chemotherapy. Patients 70 years and older were less likely to receive intensive therapy ($P = 0.007$). Blast count in the blood and marrow did not differ between patients receiving intensive treatment vs palliative care, suggesting perceived patient fitness and age most strongly influenced treatment selection. Comorbid conditions were more prevalent among older adults. QOL scores across the various domains of the instruments (e.g., functional, social, fatigue) did not differ for patients undergoing intensive therapy vs palliative treatment despite older age or more comorbidity among patients receiving palliative care. However, QOL scores at diagnosis showed a strong association with survival. Patients reporting low scores (i.e., < 60) only achieved median survival of 15 weeks compared to 55 weeks ($P = 0.002$) for patients demonstrating better QOL.

After adjusting for age, disease, and treatment, both instruments maintained their prognostic value. Physician-rated performance status did not accurately identify poor patient-reported physical function. Specifically, among patients rated in excellent health as gauged by a PS of 0 (i.e., normal), 27% reported a low score on physical function by EORTC and 33% by QOL-E. Among those with normal PS, impaired QOL score still was associated with worse survival. The value of QOL appeared greatest in adults 70 years and older. In contrast, for patients 60-69 years receiving intensive therapy, baseline QOL-E functional measures showed no association with survival ($P = 0.617$).

COMMENTARY

Standard therapy for AML remains intensive induction therapy. However, the majority of AML patients are older, have high rates of early death with induction, and rarely achieve long-term disease control.[4,5] Fitness for induction therapy is determined primarily by patient age and physician-rated PS. Subtle but significant limitations in physiologic reserve may not be captured by standard oncologic evaluation. Comorbidity tools using scores such as the HCT-CI have become more widespread and may enhance estimates of early death after AML induction.[6] The introduction of new therapies, in addition to standard cytarabine and anthracycline, increases the need for better assessment as physicians must select from a larger menu of treatments.[7-11]

In this study, the authors prospectively administered two QOL instruments to 113 consecutive AML patients. Treatment decisions were independent of QOL assessment. The authors report several important findings. A significant number of patients showed impaired QOL, including around 30% reporting poor physical function despite having an ECOG PS of 0. Moreover, QOL scores did not differ for patients assigned to intensive treatment or palliative treatment, indicating that subjective QOL did not influence treatment decisions and likely was not well appreciated by physicians. As expected, age older than 70 years and the presence of comorbidity were associated with treatment assigned. Finally, impaired QOL predicted for worse survival, independent of treatment, age, or comorbidity.

As a single institutional study, the data require confirmation. Nevertheless, these findings add to a growing body of literature showing self-report QOL may serve not only as an important outcome, but impaired QOL at baseline independently portends for inferior survival. The results are not surprising. Particularly for AML, oncologists generally have only recently recognized the need to immediately determine fitness. Further, patients may not volunteer important information about health or function for fear that treatment will be withheld. QOL tools provide validated measures that may enable physicians to better collect and incorporate detailed and prognostically valuable patient information. These tools also may be less prone to the natural bias of patients to optimistically report how well they function to the treating physician.

Numerous QOL tools are under study and thus we have a paucity of data for using a specific instrument for a specific disease. Future clinical trials, especially in the cooperative groups, should incorporate QOL instruments that would permit more definitive conclusions. Thus, a specific QOL tool and algorithm cannot be recommended at present for AML. However, physicians may want to more directly inquire patients about the self-report function. For example, in our practice, we ask specific questions about daily activity and whether the level of activity has changed. Such data compliment results from disease status and standard tools of age, PS, and comorbidity.

In summary, poor self-report QOL in older AML patients is independent of treatment, age, or comorbidity and is associated with worse survival. Future studies are needed to clarify how to integrate specific QOL tools into prognostic discussions and treatment decisions. At a minimum, physicians should be more aware of patients' perceived health status at the time of AML diagnosis. ■

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ABSTRACT & COMMENTARY

Denosumab vs Zoledronic Acid for Patients with Prostatic Bone Metastases

By Jerome W. Yates, MD

Hematology/Immunology Unit, National Institute on Aging, NIH

Dr. Yates reports on financial relationships relevant to this field of study.

SYNOPSIS: **In a Phase 3 trial comparing the recently introduced monoclonal antibody denosumab with zoledronic acid for the treatment of patients with prostate cancer metastatic to bone, the incidence of skeletal events — including pathological fracture, radiation, skeletal surgery, or cord compression — was delayed on average by more than 3 months for those treated with denosumab. Adverse events were comparable. Denosumab is administered subcutaneously and can be given to patients with renal insufficiency. Clinicians have become familiar with zoledronic acid in this setting, and it remains unclear whether its role as the standard approach will be supplanted.**

SOURCE: Fizazi K, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomized, double blind trial. *Lancet* 2011;377:813-822.

For men with prostate cancer, the presence of metastatic foci within bone remains a major source of pain and disability. There have been improvements over the years, most notably the use of zoledronic acid, which has proven to delay the progression of bone disease in patients with hormone independent metastatic prostate cancer.[1,2] More recently, Amgen Inc. has developed and introduced denosumab for this purpose as well, and the drug recently was approved by the FDA for use in this setting.

Denosumab is a full-length human monoclonal IgG2 that targets receptor activator of nuclear factor kappa B ligand (RANKL). The antibody blocks the binding of RANKL to its receptor (RANK)

and thus inhibits its downstream signaling. Of the myriad of consequences of RANKL-RANK signaling are the formation, function, and survival of mature osteoclasts, the cells responsible for bone resorption.[3] The resulting decrease in bone resorption theoretically would counter destructive bone metastases and thereby reduce or delay subsequent skeletal events such as fracture or cord compression.

To compare whether denosumab is comparable (i.e., not inferior) to zoledronic acid for patients with metastatic prostate cancer, Fizazi and colleagues from 42 centers in 39 countries conducted an Amgen-sponsored Phase 3 clinical trial in which approximately 2000 patients were randomized to receive 120 mg subcutaneous denosumab plus intravenous placebo, or 4 mg intravenous zoledronic acid plus subcutaneous placebo, every 4 weeks until the primary analysis cutoff date (median, approximately 1 year; IQR approximately 6-18 months for both groups). Randomization was stratified by previous skeletal-related event, PSA, and prior prostate cancer chemotherapy. The primary endpoint was time to first on-study skeletal-related event (pathological fracture, radiation therapy, surgery to bone, or spinal cord compression), and was assessed for non-inferiority. The data were further assessed to determine superiority as a secondary outcome. Efficacy analysis was by intention to treat.

[As clinicians become comfortable with the use of denosumab, it may become a new standard for treatment of patients with bone metastases.]

The median time to first on-study skeletal-related event was 20.7 months (95% confidence interval [CI] 18.8–24.9) with denosumab compared with 17.1 months (15.0–19.4) with zoledronic acid (hazard ratio 0.82, 95% CI 0.71–0.95; $P = 0.0002$ for non-inferiority; $P = 0.008$ for superiority). Adverse events were recorded in 916 patients (97%) on denosumab and 918 patients (97%) on zoledronic acid, and serious adverse events were recorded in 594 patients (63%) on denosumab and 568 patients (60%) on zoledronic acid. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; $P < 0.0001$). Osteonecrosis of the jaw occurred infrequently in both groups; 2% vs 1% for denosumab and zoledronic acid, respectively ($P = 0.09$).

COMMENTARY

The primary objective of this trial was to demonstrate that denosumab was not inferior to zoledronic acid for prevention of skeletal-related events, and as it turns out it appears that it might even be slightly better, in that events occurred on average 3.5 months later. From the Kaplan-Meier graphs presented, it seems the cumulative number of events will be the same for both groups, although at the time of publication the data were not sufficiently mature to make that conclusion. However, despite the delay in skeletal events, progression-free and overall survival were virtually superimposable between the two groups.

This study is one of three virtually identical trials comparing denosumab with zoledronic acid. In the other two, the comparison was made in patients with bone involvement from either breast cancer[4] or from other cancers, excluding breast and prostate but including multiple myeloma[5] and the results were similar to the current report; skeletal events including fracture, radiation, skeletal surgery, or cord compression were delayed to a greater extent by denosumab.

In summary, it is likely that denosumab delays for a few months the occurrence of adverse skeletal events for patients with prostatic bone metastases beyond that achieved by zoledronic acid. Furthermore, the drug has the advantage of subcutaneous rather than intravenous administration and it can be administered safely in patients with renal insufficiency. On the other hand, zoledronic acid has the advantage of greater accumulated clinical experience. Neither drug appears to provide survival advantage compared to the other. Both drugs are expensive and both are associated with a spectrum of adverse events, including the infrequent but important occurrence of osteonecrosis of the jaw. As clinicians become comfortable with the use of denosumab, it may become a new standard for treatment of patients with bone metastases, but it is early to make that conclusion. The question also arises whether its use in patients at risk for bone metastases, such as those with high-grade or locally extensive prostate cancer, may benefit from adjuvant use of either of these two agents. Hopefully, this approach would be shown to reduce the frequency of bone involvement and greatly reduce the occurrence of skeletal events. ■

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ILLUSTRATIVE CASE SERIES

Disseminated Prostate Cancer

By William B. Ershler, MD

A 51-year-old man, a foreman for a local construction business, presented to the emergency department with progressive lower back pain of 2 weeks duration and shortness of breath. Initially mild, the pain had become incapacitating within the prior 48 hours. A two-pack per day cigarette smoker, the patient had no other known medical problems and was on no prescription medications. Physical examination revealed him to be in distress, unable to find a comfortable position, and with mild dyspnea at rest. Blood pressure was 150/88, pulse 93/min, and O_2 saturation was 91% on room air. He had a ruddy complexion that was accentuated by non-descript fullness in his neck and prominent neck and chest wall veins. Lung sounds were clear but distant bilaterally, and heart sounds were unremarkable. The abdomen was soft, without mass, tenderness, or organomegaly. Complete blood count showed a white blood count of 9.3 K/uL, platelet count of 450 K/uL, and a hemoglobin concentration of 13.9 g/dL. Chemistries revealed a sodium of 140 mmol/L, potassium 4.0 mmol/L, alkaline phosphatase 483 unit/L, and lactate dehydrogenase of 420 Unit/L [313-618]. An MRI revealed an irregular contour of the T12 and L5 vertebral bodies and an abnormal bone marrow fat-signal diffusely throughout the visualized osseous structures, changes consistent with metastatic tumor. The patient was admitted for pain control and for diagnosis procedures.

Upon achieving pain control, a CT scan of the chest, abdomen, and pelvis revealed mediastinal (paratracheal) lymphadenopathy extending into the neck, enlarged abdominal paraaortic and retroperitonal lymph nodes, and a diffusely enlarged prostate gland with irregular contour. Also demonstrated by CT were extensive and destructive bone lesions. A serum PSA level was 145 ng/mL. Pelvic lymph node biopsy demonstrated well-differentiated adenocarcinoma with a positive staining reaction for PSA and PSAP.

The patient was treated with leuprolide, zoledronic acid, and analgesics. One month later there was remarkable reduction in signs of superior vena cava obstruction and significant reduction in chest adenopathy as detected by chest x-ray.

CASE DISCUSSION

The patient has disseminated prostate cancer, which, in all likelihood, accounts for all of his current symptoms, including the prominent skeletal pain and shortness of breath. What makes the case unusual is the presentation with what appears to be superior vena cava (SVC) syndrome. Admitting clinicians, considering this presentation, were likely entertaining SVC secondary to either lung carcinoma or lymphoma. The prominent bone involvement and smoking history would favor the former, whereas the extensive lymphadenopathy and perhaps age might have pointed to the latter. Indeed, prostate cancer would have been low on my differential, and it is fortunate that the radiologist called attention to the pelvic CT findings.

[Prostate cancer presenting as superior vena cava has been noted in several reports, but certainly it is uncommon.]

Prostate cancer presenting as SVC has been noted in several prior reports,[1-8] but certainly it is very uncommon. In one series of 47 patients presenting with malignancy-associated SVC syndrome, Rice and colleagues reported only one case had resulted from prostate cancer metastases.[9] The majority (82%) of patients in that series presented with face and neck swelling, such as observed in the current case.

The message from this case is the pursuance of tissue diagnosis. The current patient, despite widespread disease, appeared to promptly respond to androgen ablation (leuprolide) and would not likely have responded to empiric therapy directed at either presumed lung primary or lymphoma. ■

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RAPID REVIEW

Pancreatic Cancer-Associated Thrombosis: Prevention and Treatment

By William B. Ershler, MD

Venothrombotic Events and Pancreatic Cancer

Deep vein thrombosis (DVT) and pulmonary embolus (PE) occur more frequently in patients with cancer, and the risk appears to vary by tumor type. The most common venothrombotic events (VTE)-associated cancers are breast, colorectal, and lung; yet, when adjusted for prevalence, cancers of the ovary, pancreas, and brain are most strongly associated with thrombotic complications. For example, in one study of 202 patients with pancreatic cancer, the incidence of a thrombotic event was 108.3 per 1000 patient years (10.8%) resulting in a 58.6-fold increase in relative risk as compared with an age- and sex-adjusted general population.[1] Depending on the series, rates of occurrence in patients with pancreatic cancer vary from 5%-60%.[2] The wide variance probably reflects the large number of factors that interact and influence thrombotic risk, and several of these factors have been identified including stage of disease, older age, obesity, comorbidities, and prior history.[3] Furthermore, treatment with chemotherapy ups the risk approximately five-fold.[4] Although it is difficult to determine the actual risk for a single patient, it is known that the occurrence of a VTE is of prognostic importance. Sorenson and colleagues found that 12% of cancer patients with VTE and 36% of cancer patients without VTE were alive after 1 year.[5] Examining data from the California Cancer Registry including 235,149 cancer patients, Chew and colleagues found that the occurrence of VTE was highest among those with pancreatic cancer (20%), and that the occurrence correlated with stage of disease and was a significant predictor of death.[6]

Mechanisms Accounting for the High Rate of VTE in Pancreatic Cancer

Several factors contribute to the pathogenesis of VTE in cancer patients and most of these are commonly observed in pancreatic cancer patients. Such patients have been shown to have circulating procoagulants including tissue factor,[7,8] thrombin,[9,10] and fibrionogen,[11-13] as well as decreased levels of coagulation inhibitors such as protein C, protein S, antithrombin III, and thrombomodulin.[11,12] These occurring in mobility-impaired patients with invasive tumor in the retroperitoneal space no doubt contribute to the hypercoaguable state. Additionally, inflammatory factors known to be elevated in patients with pancreatic cancer, including transforming growth factor (TGF) and tumor necrosis factor (TNF), enhance coagulation pathways.[14,15]

Prevention of VTE

Primary anticoagulant prophylaxis is recommended for cancer patients admitted to the hospital for either surgical or medical reasons.[16] In this regard, unfractionated heparin, low molecular weight heparin (LMWH), and warfarin each have been used, but most physicians currently recommend LMWH in this setting. Ambulatory patients receiving chemotherapy for pancreatic cancer also are at risk for VTE. Recent trials conducted in patients with advanced disease have shown positive results with LMWH prophylaxis. The CONKO-004 trial found an 87% risk reduction of VTE using enoxaparin at 1 mg/kg once daily for 3 months compared with no prophylaxis (9.9% vs. 1.3%, $P < 0.01$).[17] Similarly, the UK FRAGEM study reported a 62% reduction in VTE with dalteparin (31% vs 12%; $P = 0.02$). These data are in conflict with the negative results from LMWH prophylaxis studies conducted in ambulatory cancer (primarily breast, gastrointestinal, and lung) patients. Thus, it seems LMWH is effective in reducing clinically important VTE in selected patients receiving chemotherapy, but the optimal dose, duration, and specific patient populations have to be further defined.

Treatment of Cancer-Associated VTE

The recommended treatment for cancer-associated VTE is LMWH, as it has proven effective both in the short- and long-term when compared with warfarin.[16] The data for the newer oral anticoagulants, including dabigatran and rivaroxaban, are not yet available in the setting of cancer-associated VTE. Despite treatment for the initial VTE, recurrent VTE occurs in approximately 10%-20% of cancer-associated cases. Studies have suggested that in more advanced disease, a shorter interval between diagnosis and initial VTE (3 months or less) or young age are predictors of recurrent thrombosis despite anticoagulation. Data to guide the management of such patients are limited. For those being treated with LMWH, dose escalation (e.g., by 25%) has proven effective in the majority of patients. For those who were treated initially with warfarin, switching to LMWH would seem advisable rather than increasing warfarin to higher than therapeutic levels. The role for IVC filters remains to be established in cancer patients with VTE.

[Low molecular weight heparin has proven effective in prophylaxis and venothrombotic event treatment in pancreatic patients. More research is needed to determine dose, schedule and duration of treatment.]

Summary

Pancreatic cancer is a hypercoaguable state with the occurrence of VTE ranging from 10%-60%. Notably, thromboembolic events are associated with poorer prognosis, and such events predict disease recurrence and shorter survival. LMWH has proven effective in both prophylaxis and VTE treatment in pancreatic cancer patients although much research is needed to determine the optimal dose, schedule, and duration of treatment. The new oral direct thrombin inhibitors (such as the recently approved dabigatran) are of great interest and need to be explored in the setting of VTE prophylaxis and treatment in cancer patients. ■

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CME Questions

For older AML patients, which statement describes the associations with self-report quality of life?

a. Quality of life was NOT associated with the decision to purse intensive or palliative treatment.
b. For patients with excellent health as gauged by physician rated ECOG PS of 0, QOL was normal, indicated limited value in this population.
c. After adjusting for age, the prognostic value of quality of life was lost.
d. Most patients at the time of AML diagnosis report normal QOL score, suggesting assessment should be reserved for after treatment.

From the study comparing denosumab with zoledronic acid for patients with metastatic prostate cancer, which of the following conclusions can be drawn?

a. Progression-free survival was greater for those treated with denosumab.
b. Skeletal events occurred later for those treated with denosumab.
c. Osteonecrosis of the joint was less frequent for those treated with denosumab.
d. The overall frequency of adverse events was less for those treated with denosumab.
e. All of the above

The optimal approach for patients presenting with mediastinal lymphadenopathy and superior vena cava syndrome from a yet to be diagnosed condition would include:

a. initiation of chemotherapy directed at the presumed primary disease.
b. immediate radiation therapy with dose and schedule adjusted once primary condition identified.
c. initiation of condition specific therapy once biopsy has been obtained and reviewed.

Answers: a, b, c.

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]

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Rethinking Postmenopausal HRT

Source: LaCroix AZ, et al. *JAMA* 2011; 305:1305-1314.

The final results of the women's Health Initiative trial (WHI) may not be the end of the story. Much-anticipated favorable cardiovascular outcomes from hormone replacement therapy (HRT) were conspicuously absent from the trial results at 7.1 years; when coupled with increases in stroke, thrombotic events, and breast cancer, most clinicians walked away from HRT. But the story doesn't end there.

Remember that the mean age of the WHI participants was 63 years; hence, most of the study subjects were more than a decade postmenopausal, not representative of the patients who typically seek relief of menopausal symptoms during the perimenopause and early menopausal years (usually ages 50-52 years).

The WHI included a large subset of hysterectomized women (n = 10,739) who received only estrogen therapy (i.e., no progestin). LaCroix et al report on extended post-trial follow-up of this population, adding another 5.8 years of observation to the original mean 5.9 years of the clinical trial.

At the 10.7 year mark, some of the initially described differences between estrogen and placebo were eradicated. Risk of coronary heart disease (CHD), deep vein thrombosis, stroke, hip fracture, and total mortality were not statistically significantly different in the two populations, even though initial results indicated some detrimental estrogen effects. At 10.7 years, there was a statistically significant 23% lower risk of breast cancer in women receiving estrogen replacement than placebo. As has been noted in previous recent publications about the WHI, younger women (age 50-59 years) had neutral or favorable outcomes for CHD, myocardial infarction, and total mortality, whereas older women incurred negative effects. Young (age 50-59 years) symptomatic women should have such considerations incorporated into decisions about HRT. ■

The Pistachio Diet for Erectile Dysfunction

Source: Aldemir M, et al. *Int J Impot Res* 2011;23:32-38.

Erectile dysfunction (ED) in mid-life males is recognized to stem most often from endothelial dysfunction, a commonplace consequence of dyslipidemia, diabetes, hypertension, or cigarette smoking. Pistachios have been shown to improve lipid fractions, but have not been studied in reference to functional improvement in endothelial function. To that end, Aldemir et al studied 17 men with established ED.

Study subjects ingested about 3½ ounces (570 kcal) of pistachios daily at lunch for 3 weeks. No other health interventions were used and subjects were asked to maintain similar exercise and other dietary patterns unchanged. At baseline and 3 weeks, the International Index of Erectile Function (IIEF) score and penile Doppler ultrasound were measured.

Compared to baseline, there was a statistically significant and clinically relevant increase in the IIEF score (from 36 at baseline to 54 at 3 weeks). Penile flow velocity improved by more than 20%. As had been confirmed in prior studies, favorable effects on total cholesterol, LDL, and HDL were seen.

The authors attributed the positive effects of pistachios potentially to antioxidant effects, as well as healthful lipid effects, the latter of which has previously been shown to promptly improve endothelial function. Because the studied "dose" of pistachios has substantial caloric impact (almost 600 calories), dietary restriction of other components for some patients might be necessary if they desire to add this amount of pistachios to their menu. ■

Vitamin D and Hypertension

Source: Bhandari SK, et al. *J Clin Hypertens* 2011;13:170-177.

Let's make this simple: vitamin D deficiency causes EVERYTHING. Well, at least that's the way things seem these days. In addition to the widespread awareness that insufficient vitamin D — as demonstrated by measurement of serum 25-hydroxy-vitamin D — is rampant, maladies from all spheres of medicine are increasingly recognized to be associated, to one degree or another, with vitamin D. Today, it is hypertension.

Bhandari et al begin their discussion of the relationship between vitamin D and hypertension (HTN) by pointing out that as many as 40% of U.S. adults are vitamin D deficient. Epidemiologic analyses suggest that all-cause mortality is lower in vitamin D supplemented

persons. Because vitamin D is involved with the renin-angiotensin-aldosterone system, it does not require a great stretch of the imagination to visualize a vitamin D-HTN linkage.

The data studied by the authors include 2,722 adult members of the Southern California Kaiser Permanente health care system. Rates of HTN were compared with quartiles of vitamin D. A linear and inverse relationship between vitamin D status and HTN was observed, such that individuals in the lowest vitamin D quartile were almost three times as likely to have HTN as those in the highest quartile.

Whether vitamin D supplementation could improve blood pressure or prevent development of HTN remains to be determined. In the meantime, add another item to the growing list of health issues in some way linked to vitamin D status. ■

Bromocriptine for Type 2 Diabetes

Source: DeFronzo RA. *Diabetes Care* 2011;34:789-794.

BROMOCRIPTINE (BRO) IS A NEW AND novel treatment for type 2 diabetes (DM2). In contrast to other classes of DM2 pharmacotherapy, which act at well-defined receptor sites to induce insulin secretion or improve insulin sensitivity, BRO works in a more global fashion by resetting levels of dopaminergic and sympathetic tone within the central nervous system (CNS). For example, elevation of hypothalamic dopamine levels reduces sympathetic nervous system activity resulting in improved glucose tolerance, reduced free fatty acids, and enhanced insulin sensitivity. The CNS effects can be harnessed by ingesting BRO in a rapid-release form (the form currently approved for DM2 treatment) in the morning, which is believed to reduce metabolic consequences of the morning dopamine decline often seen in diabetics.

A large (n = 3,070) 1-year randomized, placebo-controlled trial added BRO to various diabetes regimens, including diet, oral agents, and/or insulin. The BRO treatment group enjoyed a 40% reduction in the pre-specified cardiovascular endpoint (a composite of myocardial infarction, stroke, death, coronary revascularization, and hospitalization for angina or congestive heart failure). Although the mechanism by which BRO results in improved cardiovascular outcomes is uncertain, reductions in blood pressure and heart rate might be contributors. BRO is generally well tolerated and provides another category of treatment that may be used in combination with essentially any other diabetes medication. ■

Amitriptyline vs Duloxetine for Diabetic Peripheral Neuropathic Pain

Source: Kaur H, et al. *Diabetes Care* 2011;34:818-822.

DIABETIC PERIPHERAL NEUROPATHIC PAIN (DPNP) is challenging because not only does it induce a substantial pain burden, but also the pain is typically worse at night — resulting in sleep deprivation — and exacerbated by activity, compromising the ability for patients to perform the exercise that is so critical in weight maintenance. Although only two drugs have received specific FDA approval for management of DPNP (pregabalin, duloxetine), clinicians often use drugs off-label, including amitriptyline. Few head-to-head trials are available with which to compare various commonly used agents.

Kaur et al performed a double-blind crossover trial of amitriptyline (up to 50 mg/d) vs duloxetine (up to 60 mg/d) in 58 study subjects. The primary outcome was patient-assessed global efficacy at 6 weeks.

The outcomes with duloxetine and amitriptyline were essentially equivalent, and tolerability was also quite similar, although dry mouth was statistically significantly more common with amitriptyline. Comparable improvement in sleep was also seen with both medications. Since amitriptyline is available generically at a low price, it presents a viable therapeutic alternative for patients whose dry mouth is not a limiting adverse effect. ■

Testosterone Replacement in Diabetes and the Metabolic Syndrome

Source: Jones TH, et al. *Diabetes Care* 2011;34:828-837.

BOTH METABOLIC SYNDROME (MBS) AND type 2 diabetes (DM2) have been consistently found to be associated with low testosterone (TST) levels. Several new formulations of topical TST have become available in the last few years, simplifying treatment of hypogonadism. Jones et al studied the effects of TST 2% gel daily applications in hypogonadal men with MBS or DM2 treated for 1 year.

TST replacement produced numerous favorable effects in these hypogonadal men, including improvements in insulin resistance, a reduction in A1c, and lower LDL and lipoprotein A. Decreased libido and reduced sexual function are the most common presenting symptoms of hypogonadism, and numerous clinical trials have confirmed a prompt, sustained favorable response in these domains, which was similarly confirmed in this trial.

Tolerability of TST 2% gel was similar to placebo. When adverse effects did occur, more than 96% were considered mild or moderate. Cardiovascular (CV) events were seen more often in the placebo group, a reassuring finding since another trial published recently found a disarmingly marked increase in CV events in frail, senior men treated with TST.

In addition to improving target symptoms for which hypogonadal men seek relief, TST replacement can provide several other favorable metabolic effects in persons with DM2 or MBS. ■

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Women's Health Issue — Adverse Medication Effects

In this issue: Calcium supplements and MI; birth control pills and VTE; ACE inhibitors and breast cancer risk; spending on pharmaceuticals; and FDA actions.

Calcium supplements and MI risk

Do calcium supplements increase the risk of myocardial infarction (MI)? Researchers from New Zealand recently reanalyzed data from the Women's Health Initiative (WHI) in an attempt to answer this question. In 2008 the same group published a randomized, placebo-controlled trial of calcium supplements in nearly 1500 healthy postmenopausal women that showed upward trends in cardiovascular event rates with calcium use (*BMJ* 2008;336:262-266). The same group subsequently carried out a meta-analysis of cardiovascular events in randomized, placebo-controlled trials of women taking calcium supplementation without vitamin D. In that study, calcium supplementation significantly increased the risk of MI by about 30% (*BMJ* 2010;341:c3691). Although these studies garnered some interest, they were also viewed with skepticism, and most physicians, especially in this country, did not change their practice of recommending calcium supplementation for postmenopausal women. The New Zealand group then turned to the WHI data, a rather strange place to look considering that one of the main outcomes of WHI was the finding of no adverse effect of calcium and vitamin D on cardiovascular risk. However, the researchers found one major caveat: WHI did not consider whether women were taking calcium on their own prior to entry into the study. The New Zealand group got access to the original NIH data and were able to tease out women who were not using personal calcium supplements at randomization. They found nearly 17,000 women who fit that category. Women in this subgroup who were randomized to calcium and vitamin D had small but significant increased risk for cardiovascular events with hazard ratios that ranged from 1.13-1.22 ($P = 0.05$ for clinical MI or stroke, $P = 0.04$ for clinical MI or revascularization). When the WHI data were added to the previously done meta-analysis of three placebo-controlled trials, calcium and vitamin D were found to increase the risk of MI (relative risk [RR] 1.21 [95% confidence interval [CI] 1.01-1.44]; $P = 0.04$), stroke (1.20 [CI 1.00-1.43], $P = 0.05$), and the composite of MI or stroke (1.16 [CI 1.02-1.32], $P = 0.02$). Trial level data was available for more than 28,000 women who were randomly assigned to calcium plus vitamin D or placebo. Calcium or calcium plus vitamin D increased the risk of MI (RR 1.24 [CI 1.07-1.45], $P = 0.004$) and a composite of MI or stroke (1.15 [CI 1.03-1.27], $P = 0.009$). The authors conclude that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially MI. They suggest that a reassessment of the role of calcium supplementation in osteoporosis management is warranted (*BMJ* 2011;342:d2040 doi:1136/*BMJ*.d2040, published April 19, 2011). This study has been hotly debated and was even criticized in an editorial in the same issue of *BMJ*. Nonetheless there is a bit of irony in using WHI data, which are largely responsible for millions of women stopping hormone replacement therapy, to show a relationship between calcium and

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: neill.kimball@ahcmedia.com.

cardiovascular disease disease. There is no suggestion in any of these data that dietary calcium leads to adverse events. It is postulated that the rapid increases in calcium that occur with calcium supplementation may somehow play a role in increased cardiovascular risk.

Birth control pills and VTE risk

A progestin commonly used in birth control pills may increase the risk of venous thromboembolism (VTE). A recent report suggests that women taking oral contraceptives containing drospirenone may be at increased risk of VTE compared to women taking contraceptives containing other progestins. Two studies were recently published in *BMJ*. The first was a case-controlled study of U.S. women that showed that women taking drospirenone-containing contraceptives were twice as likely to develop nonfatal VTE compared to women taking levonorgestrel (*BMJ* 2011;342:d2151). The other study, a case-controlled study of British women, showed a three-fold higher rate of VTE with drospirenone-containing contraceptives compared to levonorgestrel (*BMJ* 2011;342:d2139). Oral contraceptives containing drospirenone include Yaz, Yasmin, and Angeliq.

ACE inhibitors and breast cancer risk

Researchers at UCLA and Kaiser Permanente in northern California recently published data suggesting that angiotensin converting enzyme inhibitors (ACEi) may increase the risk of breast cancer recurrence in breast cancer survivors. Using a database of nearly 1800 women with a history of breast cancer, there were 292 recurrences, 174 breast cancer deaths, and 323 total deaths. Twenty-three percent of the women in the study were exposed to either a beta-blocker or an ACEi. ACEi exposure was associated with breast cancer recurrence 1.5 times baseline (HR 1.56, 95% CI 1.02-2.39, $P = 0.04$) but not increased cause-specific or overall mortality. Beta-blocker exposure was associated with lower hazard of recurrence and cause-specific mortality. There was no dose-response with either medication. When a beta-blocker was combined with an ACEi, there was a lower hazard ratio for recurrence than with ACEi alone. The authors suggest that ACEis may be associated with an increased risk of breast cancer recurrence; although beta-blockers may be somewhat protective, more research is needed (*Breast Cancer Res Treat*, published online, DOI: 1007/s10549-011-1503-3). Beta-blockers have been shown to be protective against breast cancer recurrence in other studies, but the ACEi findings were unexpected.

Spending on U.S. pharmaceuticals

Spending on pharmaceuticals in the United States grew at its smallest level in years in 2010, according to a report by the IMS Institute for Healthcare Informatics. Pharmaceutical spending increased 2.3% in 2010 compared to 5.1% in 2009. Generics dominated the pharmaceutical market in 2010 making up 78% of total market share compared to 63% in 2006. Of the top 25 drugs by volume, only three were brand-name products: atorvastatin (Lipitor), clopidogrel (Plavix), and montelukast (Singulair). By spending dollars, however, Lipitor was the top grossing product at $7.2 billion in 2010, down from $7.6 billion in 2009. Esomeprazole (Nexium) was second at $6.3 billion, while Plavix ranked third at $6.1 billion. The domination of generics is of major concern to the pharmaceutical industry since there are few new drugs in the development pipeline and several high-profile drugs are due to lose protection soon. Foremost among these is Pfizer's Lipitor. Pfizer has been battling to maintain its patent protection, but generic manufacturer Watson Pharmaceuticals is expected to introduce the first generic atorvastatin in November of this year. Likewise, Merck's Singulair will likely lose its patent protection next year. The economy also has played a role in the decrease in pharmaceutical spending as the total volume of medicines consumed decreased 0.5% in 2010 along with a decrease in the number of doctor office visits of 4.2%. This extends a decline that began in mid 2009 — likely due to higher unemployment and rising health care costs.

FDA actions

The FDA has approved rituximab (Rituxan) for the expanded indication to treat Wegener's granulomatosis and microscopic polyangiitis, two rare vasculitides. The effectiveness of rituximab was demonstrated in a single control trial in which 197 patients with either condition were randomized to rituximab plus glucocorticoids or oral cyclophosphamide plus glucocorticoids. After 6 months, 64% of the patients treated with rituximab had a complete remission compared to 53% of patients treated with cyclophosphamide. Rituximab is manufactured by Genentech.

The FDA has approved gabapentin enacarbil for the treatment of moderate-to-severe restless leg syndrome. The approval was based on two 12-week clinical trials in adults showing the effectiveness of the drug vs placebo. Gabapentin enacarbil is formulated as a once a day extended-release tablet. It is marketed by GlaxoSmithKline and Xenoport as Horizant. ■

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