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Clinical Oncology Alert's Editor, William Ershler, MD, is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Peer reviewer V.R. Veerapalli, MD, reports no financial relationship to this field of study.

Oral Vitamin K for Excessive Anticoagulation

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Division of Hematology/Oncology, University of Chicago

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

Synopsis: *Whether oral vitamin K reduces the risk of bleeding related to excessive anticoagulation from warfarin remains unclear. Across 14 anticoagulation clinics, 724 patients with an asymptomatic elevated INR between 4.5 and 10.0 were randomized to 1.25 mg of oral vitamin K or placebo. Within the first 90 days, 15.8% in the vitamin K group and 16.3% in the placebo group had at least one bleeding episode (p = 0.86). There were no differences in major bleeding, thromboembolism, or death. The INR fell more quickly in the vitamin K group. Oral vitamin K does not substantially reduce the bleeding in warfarin-treated patients with an INR from 4.5 to 10.0.*

Source: Crowther M, et al. Oral vitamin K versus placebo to correct excessive anticoagulation in patients receiving warfarin. |*Ann Intern Med*. 2009;150:293- 300.

WARFARIN IS A FREQUENTLY PRESCRIBED ORAL ANTICOAGULANT. The highly variable, dose-response characteristics mandate monitoring, and this is usually accomplished by targeting an international normalized ratio (INR) value between 2.0 to 3.0. Non-therapeutic values are common, and values above 4.5 predispose to serious bleeding.[1] Low-dose oral vitamin K can effectively reduce the INR within 24 hours in patients excessively anticoagulated from warfarin.[2] In this study, Crowther et al evaluated whether low-dose vitamin K would reduce bleeding relative to withholding warfarin alone in non-bleeding patients with a high INR from warfarin.

Adult patients from anticoagulation clinics were eligible if an outpatient INR was found to be 4.5-10.0 within the past 24 hours; the target INR was 2.0-3.5, with no bleeding. Patients with other risk factors for bleeding, or a need for acute normalization of the INR, were excluded. Patients were randomized to receive a formulated capsule of 1.25 mg

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of oral vitamin K or placebo. Patients were followed in person or over the telephone for 90 days to assess the primary endpoint of bleeding within 90 days of randomization. The INR was managed as per local practice. The mean age of enrolled patients was 69 years, and the mean INR at enrollment was 5.8 to 6.0 among the 724 enrolled patients. In the vitamin K group, 56 of 355 (15.8%) experienced a bleeding event compared to 60 of 369 (16.3%) in the placebo group. Major bleeding occurred in 2.5% and 1.1% in the vitamin K and placebo groups, respectively. There were no significant differences for the bleeding event ($p = 0.86$), major bleeding events ($p = 0.22$), thromboembolism ($P = 0.72$), or death ($p = 0.94$) by day 90. The average decrease in the INR the following day was 2.8 units for the vitamin K-treated patients but only 1.4 units for the placebo patients ($p < 0.001$).

■ COMMENTARY

Warfarin has found widespread use as an anticoagulant to prevent venous and arterial thrombosis. Despite a host of new anticoagulants, the low cost and familiarity with warfarin promote its continued use, as well as alternative management models such as telephone monitoring.[3] Supratherapeutic INR values are not uncommon, predispose to bleeding, and represent a management challenge. Multiple studies have shown that for high INR values, low doses of oral vitamin K can hasten correction, compared to holding warfarin alone.[2] It is unknown whether an asymptomatic patient with an incidentally elevated INR benefits from low-dose vitamin K.

In this study, Crowther et al randomized patients with an asymptomatic, newly elevated INR from 4.5 to 10.0 to receive 1.25 mg of oral vitamin K or placebo. They found no difference in any of the study endpoints of bleeding at 30, 60 or 90 days. The primary outcome of bleeding at 90 days was around 16% in both groups. No differences were found in major bleeding, new thromboembolism, or death. The data support a strategy of withholding warfarin without giving oral vitamin K for asymptomatic elevations of the INR.

Interestingly, only three serious bleeding events occurred among all subjects in the first seven days, two from placebo-treated patients and one case in a vitamin K-treated patient. Thus, these data suggest outpatient management appears safe, at least for those meeting the protocol criteria.

As noted by Crowther et al, the study was not powered to detect small differences in bleeding between each arm. The largest limitation rests with the restrictive criteria of a randomized study that limits generalizability. These patients were being followed closely at an anticoagulation clinic. In addition, patients at higher risk of bleeding were not included, such as those who already had bleeding, INR levels above 10.0, low platelets, or liver disease. Although data are lacking, it may be reasonable for such higher-risk patients to receive oral vitamin K. The data in this study were at least reassuring that thromboembolism was no more frequent in the vitamin K-treated patients. For patients having overt or serious bleeding, more immediate corrective actions will be needed. A practical problem related to the 1.25 mg dose of vitamin K is not readily available. However, the 2.5 mg dose could be broken in half, or an alternative is to use a 1 mg tablet.

In conclusion, low-dose oral vitamin K correction does not reduce bleeding risk for asymptomatic supratherapeutic elevations of the INR from warfarin. ■

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Azacitidine for High-risk MDS

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In an international, multi-center trial of azacitidine in patients with either intermediate-2 or high-risk MDS, overall survival was significantly increased when compared to conventional therapy, which at the discretion of the investigator and patient, could have included intense chemotherapy, low-dose cytarabine, or best supportive care.*

Source: Fenaux P, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. *Lancet Oncol*. 2009;10:223-232.

Myelodysplastic syndromes (MDS) are heterogeneous in clinical presentation but, as a group, are considered a neoplastic disorder of bone marrow stem cells.[1] Coupling the French-American-British (FAB)[2] or World Health Organization (WHO) classification system[3] with cytogenetic and clinical features, an international prognostic scoring system has been developed,[4] and is now commonly used, to assess prognosis and determine treatment strategy. Using this, patients with intermediate-2 or high-risk scores (known as higher risk myelodysplastic syndromes) have a median survival of 1.2 years or 0.4 years, respectively.[4] Unfortunately, other than allogeneic bone marrow transplantation, no interventions have consistently resulted in improved survival.[5-8]

The current phase III, international, multi-center, controlled, parallel-group, open-label trial was undertaken to assess the effect of azacitidine on overall survival compared with three conventional care regimens. For this, patients with higher risk myelodysplastic syndromes were randomly assigned one-to-one to receive azacitidine (75 mg/m² per day for 7 days every 28 days) or conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy as selected by investigators before randomization on the basis of age, general condition, comorbidities, and patient preferences). Thus, the patient received either the azacitidine or the selected conventional regimen. Patients were stratified by FAB and international prognostic scoring system classifications, and the primary endpoint was overall survival. Efficacy analyses were by intention-to-treat for all patients assigned to receive treatment.

Over approximately 2.5 years, 358 patients were randomly assigned to receive azacitidine (n = 179) or conventional care regimens (n = 179). After a median follow-up of 21.1 months (Intra Quartile Range [IQR] 15.1-26.9), median overall survival was 24.5 months (9.9-not reached) for the azacitidine group vs. 15.0 months (5.6-24.1) for the conventional care group (hazard ratio 0.58; 95% CI 0.43-0.77; stratified log rank p = 0.0001). At last follow-up, 82 patients in the azacitidine group had died, compared with 113 in the conventional care group. At two years, on the basis of Kaplan-Meier estimates, 50.8% (95% CI 42.1-58.8) of patients in the azacitidine group were alive, compared with 26.2% (18.7-34.3) in the conventional care group ($p < 0.0001$). Peripheral cytopenias were the most common grade 3-4 adverse events for all treatments.

■ COMMENTARY

In a previous trial conducted by the Cancer and Leukemia Group B (CALGB), azacitidine was compared with best supportive care.[9] However, that trial included a cross-over design (53% of patients who received best-supportive care subsequently received azacitidine), making any conclusions about an observed survival advantage somewhat tenuous. However, the data from the trial indicated azacitidine treatment was associated with improved quality of life, reduced risk of leukemic transformation and improved survival, compared with supportive care. The current trial focused on those at highest risk, was larger, and offered an active treatment comparator, rather than supportive care alone. Another feature of the trial was the novel approach to the randomization process, which allowed a comparison of the efficacy of azacitidine with that of a control group of patients that were treated much as they would be in a community practice. As such, the observed increased survival and reduced rate of leukemia transformation associated with azacitidine treatment represents a significant step forward in the management of this difficult disease. ■

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Weekly Dose-dense Paclitaxel-Carboplatin for Recurrent Ovarian Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Using a "dose-dense" regimen of paclitaxel and carboplatin in heavily pre-treated, platinum-resistant ovarian cancer patients, a UK oncology group demonstrated that a more protracted treatment schedule (six months) was both tolerable and associated with an impressive overall response rate (60%). The findings provide rationale for a randomized clinical trial to examine this approach for relapsed ovarian cancer, particularly for those who relapse within a year of completing initial platinum-based treatment.*

Source: Sharma R, et al. Extended weekly dose-dense paclitaxel/carboplatin is feasible and active in heavily pre-treated platinum-resistant recurrent ovarian cancer. *Br. J Cancer*. 2009;100:707-712.

In the treatment of recurrent ovarian cancer, it is acknowledged that a return to a platinum-based regimen may be an effective approach, particularly if the interval since the last platinum treatment is a year or more.[1] Under that circumstance, the response rate might approach 60%. However, in patients relapsing after original platinum treatment within six months, the response rate is significantly lower (10-15%).[1]

In the current report, Sharma et al report a retrospective series of 20 patients with a diagnosis of epithelial ovarian cancer that were treated with "dose-dense" scheduling of carboplatin/paclitaxel having relapsed within six months from a platinum-based regimen. The median age of the patients enrolled was 61 years (range 40-74 years), and the median number of prior therapies was three (range 1-8). Carboplatin AUC 3 and paclitaxel 70 mg/m^2 were administered on days 1, 8, and 15 every four weeks, with the intent to deliver six cycles of chemotherapy. Baseline CT imaging of the chest, abdomen, and pelvis was carried out prior to the commencement of therapy and after every two cycles. Blood samples for full blood count, biochemistry, liver function tests, and serum CA125 tests were taken prior to the commencement of therapy and before each treatment. Tumor response was assessed after every two cycles with repeat CT chest, abdomen, pelvis, and by CA125 (GCIG criteria).[2,3] Data regarding the planned and delivered weekly dose intensity of treatment, the overall treatment dose delivered, toxicity, and clinical outcome were collected.

Response rate was 60% by radiological criteria (RECIST) and 76% by CA125 assessment. Grade 3 toxicities consisted of neutropenia (29% of patients) and anemia (5%). One patient experienced grade 4 neutropenia. No grade 3 or 4 thrombocytopenia was reported. Fatigue, nausea, and peripheral neuropathy were the most frequent non-hematological side effects. Median progression-free survival was 7.9 months, and overall survival was 13.3 months. The dynamics of response-to-dose-dense therapy were as rapid as with front-line therapy within the same patient.

■ COMMENTARY

There have been several efforts to develop effective and well-tolerated chemotherapy options for patients who have platinum-resistant ovarian cancer. A number of agents, including topotecan, gemcitabine,

liposomal doxorubicin, paclitaxel, and vinorelbine have been reported but response rates are generally less than 20%.[4,5] Thus evolved the interest in applying novel dose and scheduling paradigms reintroducing platinum in association with paclitaxel or other drugs, and several "dose-dense" regimens were developed. For example, van der Burg et al[6] reported a response rate of 46% in patients with a platinum-free interval (PFI) of < 4 months, with weekly cisplatin (50-70 mg/m^2) and daily oral etoposide for six weekly cycles followed by maintenance oral etoposide. Subsequently, weekly paclitaxel was found to have activity in platinum-resistant ovarian cancer, and combinations of these two agents were shown to improve both response rate and survival. The current retrospective analysis is of added value as it demonstrates that a dose-dense regimen can be highly effective, with acceptable toxicity in this heretofore difficult group of patients. ■

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Breast Cancer During Pregnancy

By William B. Ershler, MD

Synopsis: *Of 688 breast cancers occurring in 652 women 35 years and younger, 15.6% were associated with pregnancy (either during pregnancy or during the subsequent year). Although the tumors occurring in association with pregnancy were larger, there was no significant difference in local recurrence, distant metastases, or overall survival. There was a trend toward reduced overall survival among those pregnant women who delayed primary breast cancer therapy until after delivery.*

Source: Beadle BM, et al. The impact of pregnancy on breast cancer outcomes in women < 35 years. *Cancer*. 2009;115:1174-1184.

Approximately 10% of breast cancers that occur in woman younger than age 40 is associated with pregnancy,[1] and there is some evidence to suggest that pregnancy-associated breast cancers (PABC) are particularly aggressive.[2-4] However, others have found that breast cancer is more likely to present at a more advanced stage when associated with pregnancy, and that when matched for stage, prognosis is similar for patients with PABC when compared to similarly aged breast cancer patients.

To address this issue, Beadle et al from the University of Texas M.D. Anderson Cancer Center performed a retrospective analysis of patients treated at their Center to compare locoregional recurrence (LRR), distant metastases (DM), and overall survival (OS) in young patients with PABC and non-PABC.

For this, data on 668 breast cancers in 652 patients aged < 35 years treated from 1973 to 2006 were reviewed. Of these, 104 breast cancers (15.6%) were pregnancy-associated, 51 cancers developed during pregnancy, and 53 within one year after pregnancy. The median follow-up for all patients was 91 months (range 2-411 months). Comparing the groups (PABC or non-PABC), there were no differences in age, race, family history, decade of treatment, histology, or nuclear grade. However, patients who developed PABC had more advanced T classification, N classification, and stage group (all $p < .04$) compared with patients with non-PABC. Nonetheless, patients with PABC had no statistically significant differences in 10-year rates of LRR (23.4% vs. 19.2%), DM (45.1% vs. 38.9%) or OS (64.6% vs. 64.8%) compared with patients with non-PABC.

Among the patients who developed cancer during

pregnancy, approximately one half underwent some form of treatment, and there was a trend towards improved overall survival for that group compared to those who had elected to delay therapy (78.7% vs. 44.7%; $p = 0.068$).

■ COMMENTARY

It is a commonly held notion that breast cancer, when it occurs in young women, is particularly aggressive, and there are substantial data that support that contention.[5] Although pregnancy is associated with approximately 10% of breast cancers in young women, the data from this series, and from others[3,4,6] would seem to indicate that the pregnant state does not a priori confer a negative influence. The extensive experience at M.D. Anderson has, with this report, demonstrated that young patients with PABC had no statistically significant differences in local recurrence, distant metastases, or overall survival compared with those with non-PABC. However, pregnancy contributed to a delay in breast cancer diagnosis, evaluation, and treatment and, thus, patients, at the time of diagnosis, are found to have more advanced disease. Current preliminary observations from a clinical trial conducted at their institution mentioned, only briefly in this article, suggest that chemotherapy can be safely and effectively administered to pregnant women. If these preliminary findings are substantiated, it would represent a significant advance, as earlier treatment of breast cancer in the pregnant patient would likely result in a greater chance of increasing response rates and survival. Accordingly, primary care and reproductive physicians should be aggressive in the work-up of breast symptoms in the pregnant population to arrive at a diagnosis and allow an earlier introduction of effective therapy. ■

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Combined Endocrine and Radiation Approach for Locally Advanced Prostate Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In patients with advanced- or high-risk but local prostate cancer, the addition of local radiotherapy to endocrine treatment was shown to halve the 10-year prostate cancer-specific mortality and substantially reduce overall mortality in a phase III, randomized, multi-center clinical trial conducted in Northern Europe. The impressive findings support this combined modality approach as the standard to which future interventions must be compared.*

Source: Widamark A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer: an open randomized phase III trial. *Lancet*. 2009;373:301-308

For patients with locally advanced prostate cancer, the issue of whether local radiotherapy adds to hormonal treatment alone remains to be established. To address this question, the Scandinavian Prostate Study Group and the Swedish Association for Urological Oncology have recently completed a phase III study comparing endocrine therapy with and without local radiotherapy, followed by castration at the time of progression.

This randomized trial included men from 47 centers in Norway, Sweden, and Denmark. Between February 1996 and December 2002, 875 patients with locally advanced prostate cancer were enrolled. Eligibility criteria were histologically proven prostate cancer in men younger than 76 years, with good performance status, a life expectancy of more than 10 years, and with tumors categorized as clinical T1b-T2, G2-G3, or T3 and WHO Grade 1-3. Participants had a prostate-specific antigen (PSA) of 70 ng/mL or less and no evidence of metastases, as determined by bone scanning and pulmonary radiography. Those with a PSA of 11 ng/mL or more had a pelvic lymph node dissection (fossa obturatoria); patients with nodal disease were not eligible for the trial.

Patients were randomly assigned to either endocrine alone (n = 439) or endocrine plus radiotherapy (n = 436). After randomization, all patients were

given endocrine treatment with total androgen blockade with an LHRH-agonist, leuprorelin (Procren depot; Abbott, 3.75 mg/month or 11.25 mg/every three months), for three months, and were simultaneously treated with 250 mg of an oral antiandrogen, flutamide (Eulexin, Schering-Plough), three times a day. After three months of total androgen blockade, patients continued using flutamide until progression or death. After three months, patients in the endocrine plus radiotherapy group started radiotherapy. For this, a standard 3D conformal radiotherapy technique was applied with a prescribed central dose (of 50 Gy) to the prostate and the seminal vesicles. A sequential boost of at least 20 Gy was added to the prostate, which received a total dose of a minimum of 70 Gy. A margin of 20 mm (15 mm in posterior direction) was added. If optimum immobilization could be achieved, the margins were reduced accordingly.

When antiandrogen treatment side effects were evident, flutamide was stopped and then reinstituted with a stepwise-increased dose to at least 500 mg. If this treatment failed, antiandrogen was changed to bicalutamide (150 mg/once a day). Eighty percent of all patients received breast irradiation to prevent gynecomastia.

The primary endpoint was prostate-cancer-specific survival, and analysis was by intention-to-treat. After a median follow-up of 7.6 years, 79 men in the endocrine alone group and 37 men in the endocrine plus radiotherapy group had died of prostate cancer. The cumulative incidence at 10 years for prostate-cancer-specific mortality was 23.9% in the endocrine alone group and 11.9% in the endocrine plus radiotherapy group (difference 12.0%,;95% CI 4.9-19.1%), for a relative risk of 0.44 (0.30-0.66). At 10 years, the cumulative incidence for overall mortality was 39.4% in the endocrine-alone group and 29.6% in the endocrine plus radiotherapy group (difference 9.8%; 0.8%-18.8%), for a relative risk of 0.68 (0.52-0.89). Cumulative incidence at 10 years for PSA recurrence was substantially higher in men in the endocrine-alone group (74.7% vs. 25.9%, $p < 0.0001$; HR 0.16; 0.2-0.20). After five years, urinary, rectal, and sexual problems were slightly more frequent in the endocrine plus radiotherapy group.

■ COMMENTARY

Thus, in patients with locally advanced or high-risk local prostate cancer, addition of local radiotherapy to endocrine treatment halved the 10-year prostate cancer-specific mortality and substantially decreased overall mortality with fully acceptable risk of side effects compared with endocrine treatment alone. Previous studies had shown that the combination of radiotherapy and sustained androgen-deprivation improves outcome compared with radiation therapy alone in high-risk prostate cancer.[1,2] However, in studies in which androgen was short-term or of intermediate duration, the survival advantage could only be observed in subgroups of patients.[3,4] In the current study, the survival at 10 years increased from 60.6% to 70.4% in favor of the endocrine plus radiotherapy and, thus, accentuate the importance of local radiotherapy treatment in high-risk patients with prostate cancer. It is curious that the combination of surgery and androgen ablation has not shown increased efficacy over surgery alone,[5] possibly suggesting a synergy between endocrine factors and radiation-induced biological effects. ■

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CME Questions

15. What was found when comparing treatment using low-dose oral vitamin K of 1.25 mg vs. placebo to correct supratherapeutic INRs related to warfarin?

a. Bleeding risks were similar.
b. Vitamin K greatly increased the risk of thrombosis.
c. Warfarin resistance developed in vitamin K treated patients
d. All of the above

16. **For patients with high-risk myelodysplastic syndrome, azacitidine therapy, when compared with conventional approaches (including intensive chemotherapy, low-dose cytarabine, or best supportive care), was associated with:**
    a. improved response rates but no change in overall survival.
    b. improved overall survival.
    c. improved response rates but worse overall survival.
    d. None of the above

17. **In the retrospective series of platinum-resistant patients treated with paclitaxel/carboplatin one significant difference, when compared with other published "dose -dense" regimens for ovarian cancer, was:**
    a. the larger dose of carboplatin employed with each weekly injection.
    b. the duration of treatment (six months).
    c. the larger dose of paclitaxel employed with each weekly injection.
    d. All of the above

18. **Breast cancer, when it occurs during pregnancy, compared to when it occurs in age-matched non-pregnant women, is associated with:**
    a. a higher rate of local recurrence.
    b. more frequent distant metastases.
    c. shorter overall survival.
    d. None of the above

19. **The addition of radiation to endocrine therapy for locally advanced prostate cancer was found by the Scandinavian Prostate Cancer Group 7 and Swedish Association for Urological Oncology 3 study at 10 years to be associated with:**
    a. lower rates of PSA recurrence.
    b. lower rates of cancer-related death.
    c. improved overall survival.
    d. All of the above
    e. None of the above

Answers: 1. (a); 2. (b); 3. (b); 4. (d); 5. (d)

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The objectives of *Clinical Oncology Alert* are:

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In Future Issues:

Adherence to Prescribed Tamoxifen

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
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VapoRub Revisited

Source: Abanses JC, et al. Vicks VapoRub induces mucin secretion, decreases ciliary beat frequency, and increases tracheal mucus transport in the ferret trachea. *Chest* 2009;135:143-148.

THOSE OF US IN THE BABY-BOOMER generation may recall in the 1940s-50s the application of a generous quantity of some Vicks® VapoRub-type salve (VvR) to the chest wall as a time-honored remedy that grandma suggested for the common cold. Toxicity of VvR, rather than efficacy, was the subject of this publication.

As with essentially any therapeutic agent, there is always the potential for adverse effects. Based upon a single case report of a toddler who developed respiratory distress subsequent to peri-nasal application of VvR, Abanses et al investigated potential adverse physiologic effects of VvR by experiments in ferrets.

VvR resulted in increased mucin secretion and decreased ciliary beat frequency (as observed by video microscopy), the combination of which could lead to small-airway obstruction. The authors report upon studies of menthol (an ingredient of VvR) in adults, in which, despite a decrease in nasal airflow, subjects universally report improved nasal symptoms; this change is attributed to the cooling effect of menthol in the nasal passages, which the brain interprets as increased airflow across the nostrils.

VvR appears to be a generally safe remedy, but case reports suggest caution in young children. The case presented here was initially treated as asthma; clinicians might consider asking about VvR use in children who present with new, otherwise unexplained symptoms of respiratory distress. ■

Prostate Cancer Risk with Testosterone Replacement

Source: Shabsigh R, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: A systematic review. *Int J Impot Res* 2009;21:9-23.

GROWTH AND DEVELOPMENT OF THE prostate is recognized to be testosterone (TST)-dependent. Clinicians have long held concerns that TST therapy might not only worsen symptoms of benign prostatic hyperplasia (BPH), but also stimulate the development, growth, proliferation, or aggressiveness of prostate cancer (PCa). Some of this concern stems logically from the observation that TST deprivation has salutary effects on prostate cancer growth.

This systematic review of 44 articles using FDA-approved agents was unable to directly provide a definitive answer to the question of whether TST replacement increases risk of PCa, but provides other interesting insights. First, trials of hypogonadal men treated with TST have not evidenced an increased risk for PCa; if anything, a protective effect may occur. Second, TST-treated men with a history of PCa did not experience more recurrences or metastases. Third, TST did not appear to influence Gleason scores when PCa was detected.

The authors conclude, "There is no evidence that TST increases risk of prostate cancer in hypogonadal men." Of some concern, however, are the case reports of aggressive PCa in recipients of a non-FDA-approved supplement containing TST, estradiol, chrysin, and elk velvet antler. ■

The Suicidal Process: Time to Intervene?

Source: Deisenhammer EA, et al. The duration of the suicidal process. *J Clin Psychiatry* 2009;70:19-24.

SUICIDE HAS BEEN IN THE TOP CAUSES of death in the United States for more than 20 years, usually ranking among the top 10. Clinicians would like to play a useful role in suicide prevention, yet data are sparse to inform about the interval between first suicidal ideation and a suicide attempt. Deisenhammer et al attempted to bridge this knowledge gap with a study of persons with failed suicide attempts, all of whom (n = 82) were interviewed within 72 hours of attempted suicide.

Most (83%) subjects were alone at the time of suicide conceptualization, and almost half reported the time from first suicide conception to attempt was 10 min or less. Nonetheless, during this brief interval, most (77%) had some contact (usually by telephone) with friends or family, and the majority indicated their wish to die or (according to their subjective reports) hinted at their death wish.

Interviews with subjects did not provide any insight as to what might have deterred the suicide attempt. Nonetheless, the fact that most suicidal subjects did make contact with others leaves open the possibility that some component of interpersonal communication has the potential to change the course of suicide attempts. ■

BNP to Guide Treatment of Heart Failure

Source: Pfisterer M, et al. BNP-guided vs symptom-guided heart failure therapy. *JAMA* 2009;301:383-392.

For Americans aged 65 or older, congestive heart failure (CHF) remains the most common diagnosis for hospital admission. Despite advances in therapy, the outcome of CHF remains daunting, with 5-year mortality rates as high as many malignancies. Because brain natriuretic peptide (BNP) reflects left ventricular wall stress, it can be useful to assist in diagnosis of CHF. Additionally, some, but not all, clinical trials have suggested that intensification of therapy to achieve optimization of BNP is associated with improved outcomes. The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) was devised to provide a more definitive comparison between the success of treatment intensification based upon symptoms vs level of BNP.

Patients with CHF (n = 499) were randomized to BNP-directed management (titrate treatment until BNP < 400 ng/mL) vs symptomatic management (intensify treatment until NYHA class II symptoms or better). Follow-up for the primary endpoint—hospitalization-free survival—was 18 months.

The BNP group experienced more aldosterone antagonists use, as well as more frequent increases in dose and utilization of ACE inhibitors and ARBs. However, there was no difference in the primary endpoint. In subjects age < 75 years, there was a reduction in mortality favoring BNP-directed management; however, because this was a secondary endpoint and the primary endpoint did not achieve statistical significance, it must be considered exploratory, not established. BNP-guided intensification of treatment is no more effective than standard symptom-directed methods. ■

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Clopidogrel and CV Events: One Size Does NOT Fit All

Source: Simon T, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-375.

Utilization of clopidogrel (CPG) in patients with acute coronary syndromes (ACS is well established. Similarly, long-term prophylaxis with CPG for secondary prevention of CV events is evidence-based: The CAPRIE trial indicated that CPG is marginally superior to aspirin for endpoint reduction, and the PROFESS trial demonstrated that ER-dipyridamole/aspirin (Aggrenox®) failed to meet the non-inferiority threshold when compared to CPG for stroke prevention.

Residual risk in persons receiving CPG remains substantial, suggesting that perhaps the efficacy of CPG is not universal; i.e., some subjects might metabolize CPG differently than others, leading to different levels of efficacy (or adverse effects).

The French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) study enrolled ACS patients on CPG, and studied the relationship of genetic variants that result in variations in absorption, activation, and biologic activity of CPG. Next, the relationship between these genetic variants and adverse outcomes (death, stroke, MI) were studied.

The most important genetic variant appeared to be at the P450 2C19 gene. Those with 2 loss-of-function 2C19 genes were almost 4 times as likely to have a CV event over the next year as those without. The P450 2C19 gene is utilized for metabolism of CPG to its active metabolite; lesser antiplatelet activity would be anticipated in persons with impaired P450 2C19 activity. These results support the findings of another trial in the same issue of *The New England Journal of Medicine* that identified increased CV risk in persons with reduced 2C19 P450 functionality. ■

Estrogen + Progesterone and Breast Cancer

Source: Chlebowski RT, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009;360:573-587.

The Women's Health Initiative (WHI) provided convincing evidence that the use of estrogen + progesterone (E+P) in postmenopausal women is associated with an increased risk of breast cancer (BrCa). The outcomes of this clinical trial motivated large numbers of women and their clinicians to rethink the risk-benefit balance of hormone therapy (HT), evoking a sea-change in prescribing habits.

Despite the acknowledged association between E+P and BrCa in WHI, a concomitant decline in use of mammography following the WHI news invited the possibility that post-WHI, less BrCa screening might have influenced the observed BrCa decline rather than simply less E+P use. To study this issue, WHI investigators evaluated two data sets: the original WHI population (n = 16,608 women without BrCa at baseline) and a second observational study population (n = 41,449 without BrCa at baseline). The observational study group did not receive advice about whether to use E+P, but were informed about the results of the interventional WHI when it became available. In the observational WHI population, more than 16,000 women were taking E+P at baseline.

Long-term follow-up of the observational WHI population showed an increased incidence of BrCa in women who had used E+P. BrCa incidence in this population declined subsequent to HT discontinuation. This suggests the possibility that some early breast cancers may regress or disappear if HT is stopped. The data did not, however, provide a meaningful association between lesser use of mammography and reduced BrCa. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Warfarin May Be First to Apply Pharmacogenetics

In this issue: Individualization of therapy with pharmacogenetics; the rate vs rhythm debate; the FDA's Risk Evaluation and Mitigation Strategy; FDA actions.

Individualization with pharmacogenetics

Get used to the word "pharmacogenetics" — the discipline of studying genetic variation and its effect on responses to drugs. Warfarin dosing may be one of the first clinical applications of pharmacogenetics as it now appears that genetic testing may help predict an individual patient's response to the oral anticoagulant. Warfarin dosing can vary as much as 10 times from individual to individual, and currently, slow titration with frequent testing is the only way to safely initiate therapy. A new study, however, uses pharmacogenetic testing to estimate the appropriate warfarin dose. Reviewing data from more than 4000 patients, algorithms were developed based on clinical variables only or clinical variables plus genetic information (CYP2C9 and VKORC1). Compared to algorithms employing clinical data alone, algorithms employing genetic information more accurately identified a larger proportion of patients who would require low-dose (49.4% vs 33.3%; $P < 0.001$) or high-dose warfarin (24.8% vs 7.2%; $P < 0.001$). The authors conclude that pharmacogenetic algorithms for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than algorithms derived from clinical data alone or a fixed-dose approach, particularly for those that require 49 mg or more per week or 21 mg or less per week. (*N Engl J Med* 2009;360:753-764). Although pharmacogenetic testing is not yet widely available and may be difficult to obtain prior to initiating warfarin therapy, an accompanying editorial states "pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'" (*N Engl J Med* 2009;360:811-813).

The rate vs rhythm debate

Rate control vs rhythm control for atrial fibrillation continues to be debated with most of the evidence falling on the side of rate control in recent years, primarily because of adverse effects from anti-arrhythmics. A new drug may change that however. Dronedarone, a derivative of amiodarone, lowers the hospitalization rate and death rate in atrial fibrillation according to a new phase 3 study. More than 4600 patients with atrial fibrillation and one additional risk factor for death (diabetes, stroke, CHF) were randomized to dronedarone 4 mg twice a day or placebo. The primary outcome was first hospitalization due to cardiovascular event or death. After follow-up of 21 months, 30% of patients in the treatment group and 31% patients in the placebo group stopped the drug prematurely due to adverse events. The primary outcome occurred in 31.9% of patients in the dronedarone group vs 39.4% in the placebo group (hazard ratio, 0.76; 95% confidence interval,

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0.69-0.84; $P < 0.001$). Five percent (5%) of people died in the treatment group vs 6% in the placebo group ($P = 0.18$). Deaths from cardiovascular causes were 2.7% in the dronedarone group vs 3.9% in the placebo group ($P = 0.03$). The treatment group had higher rates of bradycardia, QT interval prolongation, nausea, diarrhea, rash, and increased creatinine levels. Dronedarone was not associated with higher rates of thyroid or pulmonary-related adverse events. The authors conclude that dronedarone reduced the risk of hospitalization due to cardiovascular events or death in patients with atrial fibrillation (*N Engl J Med* 2009;360:668-678). Dronedarone is not yet approved in this country, and is being evaluated for other cardiac arrhythmias as well as atrial fibrillation. A trial in heart failure (ANDROMEDA) was terminated early because of increased mortality associated with dronedarone (*N Engl J Med* 2008;358:2678-2687).

New rules for opioid prescribing

The FDA is considering new tightened restrictions on use of opioid drugs. Manufacturers of these drugs will be required to have a Risk Evaluation and Mitigation Strategy to ensure that "the benefits of the drugs continue to outweigh the risks." The affected opioids include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. This is in response to raising rates of misuse and abuse of these drugs as well as accidental overdoses, which have increased in the last 10 years. The agency plans to have a number of meetings later this year that will include patient groups, federal agencies, and other non-government institutions. Part of the strategy is to make sure that physicians prescribing these products are properly trained in their safe use.

In February, the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel published clinical guidelines for the use of chronic opioid therapy and chronic noncancer pain. The guideline was commissioned because of the increased use of chronic opioid therapy for noncancer pain and the high risk for potentially serious harm associated with these drugs including opioid-related adverse effects. The guideline's recommendations include: Before initiating chronic opioid therapy (COT), clinicians should conduct a history, physical, and appropriate testing including assessment of risk for substance abuse, misuse, or addiction. A benefit-to-harm evaluation should be performed and documented before starting COT and on an ongoing basis for all patients on COT. Informed consent should be obtained when initiating therapy, and a continuing discussion with the patient regarding therapy should include goals, expectations, risks, and alternatives. Clinicians may consider a written COT management plan. Patients should be reassessed periodically including monitoring of pain intensity and levels of functioning.

For high-risk patients or those who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care. For patients at risk of addiction, mental health or addiction specialists should be consulted, and if aberrant drug-related behaviors continue, referral for assistance in management or discontinuation of COT should be considered. The guideline also deals with dose escalations, use of methadone, treatment of opioid-associated adverse effects, cognitive impairment associated with COT that may affect driving and workplace safety, use in pregnancy, and state and federal laws that govern the medical use of COT (*J Pain* 2009;10:113-130).

FDA Actions

The FDA has issued a public health advisory regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with use of efalizumab (Raptiva®) for the treatment of psoriasis. Four cases have been reported (3 have been confirmed). The FDA is recommending that health care professionals monitor patients on efalizumab, as well as those who have discontinued the drug, for signs and symptoms of neurologic disease.

The FDA has reaffirmed its position regarding cholesterol-lowering drugs stating that "elevated amounts of low-density lipoprotein … are a risk factor for cardiovascular diseases … and that lowering LDL cholesterol reduces the risk of these diseases." The statement is in response to results from the ENHANCE trial, which indicated that there was no significant difference between simvastatin plus ezetimibe (Vytorin®) vs simvastatin alone (Zocor®) in reducing carotid atherosclerosis. There was, however, a greater reduction in LDL in the Vytorin group vs the Zocor group (56% reduction vs 39% reduction, respectively). The statement from the FDA suggests that the results of ENHANCE do not change the FDA's position that greater LDL lowering is beneficial, and recommends that patients currently on Vytorin or other cholesterol-lowering medications should not change their therapy. The update is available on the FDA's web site at www.FDA.gov. ■