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CLINICAL ONCOLOGY ALERT

A monthly update of developments in cancer treatment and research

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INSIDE

Financial Disclosure:
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.

CA-125 Level Predicts Outcome of Maintenance Chemotherapy for Ovarian Cancer in Remission

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *There has been a suggestion that the level of CA-125 for ovarian cancer patients who are in complete remission predicts the risk of relapse. In a retrospective analysis of maintenance chemotherapy for this disease conducted by the Southwest Oncology Group (SWOG) and the Gynecologic Oncology Group (GOG), Markman and colleagues found that the baseline CA-125 level before maintenance chemotherapy (with either three or 12 monthly cycles of paclitaxel or oral altretamine) strongly predicts the risk of recurrence. Those with CA-125 levels ≤ 10 u/mL were found to have a superior progression free survival (PFS) compared with higher CA-125 levels within the normal range. Thus the CA-125 level prior to the initiation of maintenance chemotherapy may prove a useful parameter for future clinical trials addressing a major unresolved issue in ovarian cancer: optimal treatment for maintenance of remission.*

Source: Markman M, et al. Pretreatment CA-125 and risk of relapse in advanced ovarian cancer. *J Clin Oncol*. 2006;24:1454-1458.

For patients with advanced ovarian cancer, platinum-taxane-based chemotherapy has proven successful in achieving a high level of disease remission, but, unfortunately, in the great majority, relapses occur.[1] Accordingly, there has been an increased interest in developing maintenance chemotherapy strategies to enhance progression-free survival (PFS). It has been proposed that a possible predictor of successful maintenance chemotherapy is a very low level of serum CA-125 prior to the initiation of maintenance chemotherapy. Typically, one criterion for complete remission after initial chemotherapy for advanced ovarian cancer is the normalization of the CA-125 level and currently most oncologists do not choose the chemotherapy agents or duration of therapy on the basis of the CA-125 level. Thus, patients with a level of 5 u/mL

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will typically receive the same treatment as those with levels closer to the upper limit of normal (near 35 u/mL). In the current report, Markman and other investigators of the Southwest Oncology Group (SWOG) and the Gynecologic Oncology Group (GOG) conducted a retrospective analysis of two previously reported trials of maintenance chemotherapy (3 vs 12 monthly cycles of paclitaxel; oral altretamine). All patients were in complete remission and all had a baseline CA-125 level of less than 35 u/mL. For the purpose of analysis, patients were identified as in one of three groups based upon their pretreatment CA-125 level: A) ≤ 10 u/dL; B) 11-20 u/dL; or C) 21-35 u/dL. PFS from study entry was analyzed by the Cox regression model.

The distribution of pre-maintenance baseline CA-125 levels for 384 patients was 58% less than or equal to 10 u/mL, 34% between 11 and 20 u/mL, and 8% between 21 and 35 u/mL. The baseline CA-125 was highly significant either as a categoric variable ($P < 0.001$) or as a continuous variable ($P < 0.0001$). Median PFS was 24 months, 17 months, and 7 months for groups A, B, and C noted above respectively. Although the patients were enrolled from different trials, there was no evidence that the CA-125 level effect differed by treatment using an interaction analysis. Thus, the baseline CA-125 level before initiation of maintenance chemotherapy was found to strongly predict the risk of subsequent relapse. The patients with pre-maintenance baseline CA-125 values of ≤ 10 u/mL have a superior PFS compared with higher levels in the normal range.

COMMENTARY

It is apparent that maintenance chemotherapy for those who achieve complete remission after primary chemotherapy for advanced ovarian cancer has a role in improving overall survival. However, it is not yet clear which drugs to use, and for how long. Furthermore, in the context of added toxicities and infringements on quality of life, it is not absolutely clear that the improvements in PFS are of sufficient magnitude to warrant uniform recommendation at this time. Thus, the availability of information relating the likelihood of relapse and expected remission duration to a pretreatment serum marker is likely to be considered valuable by both physician and patient.

The current report provides significant insight in this regard. For those who completed initial therapy and prior to maintenance were found to have a low CA-125 level (≤ 10 u/mL), the PFS was significantly longer in each of the various treatment schedules examined in this analysis. Higher pretreatment CA-125 levels were associated with shorter durations of remission. Why should this be? One likely explanation is that those with very low levels of CA-125 have a smaller tumor burden. Another is that they have more chemosensitive tumors. Of course, in a retrospective analysis such as this, it would be impossible to discern these or other explanations; perhaps this will be addressed in future investigations. Nonetheless, clinicians might find the observation of practical value while formulating post-remission plans for their patients.

Furthermore, clinical investigators attempting to define optimal maintenance chemotherapy regimens might be advised to consider and perhaps stratify on the basis of the pretreatment CA-125 level. ■

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Hemophilia Carriers and Bleeding Risk in Anemic Older Adults

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Section of Hematology/Oncology, University of Chicago

Dr. Artz reports no financial relationship to this field of study.

Synopsis: *Female hemophilia carriers have not usually been considered at increased risk of bleeding unless factor levels are below 40%. In this observational study of comparing female carriers and non-carriers, carriers showed an increased risk of bleeding, particularly after medical interventions. The risk appeared to increase with levels below 60%. Clinicians should be aware that female carriers of hemophilia may be at increased risk of bleeding. Future research is needed to confirm the bleeding risk, identify factor levels predisposing to bleeding, and determine optimal prophylaxis/intervention strategies.*

Source: Plug I, et al. Bleeding in Carriers of Hemophilia. *Blood*. 2006:108:52-56.

Hemophilias refer to bleeding disorders from deficiencies of factor VIII (hemophilia A) or factor IX (hemophilia B). Common bleeding sites include joints, muscles, and the GI tract, although clinical severity varies depending in large part to factor levels. As an X-linked recessive disorder, men are mostly affected and women are heterozygous carriers. The factor levels in female carriers average about 50% of normal although wide variation occurs attributable to random X-chromosome inactivation and potentially other factors as well. In general, carriers have not been considered at increased bleeding risk unless levels were below 40%. Minimal data have actually examined the association of carriers and factor levels with bleeding risk and severity.

In this observational study, all women who were tested for being carriers of hemophilia A or B in the Netherlands were contacted. Factor levels were documented from medical charts. Among the 766 questionnaires on bleeding history, 546 were returned (80%). The final analysis entailed 274 carriers and 245 non-carriers. The mean age was similar at 39 and 40 years, respectively although more carriers had factor levels ascertained. The median factor levels were 0.60 IU/mL for carriers and 1.02 IU/mL for non-carriers. Carriers showed an increased risk of small wound (RR = 2.2) and joint bleeds (RR = 1.9), but no increased risk of epistaxis, bruising, or gum bleeding. Bleeding for greater than 3 hours after a medical intervention was increased in carriers as was the need to receive a medical intervention (intervention not specified). A trend existed for increased bleeding risk for clotting factor levels between 0.60 to 0.41 IU/mL and more severe bleeding for levels 0.40 IU/mL and below.

COMMENTARY

The authors conclude that female hemophilia carriers have an increased risk of bleeding and that levels below 0.60 IU/mL serve as a marker for increased risk. The data are provocative and challenge traditional assumptions that bleeding risk may only be increased at levels of < 40% (40 IU/mL). Limited data have explored at what factor level, particularly for hemophilia carriers, does the risk of bleeding increase.

Important bias may exist in observational studies. Because carriers and non-carriers were ascertained from living in a household with a known case, the impact of environment should have been similar. The authors believe that awareness of carrier status does not necessarily impact report of bleeding tendency[1] but one can not exclude this. The important finding that carriers have an increased risk of bleeding after trauma and medical interventions related to factor levels may be biased from health care providers knowledge of carrier status and/or factor levels. Physicians may be more likely to monitor and/or treat bleeding symptoms in a known carrier, particularly if factor levels were low. Another limitation is that factor levels analyzed were the lowest level available in the chart. If factors levels were lower at the time of bleeding, the risk of bleeding from low factors levels would be underestimated.

The authors' work does challenge traditional assumptions and raises awareness of the potential for bleeding in carriers of hemophilia, even at factor levels below between 40 and 60% of normal. The data have enough limitations to definitive recommendations. Prospective data on bleeding risk and severity related to factor levels are needed. Many questions remain unanswered and require more research. Should we routinely check levels in known or suspected carriers before surgery? Should prophylaxis for high-risk surgery be considered when levels are < 0.60 IU/mL? If so, what therapy should be used?

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Obesity and Endometrial Cancer: Another Piece in the Puzzle

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Merck, and Ortho Biotech.

Synopsis: *Adiponectin level was found to be independently and inversely associated with endometrial cancer.*

Source: Soliman PT, et al. Association between adiponectin, insulin resistance and endometrial cancer. *Cancer*. 2006;106: 2376-2381.

ONE OF THE MOST RECOGNIZED RISK FACTORS FOR the development of endometrial cancer is obesity. However, recent studies have suggested that this factor alone cannot fully account for all the risk associated with obesity.[1,2] Insulin resistance has been suspected as a potential mechanism for carcinogenesis in these patients. Soliman and colleagues examined this issue by conducting a case-control, retrospective study of 117 women diagnosed with endometrial cancer (cases) and 238 women without endometrial cancer (controls) in whom adiponectin, a protein secreted by adipocytes, could be measured. Adiponectin has been shown to be a surrogate marker for insulin resistance, with low levels correlated with hyperinsulinemia and degree of insulin resistance.

The authors found that mean serum adiponectin levels were significantly lower among endometrial cancer cases than among non-cancer controls. This effect remained significant even after controlling for age, body mass index, diabetes, and hypertension. Cases were significantly more likely to have serum adiponectin levels in the lowest and intermediate tertiles when compared with controls. For instance, women with endometrial cancer were 10.5 times more likely to have adiponectin levels in the lowest tertile compared with controls. Based on a multivariate analysis, adiponectin level was found to be independently and inversely associated with endometrial cancer, even after controlling for body mass index. The authors concluded that insulin resistance, as measured by adiponectin levels is independently associated with endometrial cancer.

COMMENTARY

Endometrial cancer is the most common gynecologic malignancy and is among the few gynecologic sites increasing in annual incidence. Most patients, fortunately, are diagnosed with disease limited to the corpus where surgical extirpation is curative. Recent clinical investigative focus in this disease has been rooted in refining the nuances of surgical management and defining appropriate adjuvant therapy strategies. However, accelerating rates of obesity, a recognized national health care issue, is thought to be a dominant contributing force to disease prevalence in the US population. Our understanding as to how obesity is linked to the development of endometrial cancer is mechanistically hypothesized to occur through mitogenic endogenous estrogen exposure leading to prolonged growth signals at the target organ. The relationship is predicated on heightened peripheral conversion of androstenedione to estrone from adipose tissue. However, a well recognized cohort of patients, normal in weight is also known to develop the disease. Conversely, high body mass index has been correlated to endometrial cancer risk independent of endogenous estrogen levels. This suggests other factors associated with obesity may contribute to carcinogenesis. The authors of the current report hypothesized insulin resistance may be one of these factors.

A clear indicator of how insulin resistance is associated with this disease has been difficult to find. For instance, while hyperinsulinemia is associated with an increased risk of endometrial cancer and women who are insulin resistant and obese have the highest risk of endometrial cancer, hyperinsulinemia alone does not explain the association of obesity and cancer development. Soliman and colleagues examine the association of adiponectin, a unique protein correlated with insulin resistance, in endometrial cancer. Low levels of adiponectin have been associated with the hyperinsulinemia and the degree of insulin resistance, independent of body mass index. Their observation that low levels of adiponectin, and therefore insulin resistance, is associated with an increased risk of endometrial cancer, independent of obesity, corroborates previously reported retrospective studies and helps to understand the phenomena of diabetes and disease development. Further validation in prospective studies will help to assign individual risk on the basis of serial determinations offering a surrogate measure through which intervention may be levied to modulate acquired cancer potential. ■

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Radiation Alone: Is This Sufficient Treatment for Younger Men with Early Stage Prostate Cancer?

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a nicely executed matched pair analysis of clinical outcomes after external beam radiation as primary treatment for prostate cancer, younger patients, defined as those 55 years or younger had equivalent outcomes, defined by freedom from biochemical failure, freedom from distant metastases and overall survival at 5 years when compared to older patients. The findings suggest that younger aged patients with localized (organ-confined) disease may be as effectively treated by external beam radiation as older patients, and that the concerns that younger patients have more 'aggressive' disease should not preclude this treatment option.*

Source: Konski A, et al. Does age matter in the selection of treatment for men with early stage prostate cancer? *Cancer*. 2006;106:2598-2602.

Until recently, younger men diagnosed with prostate cancer were frequently not offered external beam radiation as primary therapy on the premise that such would be inadequate for what is likely to be more virulent disease. However, over the past decade, studies have been published which demonstrate that younger patients treated with external beam radiation therapy do not have a higher risk of biochemical failure when compared to older patients with similar stage disease.[1,2]

The current study was designed to evaluate the effect of external beam radiation alone as a treatment option for younger men with prostate cancer. A retrospective study of 252 patients treated at the Fox Chase Cancer Center between November 1989 and October 2001 were evaluated in the context of age at presentation and overall survival. A matched-pair analysis compared those patients < 55 years (Group 1; n = 84) who were treated with 3-dimension conformal radiation without androgen deprivation to similarly-treated men age > 60 to 70 years (Group 2; n = 84) and men age > 70 years (Group 3; n = 84). The groups were matched with regard to disease stage, Gleason grade, and pre-treatment PSA levels. The majority of men had low-stage, low-grade cancer and received between 70-76 Gy of radiation. Using Kaplan-Meier methodology, there was no statistically significant difference found in the biochemical disease-free survival, freedom from distant metastasis or overall survival among the 3 groups at 5 years.

COMMENTARY

The goal of the current study was to evaluate outcome in a cohort of men age < 55 years with localized prostate cancer who were treated with external beam radiation therapy with similar treatment in older patients. The commonly held notion that younger patients have more aggressive disease would predict that those younger patients would not have equivalent treatment outcomes, but this turned out not to be the case. For all examined parameters the responses among the three age groups were nearly identical.

A study such as this is only as good as the effort to assure comparability among the groups. Indeed, a credible job was done in this regard, matching individuals in each group by stage, grade and PSA. Yet, one can not help but have the concern that prostate cancer patients less than 55 years of age referred for primary external beam radiation as opposed to alternative radiotherapy approaches or radical prostatectomy are somewhat atypical, either because of existing co-morbidities or other complicating factors and that younger patients who were otherwise healthy might be the same individuals for whom aggressive tumor growth would be predicted. Thus, the report would have been strengthened had the matching process included the presence or absence of certain key co-morbidities or functional impairments.

That stated, the results are consistent with other reports comparing outcomes in younger vs. older prostate cancer patients.[1-4] The same group from Fox Chase had earlier reported that men < 65 years did not have a worse outcome compared with those > 65 years.[1] Furthermore, Zelefsky et al[2] found comparable rates of biochemical failure between younger (< 60 years) and older (> 60 years) prostate cancer patients after external beam radiation. Similar lack of age differences in outcome have been reported for those treated with surgical

approaches.[3,4] The added value from the current report is the careful effort at matching younger and older patients with regard to Gleason grade, stage and PSA, the mismatch of which could have confounded earlier analyses.

Are we to dispense with this notion that younger patients with prostate cancer have more aggressive disease? Probably not, for several reasons. In an extensive analysis of the NCI SEER (Surveillance, Epidemiology and End Results) data, Merrill and Bird[5] found that the 5-year relative survival rate increased, leveled off and then decreased over the age span. Conditional death hazards demonstrating statistically significantly higher hazard ratios in men age 40-44 years and age 45-49 years included locoregional stage, distant stage and poorly differentiated or undifferentiated tumors. Their analysis (which included nearly 290,000 cases) allowed the conclusion that younger age was a negative prognostic factor for prostate cancer survival, but this was most apparent for the youngest of patients (< 45 years), and not apparent after a certain age threshold is reached. This is a situation reminiscent of breast cancer in which indolent disease is more apparent in older patients and aggressive disease more frequently observed in the youngest.[6] ■

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Risks of Catheter-Related Thrombosis in Cancer Patients

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a prospective, observational study from a single institution, consecutive patients with cancer undergoing insertion of a central venous catheter were followed for the occurrence of symptomatic catheter-related thrombosis, symptomatic pulmonary embolus or postphlebitic syndrome. Of the 444 patients enrolled, 19 (4.3%) had symptomatic catheter-related thrombosis and risk factors included more than one insertion attempt, previous central venous catheter insertion, and ovarian cancer. There were no cases of symptomatic pulmonary embolus, and postphlebitic syndrome occurred infrequently.*

Source: Lee AY, et al. Incidence, risk factors and outcomes of catheter-related thrombosis in adult patients with cancer. *J Clin Oncol*. 2006;24:1404-1408.

ONCOLOGISTS ARE BECOMING INCREASINGLY COMfortable with use of central venous catheters (CVC) particularly for those patients receiving infusional chemotherapy, or who have poor venous access. These have been utilized with a high level of safety and efficacy yet thrombosis remains a concern for its occurrence may result in morbidity or interrupt chemotherapy schedules or transfusions. The purpose of the current report was to examine the incidence, risk factors, and long-term complications of catheter-related thrombosis (CRT) in adults with cancer.

Consecutive patients with cancer who were treated at the Juravinski Cancer Centre in Hamilton, Ontario were enrolled in a prospective, observational study. Patients remained on the study as long as the catheter was in place and for 4 weeks thereafter for a maximum of 52 weeks. Patients with catheter-related thrombosis were followed for an additional 52 weeks from the date of the diagnosed thrombosis. The main end points of the study were symptomatic catheter-related thrombosis, symptomatic pulmonary embolus, postphlebitic syndrome, and catheter lifespan.

Of the 444 patients enrolled, 19 (4.3%) had symptomatic CRT over 76,713 patient days of follow-up. The median time to CRT was 30 days and the median catheter

lifespan was 88 days. By multivariate analysis, three significant risk factors became apparent. These were 1) more than one insertion attempt (odds ratio [OR] = 5.5; 95% confidence interval [CI], 1.2-24.6; P = 0.03); 2) ovarian cancer (OR = 4.8; 95% CI, 1.5-15.1; P = 0.01); and, 3) previous central venous catheter insertion (OR = 3.8; 95% CI, 1.4-10.4; P = 0.01). Of the 19 patients with catheter-related thrombosis, 9 were treated with anticoagulants alone, 8 patients were treated with anticoagulants and catheter removal, and two patients did not receive anticoagulation. None of the 19 patients had recurrent CRT or symptomatic PE and postphlebitic symptoms were infrequent.

Thus, the authors concluded that in patients with cancer, the incidence of symptomatic CRT is low and long-term complications are uncommon.

COMMENTARY

This was a rigorous prospective analysis of the incidence of symptomatic CRT in patients with cancer and the results were encouraging. The incidence of symptomatic CRT was low (4.3%) and certain risk factors became apparent. These included difficulty at the time of the insertion, prior central venous catheter, and the presence of ovarian cancer. The low incidence of CRT was similar to that found in other studies although all the methodologies were quite different.[1,2]

The risk identified in ovarian cancer patients is a curious finding. The investigators carefully reviewed those cases and could find no evidence for specific histologic subtype but did find that these patients were heavily pretreated at the time of CVC insertion and there was a high incidence of poor peripheral venous access in these patients. Thus, it is quite possible that vessel injury from multiple venipunctures and the heavy prior use of cytotoxic chemotherapy were the important contributing factors rather than any specific biological characteristic of the underlying ovarian cancer.

Of note, this study did not find prophylaxis with anticoagulation reduced the risk of symptomatic CRT. However, the authors were quick to point out that this was not the purpose of the current report and the numbers were insufficient to make a confident statement in this regard. Nonetheless, other recent reports have also questioned the value of routine anticoagulant prophylaxis.[3,4] Certainly, the published reports to date suggest no therapeutic value for routine or low dose anticoagulation therapy in those with CVC and possibly an increased risk of bleeding.

Thus, in summary, the study demonstrated a low risk of symptomatic catheter-related thrombosis in cancer patients. Although this was from a single institution, the evaluation was thorough and there were a sufficient number of patients to accept the study conclusion with confidence. Because there was a low incidence of symptomatic CRT and because there was no control over type of cancer therapy, anticoagulant prophylaxis and treatment of the CRT, the identification of risk factors was likely to be incomplete and additional studies will be required to confirm those identified and possibly establish others. Nonetheless, we can conclude that symptomatic catheter-related thrombosis is an uncommon occurrence in the general cancer patient population and the risk of symptomatic pulmonary embolus, or even postphlebitic syndrome is very low. ■

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CME Questions

6. Based upon this study, what factors increased bleeding risk after medical interventions for female hemophilia carriers relative to non-carriers?

a. Patients who had inexperienced surgeons
b. Factors levels below 0.60 IU/mL
c. Patients who did not receive pre-operative desmopressin prophylaxis
d. Bleeding risk was the same for carriers and non-carriers

7. Risk factors for the occurrence of symptomatic central venous catheter-related thrombosis as demonstrated by Lee et al, include all but which one of the following:

a. Multiple insertion attempts.
b. Prior central venous catheter.
c. Pancreatic cancer
d. Ovarian cancer

8. For patients with advanced ovarian cancer who have achieved remission with chemotherapy, the level of CA-125 obtained just prior to maintenance chemotherapy was shown to:

a. be of little predictive value regarding the duration of remission.
b. be of predictive value only if outside of the normal range.
c. offer significant predictive value with regard to the duration of remission.
d. offer significant predictive value with regard to

overall survival.

9. **When matched for stage, Gleason grade and PSA, primary treatment of young prostate cancer patients (< 55 years) with external beam radiation, compared to similar treatment in older patients results in:**
   a. No difference in the appearance of distant metastases.
   b. No difference in the freedom from biochemical (PSA) recurrence.
   c. No difference in overall survival.
   d. All of the above.

Answers: 6 (b); 7 (c); 8 (c); 9 (d)

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CME Objectives

The objectives of *Clinical Oncology Alert* are:

- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

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Hemoglobin and Prostate Cancer Prognosis

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.

The Safety of Long-Acting Beta Agonist Inhalers

Do long-acting beta agonist inhalers increase the severity of asthma? Yes, according to the results from a large meta-analysis recently published in the *Annals of Internal Medicine*. Pooled data from 19 trials with nearly 34,000 participants found that the long-acting beta agonists salmeterol, formoterol, and eformoterol were associated with higher rates of asthma exacerbations, requiring hospitalization, (odds ratio 2.6 [95% CI, 1.6-4.3]) and life-threatening exacerbations (odds ratio 1.8 [CI, 1.1-2.9]), compared to placebo. In subgroup analyses, the odds ratio for hospitalizations was 1.7 for salmeterol and 3.2 for formoterol. The risk of hospitalization was especially high in children on long-acting beta agonists (odds ratio 3.5 [CI, 1.3-9.3]). The odds ratio for adults was 2.0 (CI 1.1-3.9). Although the rate of death was low, the odds ratio for asthma-related death was 3.5 (CI, 1.3-9.3).

In the largest of the studies included in the meta-analysis, the Salmeterol Multicenter Asthma Research Trial (SMART), in which 26,000 patients were followed for 6 months on salmeterol or placebo, there was a 2-fold increase in life-threatening asthma exacerbations and a 4-fold increase in asthma related deaths. The authors conclude that long-acting beta agonist use increases the risk of hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. The authors also conclude that inhaled corticosteroids cannot adequately protect against the adverse effects of these drugs (*Ann Int Med*. 2006;144:904-912).

An accompanying editorial suggests that physicians should follow current guidelines which emphasize use of inhaled corticosteroids as the first-line treatment for patients with mild-to-moderate persistent asthma. Only after maximal corticosteroid doses have been reached should long-acting beta agonist be considered (*Ann Int Med*. 2006;144:936-937).

The FDA met one year ago to discuss long-acting beta agonist and required black box warnings on the labeling for these drugs; however, there usage has changed very little in the ensuing year.

Treating Chronic Primary Insomnia

Cognitive behavioral therapy is more effective than zopiclone for the treatment of chronic primary insomnia in older adults, according to a new study from Norway. In a randomized, double-blind, placebo-controlled trial, 46 adults (mean age, 60.8; 22 women) with chronic primary insomnia were randomized to cognitive behavioral therapy, sleep medication with zopiclone 7.5 mg each night, or placebo for 6 weeks. The cognitive behavioral therapy consisted of 6 weekly sessions lasting 50 minutes that covered sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, and progressive relaxation techniques. The main outcome was

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polysomnographic data and sleep diaries, which were used to determine total wake time, total sleep time, sleep efficiency, and slow-wave sleep.

Cognitive behavioral therapy (CBT) resulted in improved short-term and long-term outcomes compared with zopiclone on 3 of 4 outcome measures. CBT improved sleep efficiency from 81.4% to 90.1% at 6-month follow-up compared to a decrease from 82.3% to 81.9% with zopiclone. CBT resulted in better sleep architecture and less time awake during the night. Total sleep time was similar in all 3 treatment groups but, at 6 months, patients receiving CBT had better sleep efficiency than those taking zopiclone. The authors conclude that cognitive behavioral therapy is superior to zopiclone for management of insomnia, both in the short term and long-term. For most outcomes, zopiclone did not differ from placebo (*JAMA*. 2006;295:2851-2858).

Zopiclone is a new generation sleep medication available in Europe. The active isomer of zopiclone has been available in the United States since April 2005 (eszopiclone - Lunesta).

New Breakthrough in Smoking Cessation?

Varenicline, Pfizer's new smoking cessation drug, is the subject of 3 articles in the July 5 issue of *JAMA*. The drug, which is a partial agonist of the 4 2 nicotinic receptor, blocks the action of nicotine but provides a lower level of stimulation of dopamine release to reduce craving and withdrawal symptoms. Two of the 3 articles compared varenicline to bupropion and placebo in combination with behavioral counseling over 12 weeks of treatment. In both studies, varenicline was significantly more effective than placebo or bupropion (*JAMA*. 2006;296:47-55, 56-63). In the third study, 12 more weeks of varenicline was found to be significantly more effective than placebo in maintaining abstinence. This study also found that after 24 weeks of treatment, the benefit of the drug was maintained up to one year (*JAMA*. 2006;296:64-71). An accompanying editorial points out that while the studies of varenicline are promising and the drug represents a new agent with a different mechanism of action, it is not a panacea for smoking cessation, with quit rates still under 50% in these studies (*JAMA*. 2006;296:94-95). These studies could not come at a better time for Pfizer, as the company plans to market the drug within the next few months under the trade name Chantix.

FDA Actions

The FDA has given Biogen-Idec approval to resume marketing natalizumab (Tysabri) for the treatment of relapsing forms of multiple sclerosis. The monoclonal antibody was initially marketed in November 2004, but was withdrawn four months later, after three patients developed progressive multifocal leukoencephalopathy (PML) in clinical trials. Subsequent trials have not shown any additional cases of PML, but the drug is limited to use in patients who have failed or have not tolerated alternative therapies for multiple sclerosis. The re-approval is a restricted distribution program which includes registration of patients, prescribers, infusion centers, and pharmacies and includes patient education materials. Patients are also required to have a brain MRI prior to initiation of therapy. More information is available at: www.fda.gov/cder/drug/infopage/natalizumab/default.htm.

Duramed Pharmaceuticals have received approval to market a new 91 day birth control regimen consisting of 84 days of levonorgestrel 0.15 mg with ethinyl estradiol 0.03 mg, and seven days of ethinyl estradiol 0.01 mg (Seasonique). This product differs from the company's other 91 day birth control regimen (Seasonale) in that it incorporates estradiol rather than placebo for the last seven days in order to reduce bloating and breakthrough bleeding. Both products result in four menstrual periods per year.

The FDA has approved Genentech's ranibizumab (Lucentis) for the treatment of neovascular (wet) age-related macular degeneration (AMD). The drug, which is injected intraocularly, inhibits vascular endothelial growth factor A which is thought to contribute to proliferation, vascular leakage, and angiogenesis. Many ophthalmologists have been using Genentech's other anti-angiogenesis drug bevacizumab (Avastin) for the treatment of AMD, although it is not approved for this indication. Compounded bevacizumab injected intraocularly is approximately $17 per dose. Ranibizumab marketed as Lucentis is projected to cost approximately $2000 per dose.

Two former blockbuster drugs are making the switch to generics. Sertraline (Zoloft- Pfizer) will be available later this year in both generic pill and liquid form. In 2005, Zoloft was the most popular antidepressant in the US. The FDA has also approved a generic form of simvastatin (Zocor) Merck & Co.'s enormously popular statin for the treatment of hypercholesterolemia. Generic simvastatin is currently available 5, 10, 20, 40, and 80 mg strengths. ■