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THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

COURTESY DR. CINDY T. MCEVOY

Newborns of smoking mothers who took vitamin C supplements did better on pulmonary function testing at 48 hours of life.

Babies of Smokers Helped by Vitamin C

BY SHERRY BOSCHERT
IMNG Medical News

SAN FRANCISCO – Lung function was significantly better in the newborns of pregnant smokers who took vitamin C supplements, compared with babies of smoking mothers on placebo, in a double-blind trial that randomized 179 women.

Among 159 infants who underwent pulmonary function tests at around 48 hours of age, results in the 76 newborns of smokers taking vitamin C were similar to results for 76 newborns of nonsmoking women in a nonrandomized comparison group. Both subgroups had better pulmonary function than did the 83 newborns of placebo-treated smokers, Dr. Cindy T. McEvoy and her associates reported at an international conference of the American Thoracic Society.

"We speculate that vitamin C supplementation in pregnant women who cannot quit smoking is helpful," said Dr. McEvoy of Oregon Health and Science University, Portland.

The researchers randomized pregnant smokers aged 15 years and older (prior to 22 weeks' gestation of their singletons) to take 500 mg/day of vitamin C or placebo until delivery. The women were counseled to quit smoking but declined to do so.

Maternal plasma levels of ascorbic acid were significantly lower in the two smoking groups at randomization, compared with levels in nonsmokers. By mid-gestation, ascorbic acid levels in the vitamin C group were similar to levels in nonsmokers (59 and 58 micromol/L, respectively), but levels in the placebo group remained significantly lower (40 micromol/L).

Infant pulmonary flow volume, characterized as a ratio of the time to peak tidal expiratory flow to expiratory time, was significantly lower in the placebo group (0.345), compared with the vitamin C group (0.383) and the nonsmoking group (0.399), Dr. McEvoy said.

Investigators also measured the newborns' passive respiratory mechanics, or compliance of

See **Vitamin C** • *page 11*

Survival Boosted With Carboplatin Plus Pemetrexed

More NSCLC patients alive at 1 year.

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – Coupling carboplatin chemotherapy with pemetrexed significantly improved survival in the subset of hard-to-treat patients with advanced non–small cell lung cancer and an Eastern Cooperative Oncology Group performance status of 2.

Progression-free survival increased from a median of 3.0 months to 5.9 months (hazard ratio, 0.46; *P* less than .001), and overall survival from 5.6 months to 9.1 months (HR, 0.57; $P = .001$) with the addition of carboplatin to pemetrexed (Alimta), according to final results of a phase III trial.

This represents a 43% reduction in the risk of death, with 43% of patients on the combination alive at 12 months vs. 18% on pemetrexed alone. None of the patients had received prior chemotherapy.

The results can be generalized to patients of all histologic subtypes who have an ECOG performance status of 2, Dr. Rogerio Lilenbaum said at the annual meeting of the American Society of Clinical Oncology.

"Although carboplatin plus pemetrexed may be a particularly suitable regimen in this population because of its safety profile, we do not think these results are unique to this regimen or nonsquamous patients," he said.

"Given the magnitude of the benefit seen in this study, and the immediate applicability of these data to clinical practice, we urge the appropriate organizations to revise their guidelines, which to this date, by and large, still recommend single-agent therapy for these patients."

Patients with non–small cell

See **Survival** • *page 8*

INSIDE

Cancer More Common in OSA Patients

BY SHERRY BOSCHERT
IMNG Medical News

SAN FRANCISCO – Recent findings of significantly increased risk for cancer incidence and mortality in people with obstructive sleep apnea echo previous in vitro and animal studies that found repeated episodes of hypoxia were tied to accelerated cancer progression.

In one of two new studies, OSA patients were 10%-480% more likely to die of cancer, depending on apnea severity, compared with those without OSA, in a 20-year follow-up study of 1,522 participants in the Wisconsin Sleep Cohort.

Both the number of hypoxic episodes during sleep and the severity of hypoxia were associated with increased risk of cancer mortality, but the association was stronger with hypoxia severity. Patients who spent most of their sleep time with an oxyhemoglobin saturation under 90% were nearly nine times more likely to die of cancer during the study, compared with controls, Dr. F. Javier Nieto and his associates

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Generic Clopidogrel: Good for Patients or Payers?

Cost concerns have been 'a major detriment to long-term treatment adherence.'

BY ELIZABETH MECHCATIE
IMNG Medical News

Just as Sanofi-Aventis lost its exclusivity for its blockbuster drug Plavix (clopidogrel), several generic formulations of the antiplatelet agent have been approved, the Food and Drug Administration announced.

In an FDA statement, Keith Webber, Ph.D., deputy director of the Office of Pharmaceutical Science in the FDA's Center for Drug Evaluation and Research, referred to the importance of having effective and affordable medications available for people with chronic health conditions. "The generic products approved today will expand those options for patients," he said.

The anticipated reduction in cost is expected to keep the drug on its perch as the leading nonaspirin antiplatelet agent, experts agreed.

The availability of generic clopidogrel was welcome news, "especially for cost-prohibitive environments, where affordability is a major detriment to long-term treatment adherence and, consequently, an optimal benefit-risk balance," Dr. Sanjay Kaul said in an interview.

"It must, however, be acknowledged that for a drug that never got the claim of superiority over aspirin, its rise to be the second highest selling pharmaceutical agent speaks more to the miracle of marketing than the miracle of medicine," added Dr. Kaul, director of the cardiovascular diseases fellowship training program at Cedars-Sinai Heart Institute, Los Angeles. "Nonetheless, clopidogrel will continue to be the dominant oral antiplatelet agent – besides aspirin – that will be used for a broad spectrum of cardiovascular disease indications in the foreseeable future."

Dr. Eric Bates, professor of internal medicine at the University of Michigan, Ann Arbor, said that it will be interesting to follow pricing trends over the next 1-2 years and to see how the availability of generic clopidogrel affects the market shares of the new entrants to the antiplatelet field, prasugrel (Effient) and ticagrelor (Brilinta). "It is possible that the large payers will require genetic or platelet function testing proof of poor clopidogrel responsiveness before they agree to pay for prasugrel or ticagrelor," he said in an interview.

Dr. Peter Kowey, professor of medicine at Thomas Jefferson University in Philadelphia, noted that the availability of generic clopidogrel will help many patients who have a difficult time paying for the proprietary formulation, but said he has two concerns. First, "generic reproduction of cardiac drugs can expose patients to risk if the quality of the generic is compromised in any way," he said. And second, "the availability of cheaper clopidogrel will discourage doctors from using prasugrel or ticlopidine, even though we know that those drugs are superior for the indication and may have real advantages for some of our patients."

"As with so many things in medicine these days, economics may become the most compelling issue in drug selection and patient care – and that is not something any doctor desires," added Dr. Kowey.

Clopidogrel, a P2Y12 platelet inhibitor taken orally once a day, is approved for the treatment of acute coronary syndrome and for patients who have had a recent myocardial infarction, recent stroke, or established peripheral artery disease. The approved indication includes the statement that clopidogrel "has been shown to reduce the combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death."

Clopidogrel was initially approved by the FDA in 1997, and has been marketed as Plavix by Sanofi-Aventis. The agent generated $5 billion in sales in 2010 alone.

Generic formulations of both the 75-mg daily dose and the 300-mg loading dose have been approved, the FDA said.

Dr. Kaul had no relevant disclosures. Dr. Bates receives advisory board honoraria from all antiplatelet manufacturers. Dr. Kowey said he serves as a consultant for Sanofi and Bristol Myers Squibb, which markets Plavix with Sanofi; he has no equity interest in those companies or any other drug company. ■

COMMENTARY

Dr. Lary Robinson, FCCP, comments: The loss of patent protection of almost any high-priced, widely prescribed drug (2.5 to 3 million Plavix prescriptions written per month in the United States) is generally cause for joy, especially for the aging population, the predominant consumers of clopidogrel (Plavix). This drug will continue to be widely available but at considerably less cost with the FDA-approved generic formulations. Although this loss of patent protection shouldn't change prescribing habits, let us hope that accelerated marketing of the newer antiplatelet drugs Effient and Brilinta will not push physicians to switch patients to these much higher-priced alternatives, which have no evidence of improved efficacy. In fact, I agree with Dr. Kaul that clopidogrel never earned "the claim of superiority over aspirin."

IN THIS ISSUE

Dr. W. Michael Alberts, FCCP, is Medical Editor in Chief of CHEST PHYSICIAN.

CHEST PHYSICIAN

CHEST PHYSICIAN, the newspaper of the American College of Chest Physicians, provides cutting-edge reports from clinical meetings, FDA coverage, clinical trial results, expert commentary, and reporting on the business and politics of chest medicine. Each issue also provides material exclusive to the members of the American College of Chest Physicians. Content for **CHEST PHYSICIAN** is provided by International Medical News Group, an Elsevier company. Content for NEWS FROM THE COLLEGE is provided by the American College of Chest Physicians.

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For PAH (WHO Group 1) patients on oral monotherapy

TYVASO: the ONLY inhaled prostacyclin analogue approved for 4x-daily dosing[1]

Short treatment sessions: just 2 to 3 minutes each[2]

ONLY inhaled prostacyclin analogue approved as an add-on to oral PAH monotherapy[1]

- 52% of patients improved 6MWD by greater than 20 m[3]
- Improvement in 6MWD at peak (20 m) and trough (14 m) exposure[3]

Dosing regimen fits into patients' schedules

- Short treatment sessions: just 2 to 3 minutes, 4x daily[2]
- Set up once daily[1,2]
  - —One plastic ampule per day—no need to replace ampule for each treatment session[1]
  - —About 5 minutes a day for device preparation—once in the morning, and the device is ready to go all day[2]
- Treatment timing can be adjusted for planned activities[1]

Adverse events

- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope[1]

STUDY DESIGN: TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=235) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.[3]

INDICATION

Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

IMPORTANT SAFETY INFORMATION

- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%)
- Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women

Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and the Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

6MWD=6-minute walk distance. MLWHF=Minnesota Living With Heart Failure. NYHA=New York Heart Association. WHO=World Health Organization.

References: 1. Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2011. **2.** Tyvaso [patient package insert]. Research Triangle Park, NC: United Therapeutics Corporation; 2011. **3.** McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915-1922.

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PROSTACYCLIN MADE PRACTICAL

About 14 Million Americans Have Undiagnosed COPD

BY BRUCE JANCIN
IMNG Medical News

NEW ORLEANS – The most likely place to look for missed cases of chronic obstructive pulmonary disease – and they exist in abundance – is among women younger than age 65.

COPD, the fourth leading cause of death in the United States, is far and away the most widely underdiagnosed serious illness. The best available prevalence data on COPD come from the NHANES III (National Health and Nutrition Examination Survey III), which included spirometric testing in a proportionate sample of the U.S. population.

Extrapolating from those data, roughly 12 million Americans carry the diagnosis of COPD, and another 12 million have evidence of impaired lung function consistent with COPD but remain undiagnosed. Of those 12 million undiagnosed individuals, NHANES III data indicate that roughly a third have clinically relevant COPD warranting application of treatment guidelines, according to Dr. Fernando J. Martinez, FCCP, professor of internal medicine and director of pulmonary diagnostic services at the University of Michigan, Ann Arbor.

He added that the latest data from NHANES IV, now under review, bump those estimates up to roughly 14 million patients with diagnosed COPD, and an equal number with undiagnosed COPD.

The NHANES III data showed that 70% of individuals with undiagnosed COPD are younger than age 65. Other studies point to a marked sex discrepancy in misdiagnosis. In one landmark study, investigators presented American and Canadian primary care physicians with a classic clinical scenario for COPD (that is, a patient with a strong smoking history, progressive shortness of breath, and chronic cough with morning sputum production). Half the time, investigators identified this hypothetical patient as male, the other half female. Physicians diagnosed COPD 58% of the time when the patient was male, but in only 42% of cases when the otherwise identical hypothetical patient was female (Chest 2001;119:1691-5).

This sex discrepancy in COPD diagnosis has been replicated in similar studies conducted in Spain and Israel, Dr. Martinez added.

Interestingly, the first diagnostic test most participating primary care physicians indicated they would order for this hypothetical patient was a chest x-ray, which Dr. Martinez dismissed as a "terrible" tool for diagnosing COPD. Spirometry, which is in fact the diagnostic test for COPD, would have been ordered initially by only 22% of the physicians.

ROUGHLY A THIRD OF UNDIAGNOSED INDIVIDUALS HAVE CLINICALLY RELEVANT COPD WARRANTING APPLICATION OF TREATMENT GUIDELINES.

The pulmonologist stressed that even though spirometry is the diagnostic test for airflow obstruction, three major sets of guidelines released within the past year uniformly emphasize that its use should be restricted to patients with respiratory symptoms. The recent guidelines he referred to are the latest update from the Global Initiative for Chronic Obstructive Lung Disease, which Dr. Martinez coauthored; the joint American College of Physicians/American College of Chest Physicians/American Thoracic Society/European Respiratory Society guidelines (Ann. Intern. Med. 2011;155:179-91); and the U.K. National Institute for Health and Clinical Excellence guideline.

Spirometry continues to be greatly underutilized in primary care medicine, perhaps in part because some insurers are unwilling to pay for the test in the office setting, insisting instead that it be performed in a specialized pulmonary clinic. That policy is destined for the scrap heap, Dr. Martinez predicted.

In the study that identified sex bias in COPD diagnosis, classic COPD symptoms in women were misdiagnosed most frequently as asthma. That's a crucial mistake, because the first-choice treatments for these two common respiratory diseases are "diametrically opposite," Dr. Martinez said at the annual meeting of the American College of Physicians.

Continued on following page

Combination Provides Another Option for COPD

BY MIRIAM E. TUCKER
IMNG Medical News

ORLANDO – A combination of fixed-dose mometasone furoate and formoterol fumarate improved lung function in patients with moderate to very severe chronic obstructive pulmonary disease.

The finding came from a 26-week, phase III, multicenter, double-blind, placebo-controlled study of 1,055 adults who were current or former smokers and had a prebronchodilator forced expiratory volume in 1 second (FEV_1)/ forced vital capacity ratio of 0.70 or less. Currently, three combinations of inhaled corticosteroid plus long-acting beta agonists are available for the treatment of COPD, but not this particular combination of mometasone furoate with formoterol fumarate administered with a metered-dose inhaler, which is licensed for asthma treatment in the United States under the name Dulera, Dr. Edward Kerwin said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

The patients were randomized to one of five twice-daily metered-dose inhaler treatment arms: mometasone furoate 400 mcg/formoterol 10 mcg (MF400/F10), mometasone furoate 200 mcg/formoterol 10 mcg (MF200/F10), mometasone furoate 400 mcg alone (MF400), formoterol 10 mcg alone (F10), or placebo. A total of 840 of the 1,055 randomized patients completed the treatment period. About 80% of the patients were male, with a mean age of 59 years, and about three-quarters were white. Nearly half were current smokers, and all had smoked at one point in time, with an average of 40 pack-years.

VITALS

Major Finding: The contribution of F10 to the MF400/F10 combination at week 13 was shown by a statistically significant 109-mL difference in FEV_1 area under the curve, compared with MF400 alone. The mean change from baseline in morning predose FEV_1 at the week 13 end point showed the contribution of the MF400 component, with a statistically significant difference of 111 mL between MF400/F10 and F10 alone.

Data Source: Data are from a 26-week, phase III, multicenter, double-blind, placebo-controlled study of 1,055 adults with moderate to very severe COPD.

Disclosures: The study was sponsored by Merck Sharp & Dohme. Dr. Kerwin disclosed receiving consulting fees and/or speaking fees from Dey Laboratories, GlaxoSmithKline, MAP Pharma (AstraZeneca), Merck, Teva, and Sepracor.

The findings of this study also were published online in the International Journal of Chronic Obstructive Pulmonary Disease (Int. J. Chron. Obstruct. Pulmon. Dis. 2012;7:43-55).

One of the two coprimary end points, the contribution of F10 to the MF400/F10 combination at week 13, was reached with a statistically significant 109-mL difference in FEV_1 area under the curve, compared with MF 400 alone. The overall effect size was a 163-mL difference for MF400/F10 over placebo at 13 weeks. A comparison of MF 400/F10 with MF 400 monotherapy also demonstrated a statistically significant effect of the F10, with an improvement of 69 mL, reported Dr. Kerwin, of the Clinical Research Institute of Southern Oregon, Medford.

The other coprimary end point, the mean change from baseline in morning predose FEV_1 at the week 13 end point, showed the contribution of the MF component. It was statistically significant for MF400/F10 over F10 alone, at 111 mL, and for MF200/F10 over F10 alone, at 58 mL. An overall effect size of 128 mL was seen for MF400/F10 over placebo.

Among the secondary efficacy variables, the MF 400/F10 group exceeded the 4-point minimum clinically important difference on the St. George's Respiratory Questionnaire, compared with placebo, with a significant effect size of 4.56 points at week 26. Statistically significant improvements in questionnaire total score for MF400/F10 over placebo were demonstrated at weeks 4, 13, and 26. However, the MF200/F10 dosage did not achieve the minimum clinically important difference, with only a 2.82 reduction, compared with placebo.

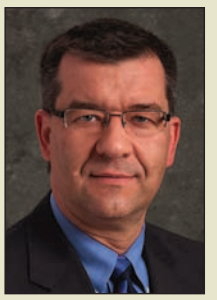
The proportion of COPD symptom–free nights improved by 0.15 with MF400/F10, compared with 0.06 for placebo, a significant difference over the 26-week period. However, there was no treatment difference between MF400/F10 and placebo in the proportion of patients with partly stable COPD at 26 weeks, with percentages ranging from 38% to 46% across treatment groups.

Time to first COPD exacerbation significantly improved with MF400/F10 over F10 alone; an analysis excluding mild exacerbations showed that moderate to severe exacerbations were significantly more frequent with placebo than with MF400/F10 (16.5% vs. 8.8%), he said.

Treatment with MF400/F10 was well tolerated, and the proportion of patients reporting treatment-emergent adverse events during the 26-week treatment period was similar between treatment groups, ranging from 26% in the MF400/F10 group to 33% in the F10 alone group. The most common of these were headache, upper respiratory tract infection, cough, COPD, and hypertension. Pneumonia did not occur in more than 1% of any treatment group. The incidence of oral candidiasis was low, occurring in no more than 2.4% of any group (five of the MF 400 alone patients), he reported. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: This registration study confirms prior findings with other similar agents. Combination ICS/LABA therapy once again led to meaningful improvement in lung function, quality of life, and exacerbations in this cohort of patients with moderate to very severe COPD.



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"In asthma, you use inhaled corticosteroids up front as first-line therapy. That's not the case in COPD. In COPD you use a long-acting bronchodilator up front, and you add an inhaled corticosteroid to reduce the exacerbation rate in people at increased risk based on a history of two or more exacerbations in the past year," he explained.

All of the latest guidelines emphasize exacerbation reduction as a key component of COPD management. Exacerbations accelerate disease progression by worsening lung function and symptoms, and they drive up costs as well.

The National Heart, Lung, and Blood Institute is interested in developing a novel, practical means of screening the general population for COPD in primary care physicians' offices. Toward that end, the institute recently awarded a large research grant to a team of investigators that includes Dr. Martinez. He said that while he and his coworkers are still in the brainstorming stage, they are drawn to a staged approach involving a very brief questionnaire, in-office measurement of peak expiratory flow via a pocket spirometer, followed by diagnostic-quality spirometry when indicated.

Polls of busy general internists and family physicians indicate that if this screening questionnaire is more than four questions long, they won't use it. So, hypothetically, Dr. Martinez said, a three-item questionnaire might consist of something along these lines: How old are you? (Epidemiologic data indicate COPD risk rises at about age 40.) How much do you smoke? (COPD risk begins climbing with a lifetime history of just 100 cigarettes, a mere five packs.) And, do you have symptoms?

Dr. Martinez said that he would like to incorporate in-office peak expiratory flow measurement using a pocket spirometer into the future screening tool in light of the findings of a recent study in which he was a principal investigator.

This study of 5,761 patients demonstrated that it's rare to find severe airflow obstruction in an individual whose FEV_1 is at least 60% of the predicted value (Chest 2011 Dec. 22 [Epub ahead of print; PMID 22194590]). "A peak flow measurement has very good negative predictive value. That could be a useful part of a screening instrument that's going to need to be very practical," he observed.

The use of peak expiratory flow meters for this use in COPD is currently still under investigation.

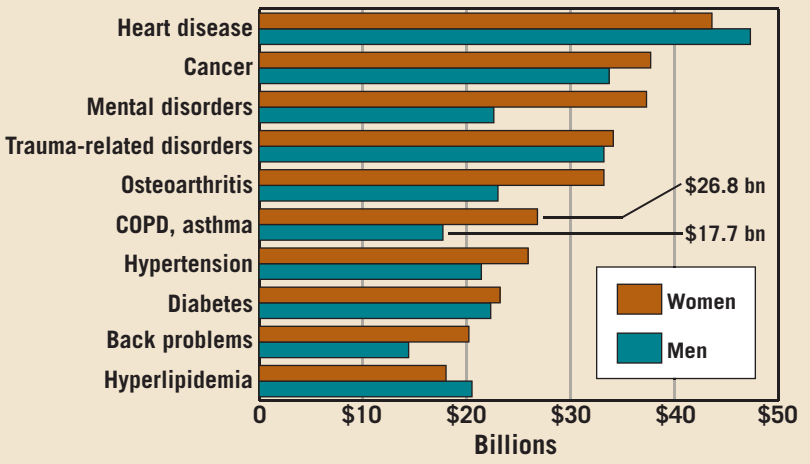
Dr. Martinez reported that he serves as a consultant to Actelion, Almirall, AstraZeneca, Bayer, Forest, GlaxoSmithKline, Ikaria, MedImmune, Merck, Novartis, Nycomed, Pearl, and Pfizer. ■

COMMENTARY

Dr. Darcy Marciniuk, FCCP, comments: It is clear that spirometry is underutilized and COPD is underdiagnosed. COPD is both treatable and preventable, and utilizing spirometry to appropriately diagnosis COPD in symptomatic patients is the first step in achieving those goals. It's time to spread the word!

DATA WATCH

Cost of COPD and Asthma 51% Higher for Women



Note: Based on data for adults from the Medical Expenditure Panel Survey, 2008.
Source: Agency for Healthcare Research and Quality statistical brief 331 (July 2011)

IMNG Medical Media

Delamanid Boosts Treatment Punch in Resistant TB

BY MICHELE G. SULLIVAN
IMNG Medical News

Combining the investigational drug delamanid with standard tuberculosis treatment significantly increased sputum-culture conversion rates in multidrug-resistant tuberculosis, an international study showed.

The results could be particularly good news for China, which now has one-quarter of the world's cases of MDR TB, according to a second study.

In the delamanid study, the conversion proportion was 45% after 2 months of treatment among those who received the new drug plus standard therapy, compared with a 30% rate for standard therapy alone, Dr. Maria T. Gler and her coauthors reported.

"It is important to learn more about the use of delamanid in combination with other new and existing antimycobacterial agents to develop better regimens for multidrug-resistant tuberculosis," wrote Dr. Gler, of Makati Medical Center and the Tropical Disease Foundation, Makati City, Philippines, and her colleagues (N. Engl. J. Med. 2012;366:2151-60).

Delamanid, which inhibits mycolic acid synthesis, has shown effectiveness against drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis* in preclinical tests.

The team investigated the drug's effect at 200 mg/day and 400 mg/day, plus a background treatment regimen approved by the World Health Organization for MDR TB. A placebo group received only the background treatment – the current standard of care. The 2-month study was carried out in nine countries: China, Egypt, Estonia, Japan, Korea, Latvia, Peru, the Philippines, and the United States.

The study group included 481 patients with sputum culture–proven MDR tuberculosis infections. The patients' mean age was 35 years. More than 90% of the group had received prior treatment for tuberculosis, including 50% who had already taken only first-line antitubercular agents and 40% who had received a second- or third-line agent. Only four of the patients were coinfected with HIV.

VITALS

Major Finding: Delamanid combined with a standard tuberculosis treatment regimen was associated with significantly greater sputum-culture conversion rates than standard treatment alone (45% vs. 30%) in patients with MDR TB.

Data Source: This was a 2-month placebo-controlled trial of 481 patients with MDR TB.

Disclosures: Otsuka Novel Products sponsored the study. Dr. Gler reported that she has received consulting fees from the company.

By the end of 2 months, both groups receiving delamanid had significantly higher proportions of sputum-culture conversion than the placebo groups. Similar conversion proportions occurred in both active groups: 45% of the 200-mg/day delamanid group, and 42% of the 400-mg/day group. Conversion in the placebo group (30%) was significantly less than in both of the active groups.

The time to conversion also differed significantly between the active and placebo groups, with conversion proportions beginning to separate by 30 days of treatment.

There were more adverse events in the delamanid groups, although the investigators found that only the incidence of QT prolongation was significantly less in the placebo group (4%) than in the 200- and 400-mg/day delamanid groups (10% and 13%, respectively). None of the arrhythmias were clinically significant, they noted.

There were no between-group differences in the rate of hepatotoxicity. One patient died from TB during the trial.

A longer trial is underway to more closely examine delamanid's effect on the hard-to-treat disease in patients taking antiretroviral drugs for HIV infections.

Finding an effective treatment for MDR tuberculosis is especially important in China, which has the greatest number of cases in the world, Yanlin Zhao, Ph.D., reported in an accompanying study (N. Engl. J. Med. 2012;366:2161-70).

Dr. Zhao, of the Chinese Center for Disease Control and Prevention, and colleagues reported on a national disease survey conducted in 2007. The survey showed that about 110,000 MDR cases were reported that year, and that 8,200 showed extensive drug resistance (XDR) – defined as resistance to isoniazid, rifampin, ofloxacin, and kanamycin.

China's prevalence rate of multidrug resistance among new cases of tuberculosis was 3.5 times greater than the global median, and nearly twice the global average.

"With the use of the World Health Organization estimate of multidrug-resistant tuberculosis in various countries as a reference, China has the highest annual number of cases of MDR tuberculosis in the world – a quarter of the cases worldwide," the authors wrote.

A number of factors were linked to drug-resistant disease. Patients with multiple previous treatments – with the most recent taken in a tuberculosis hospital – were at the highest risk.

Poor compliance also influenced drug resistance. In a subanalysis of 226 patients who had received prior treatment, 44% had not completed their prior regimen. Among the 127 patients who had completed treatment, 115 had relapsed TB, and 62% had received that last treatment in the Chinese Center for Disease Control (CDC) system.

"This finding points to the need for interventions that will increase the continuity of treatment and reduce the rate of treatment default, especially among patients treated within the hospital system," the authors noted.

Because national facilities provide limited follow-up, the Chinese Ministry of Health has strengthened the hospitals' follow-up capabilities, they added.

More needs to be done, however, they noted. China's CDC system, which is responsible for monitoring patients with tuberculosis in the community, could test new approaches to improving adherence to treatment, such as mobile-phone text messaging, and expand such approaches if they prove to be effective.

Improvements are imperative, the study authors cautioned, as the future does not bode well. About 11% of new cases and 16% of previously treated cases are already resistant to either isoniazid or rifampin, "placing them one step away from having MDR tuberculosis."

In addition, in patients with MDR but not XDR tuberculosis, more than one-third of cases were resistant to either ofloxacin or kanamycin – leaving those patients also just one step away from XDR tuberculosis. ■

COMMENTARY

Dr. Marcos Restrepo, FCCP, comments: There is a great need for finding new alternatives to treat patients with multidrug-resistant tuberculosis, and it seems that delamanid may have efficacy in addition to the standard tuberculous medications. Although the results are encouraging for countries like China, where higher rates of MDR tuberculosis are a major public health problem, the agent's higher rate of QT prolongation may need further evaluation regarding patient safety.

9/11 Survivors 50% More Likely to Have Lung Problems

BY M. ALEXANDER OTTO
IMNG Medical News

SAN FRANCISCO – More than a decade after the event, asthma, chronic obstructive pulmonary disease, and other respiratory symptoms are more common among lower Manhattan residents whose homes were covered with dust from the 9/11 attacks.

"All of these [respiratory] symptoms and diseases have elevated rates in this population," said Dr. Vinicius Antao of the Centers for Disease Control and Prevention's Agency for Toxic Substances and Disease Registry, who led an investigation into the issue.

"We found that after controlling for variables" such as age, sex, and smoking, "they are at least 50% more likely to report these [problems than are] those who didn't have any damage done to their homes," he said at an international conference of the American Thoracic Society.

People who cleaned up the dust with a wet mop, instead of a broom and dustpan, have fewer respiratory problems today. Wet mopping probably kept dust particles from resuspending.

"Now we know" that even brief catastrophic dust exposure can cause "symptoms for a long time," Dr. Antao said. That finding "will inform public health decision making in terms of emergency preparedness. We need to evacuate a population in a circumstance like this," he said.

His team linked the self-reported health status of 6,463 people in the World Trade Center Health Registry, a longitudinal project that tracks outcomes for 9/11 survivors with the amount of damage they said the attacks did to their homes. The respondents all lived below Canal Street in lower Manhattan on Sept. 11, 2001. The research is ongoing, but the data analyzed were from 2003 to 2007.

Dr. Antao and his colleagues excluded people who helped with the cleanup at ground zero, and controlled for people caught up in the dust cloud that billowed through Manhattan after the towers came down. The dust was a mixture of fine powdered concrete products, metals, and minerals, including asbestos, among other things.

People who said there was a heavy dust layer in their home – so much dust, for instance, that they couldn't read a newspaper that was covered with it – were more likely than were those with no dust in their homes to report shortness of breath (odds ratio, 1.74; 95% confidence interval, 1.45-2.10), wheezing (OR, 1.68; 95% CI, 1.36-2.08), chronic cough (OR, 1.58; 95% CI, 1.23-2.01), upper respiratory symptoms (OR, 1.37; 95% CI, 1.17-1.60), asthma (OR, 1.30; 95% CI, 1.01-1.70), and COPD (OR, 1.37; 95% CI, 1.02-1.84).

Their rates of asthma and COPD are "slightly higher" than rates in the general population, Dr. Antao said.

His team also found a significant, but less pervasive, association with respiratory symptoms in people who said the shock wave from the towers' collapse blew out their windows or damaged their furniture.

Dr. Antao said he doesn't think recall bias is at work, especially since years have passed since the 9/11 attacks, meaning that the shock of the event has worn off to some extent and is less likely to color survivors' perceptions of its effects on their health. "We've looked at different aspects of that, and most of the results that we have indicate that these data are real," he said.

Dr. Antao has no relevant financial disclosures. ■

Oxygen Desaturations Flag Pulmonary GERD

BY MITCHEL L. ZOLER
IMNG Medical News

SAN DIEGO – Measuring the number of oxygen desaturations a patient has that are coincident with episodes of esophageal acidity may be an effective way to identify patients who have respiratory symptoms secondary to gastroesophageal reflux, based on results from a controlled study of 103 patients.

"Looking at the reflux-associated desaturations could identify patients who have pulmonary symptoms due to reflux, as opposed to primarily pulmonary pathology," Dr. Candice L. Wilshire said at the annual Digestive Disease Week.

But she cautioned that counting a patient's reflux-associated oxygen desaturations is not ready for routine diagnostic use. "Our indications for [antireflux] surgery have not changed," Dr. Wilshire, a thoracic surgeon at the University of Rochester (N.Y.), said in an interview.

Having a reliable way to identify patients who experience frequent oxygen desaturation episodes secondary to reflux should streamline delivery of appropriate treatment to patients, Dr. Wilshire said. "A subgroup of GERD patients have no gastrointestinal symptoms and just complain of a chronic cough. They get sent to us when they're far down the road, after seeing pulmonologists."

Her study enrolled 37 GERD patients who primarily had respiratory symptoms (cough, hoarseness, or throat clearing), 26 GERD patients who primarily had GI symptoms (such as heartburn or epigastric pain), and 40 asymptomatic controls. The researchers considered reflux-associated oxygen desaturations (RADs) to be desaturations that occurred within 5 minutes of a reflux episode.

The controls had a median of 3.0 distal RADs during 24 hours, the patients with GI GERD had a median of 6.5 RADs, and those with GERD and pulmonary symptoms had a median of 17.0 RADs, significantly more than both other groups.

In proximal acid-episode RADs, the control group had a median of 1.0 episode during 24 hours, patients with GI GERD symptoms had a median of 3.0 RADs, and those with primarily pulmonary symptoms of GERD had a median of 8.0 RADs, significantly more than the other two groups.

The percentage of patients with 11 or more distal RADs was 27% in GI GERD patients and 70% in those with primarily pulmonary symptoms of GERD. The percentage with more than 7 proximal RADs was 19% in the GI group and 62% in the pulmonary group, Dr. Wilshire reported.

RAD numbers substantially declined in the small number of patients in the study who underwent antireflux surgery and who had their RADs measured before and after surgery. ■

VITALS

Major Finding: Patients with primarily pulmonary gastroesophageal-reflux symptoms had a median 17 distal reflux–associated oxygen desaturations in 24 hours, compared with 3 in controls.

Data Source: This was a single-center study of 103 patients.

Disclosures: Dr. Wilshire reported having no disclosures.

COMMENTARY

Dr. Vera DePalo, FCCP, comments: Gastroespohageal reflux symptoms can be linked to various respiratory manifestations, from cough to oxygen desaturation. While counting oxygen desaturations coincident with esophageal acidity as an assessment tool may not be ready for routine diagnostic use yet, it may be useful in the future to facilitate a more rapid diagnosis and initiation of definitive therapy. Early analysis showed a decrease in the number of reflux-associated oxygen desaturations after surgery. With further study, this may prove to be a very useful patient identification modality for respiratory symptoms secondary to GERD.

Afatinib Beats Chemo in EGFR-Positive Lung Cancer

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – First-line afatinib delayed progression for nearly a year in patients with advanced lung cancer carrying epidermal growth factor mutations, according to much-anticipated results from the phase III LUX-Lung 3 trial.

Median progression-free survival reached 11.1 months with the experimental oral agent, compared with 6.9 months with cisplatin plus pemetrexed (Alimta) chemotherapy (hazard ratio, 0.58; $P = .0004$), investigators reported. At 1 year, more than twice as many patients were progression free on afatinib (47% vs. 22%).

The median reached 13.6 months in afatinib-treated patients who harbored the most common EGFR mutations – exon deletion 19 or exon 21 L858R – which account for 90% of all EGFR mutations, but stayed at 6.9 months in the control group (HR, 0.47; *P* less than .0001). The progression-free survival rate in those with EGFR mutations was more than twice as high at 1 year with afatinib (51% vs. 21%).

Patients who were treated with the novel, second-generation tyrosine kinase inhibitor (TKI) also had better sustained tumor shrinkage and improved quality of life than did those treated with standard cisplatin plus pemetrexed chemotherapy, Dr. James Chih-Hsin Yang said at the annual meeting of the American Society of Clinical Oncology.

Overall survival data, from what was described as the largest global prospective trial in EGFR mutation–positive lung cancer to date, are expected in about 18-24 months, he said.

The available data cannot, however, answer questions of how afatinib compares against the first-generation TKIs in this setting, nor whether the increased efficacy outweighs any additional toxicity, said discussant Benjamin J. Solomon, Ph.D. Notably, the LUX-Lung 7 trial has begun comparing afatinib 40 mg/day with gefitinib 250 mg/day in EGFR mutation–positive, non–small cell lung cancer.

In the current trial, the efficacy of afatinib came at a cost of increased rates of diarrhea, rash, stomatitis, and paronychia that appear higher than those seen with the first-generation TKIs, added Dr. Solomon of the lung cancer service at Australia's Peter MacCallum Cancer Centre in East Melbourne, Victoria. Still, the rate of afatinib discontinuation was lower than with chemotherapy.

LUX-Lung 3 investigators at 133 sites in 25 countries in North and South America, Europe, and Asia randomized 345 chemotherapy-naive patients with stage IIIB or IV adenocarcinoma of the lung and EGFR mutations confirmed by central lab testing. In all, 230 were assigned to afatinib 40 mg daily and 115 to intravenous pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) every 21 days for up to six cycles.

VITALS

Major Finding: Progression-free survival was 11.1 months with afatinib and 6.9 months with cisplatin plus pemetrexed (HR, 0.58; $P = .0004$).

Data Source: Investigators conducted a phase III, open-label, randomized trial in 345 patients with advanced adenocarcinoma harboring EGFR-activating mutations.

Disclosures: Dr. Yang reported serving as a consultant or adviser and receiving honoraria from Boehringer Ingelheim, the study sponsor. Several coauthors had financial relationships with firms including Boehringer Ingelheim. Dr. Solomon reported serving as a consultant or adviser to AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Lilly, Pfizer, and Roche.

In all, 61% of patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 1, 65% were women, 72% were Asian, 89% had stage IV disease, 49% had the exon 19 deletion, 40% had the L858R mutation, and 11% had other mutations. Their median age was 61 years. Median follow-up was 16.4 months.

The investigators had hypothesized that afatinib would be stronger than first-generation, reversible EGFR TKIs because it irreversibly binds to and inhibits the entire ErbB family of receptors (ErbB1, HER2, ErbB3, and ErbB4). The ErbB family plays a critical role in tumor cell growth and is overexpressed or mutated in most cancers, including lung cancers.

In all, 56% of afatinib and 22.6% of the chemotherapy patients had an objective response by independent review (*P* less than .001), said Dr. Yang of the National Taiwan University Hospital in Taipei. The median duration of response was 11.1 months with afatinib vs. 5.5 months with chemotherapy.

There was also a delay in the time to deterioration of the lung cancer–related symptoms of cough (HR, 0.60; $P = .007$), dyspnea (HR, 0.68; $P = .015$), and pain (HR, 0.83; $P = .19$).

A subgroup analysis revealed that the benefit of afatinib on progression extended to most subgroups, including different races and EGFR mutations, never-smokers, and smokers with less than 15 pack-years who had stopped for at least 1 year, he said. Only current and "other" ex-smokers did not benefit.

Quality of life for those treated with afatinib was better than with cisplatin plus pemetrexed in all five domains measured on the EORTC (European Organisation for Research and Treatment of Cancer) Quality of Life Questionnaire–C30 including physical, cognitive, and social functioning.

The most common grade 3 adverse events with afatinib were diarrhea (14.4%), rash (16.2%), stomatitis/mucositis (8.3%) and paronychia (11.4%), with one case of grade 4 stomatitis/mucositis (0.4%). There were four deaths related to afatinib.

The duration of treatment likely had an impact on adverse events, as patients received 16 cycles of afatinib (median, 336 days) vs. just 6 cycles of chemotherapy, Dr. Yang pointed out. Drug-related adverse events leading to discontinuation were reported in 7.9% of patients who were given afatinib and in 11.7% of those given cisplatin plus pemetrexed chemotherapy.

Finally, Dr. Solomon said that "as impressive as the progression-free survival seen with afatinib is … all these patients eventually develop acquired resistance." He highlighted a recent study in which the T790M secondary mutation was implicated as a mechanism of acquired resistance to second-generation irreversible TKIs in a clinical case and in an in vitro cell culture model (Mol. Cancer Ther. 2012;11:784-91). ■

Hard-to-Treat Patients Benefited

Survival • *from page 1*

lung cancer (NSCLC) and an ECOG performance status (PS) of 2 are ambulatory and can care for themselves, but are unable to work. The optimal management strategy for these patients remains unresolved in the wake of mixed results from several phase III trials, including the IFCT-0501 (Intergroupe Francophone de Cancerologie Thoracique 1501) trial of carboplatin and paclitaxel vs. vinorelbine or gemcitabine (Gemzar) monotherapy (Lancet 2011;378:1079-88) and the U.S. Oncology trial of gemcitabine plus carboplatin vs. gemcitabine (J. Clin. Oncol. 2009;27:5808-15).

In contrast, the current results were so robust that one audience member asked whether they were "contaminated" with patients with better performance status.

Discussant Dr. Gregory P. Kalemkerian, codirector of thoracic oncology at the University of Michigan in Ann Arbor, said the results clearly demonstrate – as other trials have suggested – that two-drug regimens can improve response rate and survival, and should be an option in PS 2 patients. He applauded the investigators for choosing a tolerable regimen and avoiding the "cult of cisplatin," but went on to say that PS 2 denotes a very heterogeneous population. Thus, single-agent therapy should remain an option for very elderly patients, those with excessive comorbidities, and those who do not tolerate a two-drug therapy.

Investigators at eight centers in Brazil and one in the United States stratified 203 chemotherapy-naive patients with stage IIIB or IV advanced NSCLC by stage, age, and weight loss, and then randomly assigned them to pemetrexed 500 mg/m^2 or the same pemetrexed dose plus carboplatin AUC (area under the curve) 5 every 3 weeks for four cycles. All patients received folic acid, vitamin B_{12}, and dexamethasone. The protocol was amended in May 2009 to exclude patients with squamous cell histology, for which pemetrexed is not indicated.

Median follow-up was 6.1 months in all patients. Their median age was 65 years, 95% had stage IV disease, two-thirds were former smokers, and 81% had adenocarcinoma histology. Squamous cell histology was slightly imbalanced at 11% of the single-agent and 3% of the pemetrexed/carboplatin arm, but the difference was not significant.

The overall response rate was 24% with the combination vs. 10.5% with pemetrexed alone (*P* less than .029), despite the fact that 33.3% and 23.3% of patients, respectively, did not reach the point of a formal response assessment, said Dr. Lilenbaum, chair of solid tumor oncology at the Cleveland Clinic Florida in Weston.

PATRICE WENDLING/IMNG MEDICAL MEDIA

Overall survival increased from 5.6 to 9.1 months, Dr. Rogerio Lilenbaum said.

The investigators repeated the survival analysis excluding patients with squamous cell or unknown histology, and the hazard ratios were nearly identical to the intent-to-treat population for both progression-free and overall survival (HR, 0.45 and 0.59, respectively).

Subgroup analyses revealed a significant reduction in the risk of death with pemetrexed plus carboplatin in elderly patients (HR, 0.49; *P* less than .015) and never smokers (HR, 0.47; *P* less than .035).

The use of second-line therapy was similar, at 31% in the pemetrexed arm and 29.5% in the combination arm. Docetaxel was most commonly used among the pemetrexed-plus-carboplatin patients (30% vs. 19%), whereas carboplatin was more common in the single-agent pemetrexed arm (31% vs. 15%).

Toxicity was mild, although the combination arm had slightly more grade 3/4 anemia (11.7% vs. 3.9%) and neutropenia (5.8% vs. 1%). Nonhematologic toxicity was largely absent.

There were four treatment-related deaths in the combination arm and none in the pemetrexed alone arm ($P = .121$).

Dr. Lilenbaum disclosed research funding from Eli Lilly, and a coauthor reported serving as a consultant for Lilly. Dr. Kalemkerian reported research funding from Lilly. ■

Pages 8a—8b

Docetaxel Bests Erlotinib in EGFR Wild-Type NSCLC

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – Second-line treatment with docetaxel led to significantly better outcomes than with erlotinib in a head-to-head comparison among patients whose non–small cell lung cancer did not have a mutation in the epidermal growth factor receptor.

Progression-free survival, response, and disease control rates all favored docetaxel (Taxotere) in the phase III TAILOR (Tarceva Italian Lung Optimization Trial) study, investigators reported. "TAILOR does not support the use of erlotinib over docetaxel in patients with EGFR wild type," Dr. Marina C. Garassino said at the annual meeting of the American Society of Clinical Oncology.

VITALS

Major Finding: Median progression-free survival was 3.4 months with docetaxel vs. 2.4 months with erlotinib (HR, 0.69; $P = .014$).

Data Source: Investigators conducted a prospective, phase III, biomarker-based, randomized trial in 222 patients with wild-type EGFR non–small cell lung cancer.

Disclosures: TAILOR was sponsored by Agenzia Italiana del Farmaco. Dr. Garassino and her coauthors report no disclosures. Dr. Solomon reported an advisory or consultant role with AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Lilly, Pfizer, and Roche.

TAILOR is the only prospective trial to select patients with NSCLC carrying EGFR in its wild-type form for a direct comparison of docetaxel with erlotinib (Tarceva), a tyrosine kinase inhibitor (TKI) targeting EGFR. TKIs are well established in the treatment of patients harboring EGFR mutations, but their role continues to be debated in EGFR wild type, which accounts for about 85%-90% of NSCLC cases.

Investigators randomized 222 patients who had an ECOG performance status of 0-2 and had advanced or recurrent disease after prior treatment with a platinum-based doublet. They were assigned to erlotinib 150 mg daily or to either of two doses of docetaxel: 75 mg/m^2 on day 1 every 21 days, or 35 mg/m^2 on days 1, 8, and 15 every 28 days until disease progression or unacceptable toxicity.

About three-fourths of the patients had adenocarcinoma histology, were current or ex-smokers, and carried wild-type KRAS. The patients' median age was about 66 years.

The investigators noted the following findings:

- The median time to progression was 3.4 months with docetaxel and 2.4 months with erlotinib (hazard ratio, 0.69; $P = .014$). At 6 months, 29% of docetaxel patients were free of progression, compared with 17% on erlotinib, said Dr. Garassino of the medical oncology department at Fatebenefratelli and Ophthalmic Hospital in Milan.
- The disease control rate (defined as complete and partial responses and stable disease) was doubled in the docetaxel arm, compared with the erlotinib arm (41.5% vs. 22.8%; $P = .007$).
- Responses in the erlotinib arm were "rare and almost unseen" (2.2% vs. 14%; $P = .004$), she said. No erlotinib patients had a complete response, whereas 4.3% did with docetaxel.

A progression-free survival subgroup analysis favored docetaxel over erlotinib, regardless of age, sex, performance status, and smoking status, but the interactions were not statistically significant. Patients with and without KRAS mutations also benefited from docetaxel (HR, 0.84 and 0.65, respectively; $P = .237$), with median progression-free survival of 2.6 months and 2.4 months (HR, 0.91; $P = .558$).

PATRICE WENDLING/IMNG MEDICAL MEDIA

No erlotinib patients had a complete response, whereas 4.3% did with docetaxel, Dr. Marina C. Garassino said.

Overall survival, the study's primary end point, will be evaluated after the required 199 deaths have occurred.

Toxicity was as expected, with treatment-related adverse events leading to dose modifications in 22% of the docetaxel and 29% of the erlotinib arms.

Five randomized trials have compared chemotherapy vs. EGFR TKIs in previously treated NSCLC patients, but they were all were conducted in unselected patients, and only two trials reported outcomes by EGFR mutational status for a minority of patients in unplanned analyses. The hazard ratio for progression-free survival in TAILOR is consistent with the retrospective analyses from the recent TITAN (Lancet Oncology 2012;13:300-8) and INTEREST (Lancet 2008;372:1809-18) trials, suggesting benefit of chemotherapy over EGFR TKIs in EGFR wild-type patients, said discussant Benjamin Solomon, Ph.D.

"Outcomes are better with chemotherapy than EGFR TKIs in patients with EGFR wild-type non–small cell lung cancer," commented Dr. Solomon of the lung cancer service at Peter MacCallum Cancer Centre in East Melbourne, Victoria, adding that clinicians should still test for potentially actionable genetic alterations.

Attendee Dr. Steven Vogl, a N.Y. oncologist, asked whether the current results indicate "that docetaxel is not a very good drug and erlotinib is a terrible drug, and we shouldn't give it to these nonmutated patients anymore?"

After a slight pause, Dr. Garassino responded, "I think that you are right," to a round of laughter and applause. ■

COMMENTARY

Dr. Stuart Garay, FCCP, comments: It is no surprise that docetaxel bests erlotinib in wild-type EGFR NSCLC. Note, the mean difference between the two drugs is 1 month. Docetaxel provides minimal advantage. As one oncologist commented, neither treatment is very good for nonmutated disease.

Adjuvant Erlotinib Beneficial in EGFR-Mutated NSCLC

BY NEIL OSTERWEIL
IMNG Medical News

CHICAGO – For patients with resected non–small cell lung cancer bearing epidermal growth factor receptor mutations, daily maintenance with erlotinib was associated with good overall disease-free survival for at least 2 years, investigators reported at the annual meeting of the American Society of Clinical Oncology.

Among 100 patients with non–small cell lung cancer (NSCLC) positive for mutations in the epidermal growth factor receptor (EGFR) who underwent surgery and routine adjuvant chemotherapy or chemoradiotherapy, maintenance with erlotinib (Tarceva) 150 mg daily was associated with a median 2-year disease-free survival of 94%, reported Dr. Joel W. Neal of the Stanford (Calif.) Cancer Institute.

Median overall survival has not been reached, the investigators noted in a poster session.

Only one patient had disease progression while on adjuvant erlotinib, and 10 experienced progression at least 6 months after stopping the drug, suggesting the presence of residual disease that may be sensitive to retreatment with erlotinib, Dr. Neal said in an interview.

"We've encouraged repeat biopsies for patients who have progressed after treatment with adjuvant erlotinib, and of the patients who were biopsied, 6 of 8 had an identical mutation without a known mechanism of resistance," he said. Five of these patients were evaluable for additional therapy, and all were found to be sensitive to further treatment with erlotinib, Dr. Neal reported.

VITALS

Major Finding: Erlotinib 150 mg daily was associated with a median 2-year disease-free survival of 94% in patients with non–small cell lung cancer carrying EGFR mutations.

Data Source: This was a prospective study of adjuvant therapy following resection and routine chemotherapy.

Disclosures: The study was supported by Genentech. Dr. Neal has received research funding from the company. Dr. Purtell had no relevant disclosures.

However, toxicities with erlotinib required dose reductions in some patients, and six patients discontinued therapy because of adverse events that included rash, diarrhea, and fatigue.

An oncologist who was not involved in the study commented that he would need to see longer follow-up before he could be convinced of the benefits of adjuvant erlotinib in this population.

"I'm not sure about the toxicity of 2 years of therapy with a TKI [tyrosine kinase inhibitor] in a setting where you're not quite sure whether you're improving survival or just disease-free survival," Dr. Michael J. Purtell, an assistant professor of oncology at Johns Hopkins University in Baltimore, said in an interview.

The investigators designed the study, dubbed SELECT (Surgically resected EGFR-mutant Lung cancer with adjuvant Erlotinib Cancer Treatment) to determine whether adjuvant erlotinib could provide a more robust survival benefit to patients than that afforded by conventional adjuvant chemotherapy – typically about 5%-10%, they said.

Patients with EGFR mutation–positive, surgically resected stage IA-IIIA NSCLC received 6-9 months of routine adjuvant chemotherapy with or without radiation, and were then continued on oral erlotinib 150 mg daily for up to 2 years. The patients are followed with CT scans every 6 months for 3 years, then once a year for years 4 and 5.

A total of 36 patients were enrolled initially, but the study was later expanded to included 100 patients in all, after initial encouraging results.

The findings thus far suggest that "adjuvant erlotinib has, at least, a cytostatic effect on micrometastatic disease," the investigators wrote. ■

Pemetrexed Maintenance May Up Survival in NSCLC

BY PATRICE WENDLING
IMNG Medical News

CHICAGO – Final results of the phase III PARAMOUNT trial support continued use of pemetrexed after pemetrexed-plus-cisplatin induction therapy for advanced, nonsquamous non–small cell lung cancer.

More patients on pemetrexed (Alimta) maintenance were alive at 1 year (58% vs. 45% of the control group) and 2 years (32% vs. 21%), Dr. Luis Paz-Ares said at the annual meeting of the American Society of Clinical Oncology. With nearly all patients off study treatment, median overall survival from randomization was 13.9 months with pemetrexed maintenance plus best supportive care (BSC) vs. 11.0 months with BSC plus placebo.

This translates into a 22% reduction in the risk of death (hazard ratio [HR], 0.78; log-rank $P = .0195$). An analysis of overall survival from the start of induction yielded the same risk reduction, with the median reaching 16.9 months in patients maintained on pemetrexed vs. 14.0 months in the control group (HR 0.78; log-rank $P = .0191$).

The benefit of pemetrexed maintenance was consistent across all subgroups, including patients with a complete or partial response (HR 0.81) and those with stable disease (HR 0.76) after induction therapy, Dr. Paz-Ares said.

"This is the first study to show that continuation maintenance had a clear impact on the natural course" of advanced NSCLC, including an improvement in progression-free survival and overall survival, and "may support a change in the treatment paradigm in this clinical setting," said Dr. Paz-Ares of University Hospital Virgen del Rocio in Seville, Spain.

PATRICE WENDLING/IMNG MEDICAL MEDIA

The results of this study "may support a change in the treatment paradigm," Dr. Luis Paz-Ares said.

"I think we should share with our patients the information about the role of maintenance treatment, but it doesn't mean that every single patient should be treated in this way," he said.

At last year's ASCO meeting, the investigators reported that pemetrexed maintenance significantly reduced the study's primary end point, the risk of disease progression (HR 0.62) (Lancet Oncol. 2012;13:247-55).

The overall survival data were not mature at the time, leaving some clinicians to question the overall efficacy of pemetrexed maintenance and whether the delay in progression was enough to justify the potential increased toxicity with continued therapy.

In the PARAMOUNT trial, 939 chemotherapy-naive patients with advanced nonsquamous NSCLC, at least one measurable lesion, and an ECOG performance status of 0 or 1 received four cycles of induction pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on day 1 of a 21-day cycle. The 539 patients who responded were stratified by disease stage, performance status, and induction response and randomly assigned to maintenance with pemetrexed 500 mg/m^2 every 21 days plus BSC or to BSC and placebo.

The median age was 61 years, about 90% of patients had stage IV disease, 86%-89% had adenocarcinoma histology, and 42%-44% had a complete or partial response to induction therapy. The mean number of maintenance cycles was 7.9 (range 1-44) for the 359 pemetrexed patients and 5 cycles for the 180 placebo patients (range 1-38). Median follow-up for all patients was 12.5 months, and reached 24.3 months among all patients still alive.

Reassessment of progression-free survival at final analysis once again favored pemetrexed (HR 0.60), confirming the robustness of the results, Dr. Paz-Ares said.

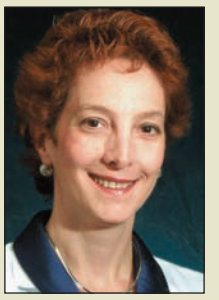
The pemetrexed maintenance arm had more grade 3/4 events than did the placebo arm, notably fatigue (4.7% vs. 1.1%), anemia (6.4% vs. 0.6%), and neutropenia (5.8% vs. 0%).

In all, 64% of the pemetrexed arm and 72% of the placebo arm received post-discontinuation therapy, mainly erlotinib (40% of the pemetrexed arm and 43% of the control group). Only docetaxel usage differed significantly between arms (32% vs. 43%; $P = .013$), he said.

"We have very few drugs that are active in non–small cell lung cancer and we have to be able to squeeze most of the benefit from each of them, and this is why I'm really in favor of this maintenance kind of treatment," he added.

PARAMOUNT was supported by Eli Lilly. Dr. Paz-Ares disclosed ties with Bayer, Lilly, Pfizer, and Roche. Coauthors include employees of Eli Lilly. ■

COMMENTARY



Dr. Jeana O'Brien, FCCP, comments: This phase III trial of different chemotherapeutic regimens for patients with advanced nonsquamous NSCLC showed a small improvement in median survival. Additional investigation is warranted to determine overall benefit.

Nab-Paclitaxel an Option in Lung Cancer With Bleeding Risk

BY DIANA MAHONEY
IMNG Medical News

CHICAGO – Combination therapy with nanoparticle albumin bound–paclitaxel and carboplatin may be an option for the subset of advanced non–small cell lung cancer patients who are ineligible for bevacizumab treatment because of bleeding risk.

The combined treatment produced an overall response rate (ORR) of more than 40% among non–small cell lung cancer patients with squamous histology or other hemorrhagic risk factors in a single-arm, single institution, phase II trial presented at the annual meeting of the American Association for Cancer Research.

The preliminary results, which include evidence of "tolerable toxicity," are especially encouraging because of the limited treatment options available to this patient population, according to senior investigator Dr. Gregory Otterson of the Ohio State University Comprehensive Cancer Center in Columbus.

Much attention has been focused on the addition of bevacizumab (Avastin) to platinum-based chemotherapy for advanced NSCLC because the combination has been shown to improve ORR, progression-free survival, and overall survival in this population, Dr. Otterson said. However, bevacizumab's link with hemorrhagic complications precludes its indication for patients at increased risk of bleeding, including those with squamous cell carcinoma, a history of hemoptysis, or anticoagulant use.

For these patients, paclitaxel – a compound that stabilizes microtubules to induce cell death – plus carboplatin is a common therapeutic option, but it is frequently associated with hypersensitivity reactions to the toxic solvent Cremophor through which paclitaxel is delivered. In contrast, nab-paclitaxel (Abraxane) is a solvent-free formulation delivered by a nanoparticle technology that binds to the natural protein albumin.

"It is thought that delivering paclitaxel with this technology causes fewer hypersensitivity reactions and may lead to greater drug uptake in tumors," Dr. Otterson said, noting that "higher doses can be administered over a shorter infusion time."

A previous randomized controlled trial comparing the nab-paclitaxel plus carboplatin combination with the conventional paclitaxel plus carboplatin combination in advanced NSCLC patients had superior ORRs with the former combination, especially in patients with squamous cell histology, Dr. Otterson said. Based on this finding, the current study focuses specifically on squamous cell patients and others whose bleeding risk precludes bevacizumab treatment, he said.

The study included 63 chemotherapy-naive NSCLC patients (21 female and 42 male, median age 63 years), including 48 with squamous cell carcinoma, 9 with adenocarcinomas, 4 with NSCLC not otherwise specified, and 2 with adenosquamous carcinoma. Of those with nonsquamous disease, 11 had a history of hemoptysis and 2 had a history of thrombosis, while 1 patient was undergoing therapeutic anticoagulation. The patients' average tobacco use history was 50 pack-years.

Treatment was administered every 21 days, initially at 300 mg per m^2/AUC = 6, then adjusted to 260 mg per m^2/AUC = 6 because of excess neuropathy, Dr. Otterson said. The study's primary end point is the ratio of ORR to safety/toxicities; progression-free survival is a secondary end point.

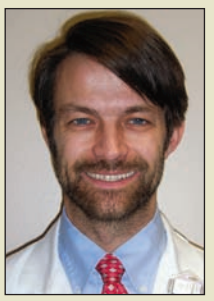
Preliminary findings for 53 patients evaluable to date indicate that 22 patients had a partial response to the therapy, while none had a complete response, for an ORR of 41.5%. The investigators observed stable disease in 21 patients and progressive disease in 10, Dr. Otterson said.

With respect to tolerability, "more than 10% of the patients experienced grade 3/4 toxicities," including hematologic toxicity in 36 patients and sensory neuropathy in 17. There were four deaths, reported as grade 5 toxicities, including sudden death in one patient and respiratory failure in another, he said.

Although median overall survival (9.7 months) and progression-free survival (5 months) "were not as high as we would have liked," the durability of the treatment – some patients did not require more treatment for 6 months – is "surprising and promising," Dr. Otterson said.

The study was supported by Abraxis Biosciences. Dr. Otterson reported no relevant conflicts of interest. ■

COMMENTARY



Dr. Joseph Barney, FCCP, comments: This small, unblinded study is clinically relevant for pulmonologists who treat primary lung cancer patients and take care of the critical care–related complications from chemotherapy. The technique is advanced, and I think we're going to see more to come in this vein.

If They Can't Quit, Supplement

Vitamin C • *from page 1*

the respiratory system (Crs/kg), and found significantly lower results in the placebo group (1.2 Crs/kg), compared with the vitamin C group (1.32 Crs/kg) or the nonsmoking group (1.36 Crs/kg). Treatment did not significantly affect respiratory rate.

There were no significant differences between the randomized groups in characteristics including maternal age, insurance coverage, cotinine levels, medication adherence, history of asthma, or the proportion of women smoking 10 or more cigarettes per day.

Infant demographics were similar in the two groups of smokers and the reference group of nonsmokers, including birth weight, gestational age at delivery, sex, rate of delivery before 32 weeks' gestation, and rate of vaginal delivery.

The investigators plan to perform infant pulmonary function tests again when the study babies are 1 year old and compare the results with clinical outcomes such as episodes of wheezing. They have secured support from the National Heart, Lung, and Blood Institute to randomize a new cohort and measure newborn forced expiratory flows as the primary outcome, she said.

The investigators did not give vitamin C supplementation to infants, but that strategy may deserve study as well, Dr. McEvoy said.

The study excluded pregnancies with multiple gestation or fetal congenital anomalies and women who currently used illicit drugs or abused alcohol, had a history of kidney stones, had insulin-dependent diabetes, or who had been taking vitamin C daily since their last menstrual period. Before the treatment period began, participants were asked to take a daily placebo; those who complied with fewer than 75% of placebo doses were excluded from randomization.

Approximately 12% of U.S. women smoke during pregnancy and at least 500,000 newborns each year have been exposed to smoke in utero. Previous studies have shown that infants of smokers have worse lung function at birth and a higher risk of developing lung diseases, including asthma, bronchitis, and pneumonia, compared with infants of nonsmokers.

The current findings support evidence from nonhuman primates that daily vitamin C can block the in utero effects of nicotine on lung development and newborn pulmonary function (Am. J. Respir. Crit. Care Med. 2005; 171:1032-9). ■

Infants With Bronchiolitis Do Fine With NG Feeds

BY MICHELE G. SULLIVAN
IMNG Medical News

BOSTON – Nasogastric feeding is safe for infants with viral bronchiolitis.

Infants who received nutrition by NG tube did not experience any exacerbation of their respiratory illness and recovered just as quickly as those who received intravenous fluids, Dr. Amir Kugelman said at the annual meeting of the Pediatric Academic Societies.

"Gastric tube feeding is more physiologic and allows mothers to continue breast-feeding" while their infant is unable to tolerate oral intake, said Dr. Kugelman, director of the pediatric pulmonary unit at Bnai Zion Medical Center, Haifa, Israel. "There is also the possibility that better nutrition might enhance recovery." IV fluids provide limited calories and no lipids or proteins, which can lead to a catabolic state during a time of increased nutritional needs.

The randomized controlled study included 51 infants (mean age, 2.5 months) with moderate viral bronchiolitis. They could not sustain oral feeding because of an increased respiratory rate of at least 60 breaths per minute. Most (41) were positive for respiratory syncytial virus; 11 had developed pneumonia. The IV group received a continuous infusion of standard 5% dextrose in normal saline solution. The NG group received a slow drip of breast milk or infant formula. There were no significant differences in duration of oxygen needed, time to full oral feeds, or length of stay and no incidences of aspiration, Dr. Kugelman said. ■

COMMENTARY

Dr. Susan Millard, FCCP, comments: This research highlights that "less is more." The results favoring NG placement for infants with bronchiolitis could be used as an argument to insurance companies who review admissions and often deny reimbursement unless an IV is placed!

CPAP Linked to Lower Incident Hypertension

BY MARY ANN MOON
IMNG Medical News

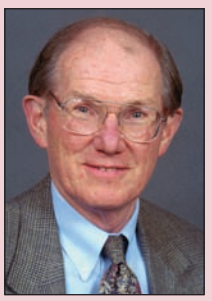
Continuous positive airway pressure therapy was linked to a lower rate of incident hypertension in one study but not in another, separate study reported online in JAMA.

However, the investigators in the second study discovered methodologic flaws that called their conclusion into question. They performed a post hoc analysis, and the results were similar to those of the first study: CPAP therapy, when adhered to, is associated with a lower rate of incident hypertension.

Neither study could definitively establish that CPAP itself decreases hypertension; both could only note the strong association between the treatment and a decreased rate of the disorder.

COMMENTARY

Dr. Paul Selecky, FCCP, comments: This study adds yet another cardiovascular comorbidity associated with untreated obstructive sleep apnea.



CPAP therapy is known to decrease overall cardiovascular risk and to lower blood pressure in certain groups of patients, but its efficacy in preventing the onset of hypertension has not been adequately studied to date, both groups of researchers noted.

In the first study, Dr. Jose M. Marin of Miguel Servet University Hospital, Zaragoza (Spain), and his associates used data from the observational Zaragoza Sleep Cohort Study to assess whether patients on long-term CPAP were less likely to develop hypertension. The cohort study involved more than 5,000 patients referred by their primary care physicians to a sleep center for assessment of sleep-disordered breathing in 1994-2000.

For his analysis, Dr. Marin and his colleagues studied 1,889 such patients who had no hypertension at baseline and who underwent overnight sleep studies to ascertain the cause of their snoring, daytime fatigue, or daytime sleepiness. A total of 824 subjects were found to have obstructive sleep apnea and then adhered to CPAP therapy; another 462 were found to have obstructive sleep apnea but were ineligible for CPAP, 195 declined to try CPAP, and 98 were nonadherent with CPAP therapy. Another 310 patients who were not found to have obstructive sleep apnea served as control subjects.

During a mean follow-up of 11 years, 705 patients developed incident hypertension.

In unadjusted analyses, the rate of new-onset HT was 3.06 per 100 person-years among patients who adhered to CPAP therapy. It was significantly higher in patients who were ineligible for CPAP (3.34 per 100 person-years), and dramatically higher in those who declined CPAP (5.84 per 100 person-years) and those who were nonadherent (5.12 per 100 person-years).

After the data were adjusted to account for several confounders, the risk of new-onset HT was the same between patients who adhered to CPAP and control subjects, but was significantly higher in all other groups (JAMA 2012;307:2169-76).

These findings were independent of the severity of obstructive sleep apnea and of patients' body mass index. Since almost all the subjects gained weight during follow-up, this suggests that weight gain does not diminish the protective association of CPAP therapy and the development of HT, Dr. Marin and his associates said.

Overall, the study results suggest that obstructive sleep apnea is a modifiable risk factor for new-onset HT. This is highly relevant to clinicians "considering that obstructive sleep apnea, despite a high prevalence in Western populations, remains overwhelmingly unrecognized and untreated," they added.

VITALS

Major Finding: The risk of new-onset HT was the same between patients with obstructive sleep apnea who adhered to CPAP therapy and control subjects who did not have apnea, but was significantly higher in patients with obstructive sleep apnea who did not receive CPAP therapy.

Data Source: Data came from an observational cohort study of 1,889 subjects who underwent sleep studies and were followed for 11 years for the development of hypertension; and a multicenter, randomized trial of 725 patients with obstructive sleep apnea but no daytime symptoms who were followed for a mean of 4 years for the development of HT and CV events.

Disclosures: Dr. Marin's study was supported by Instituto Carlos III; the Ministry of Health, Madrid; and the Spanish Society of Respiratory Medicine. Dr. Barbe's study was funded by Instituto de Salud Carlos III, the Spanish Respiratory Society, Resmed, Air Products-Carburos Metalicos, Respironics, and Breas Medical. Dr. Marin, Dr. Barbe, and their associates reported no financial conflicts of interest.

In the second study, Dr. Ferran Barbe of Arnau de Vilanova University Hospital, Lleida (Spain), and his associates assessed CPAP's effect on incident hypertension among subjects who had obstructive sleep apnea but did not have symptoms of daytime sleepiness or fatigue. This is a subgroup of apnea patients who have not been shown to benefit from the treatment, with the caveat that research in this patient population has been inadequate.

Dr. Barbe and his colleagues assessed 723 such patients who were randomly assigned to receive CPAP (357 subjects) or no CPAP (366 control subjects). During a median follow-up of 4 years, 147 patients developed incident hypertension and 59 had cardiovascular events.

In the CPAP group there were 68 cases of HT and 28 CV events, and in the control group there were 79 cases of HT and 31 CV events – a nonsignificant difference.

The rate of combined HT/CV events was 11.02 per 100 person-years with CPAP and 9.20 per 100 person-years without CPAP, also a nonsignificant difference. Apnea severity did not affect these findings.

The researchers noted that they had assessed patients who had been prescribed CPAP but not patients who had adhered to CPAP therapy, and that adherence – use of the treatment for at least 4 hours per night – is critical to CPAP's effectiveness. They therefore performed a post hoc analysis based on a cutoff of 4 hours of actual adherence to CPAP, which they substantiated by examining oxygen saturation data.

This analysis showed that CPAP was associated with a significantly reduced rate of incident HT and CV events as long as patients received 4 hours or more of the treatment each night (JAMA 2012;307:2161-8).

However, as the conclusion of a post hoc analysis, this result must be considered "hypothesis generating" rather than definitive, they noted.

In addition, Dr. Barbe and his associates realized that they had erred in designing the study and that it likely had insufficient statistical power to detect a significant difference in the rate of HT. "A larger study or longer follow-up might have been able to identify a significant association between treatment and outcome," they said. ■

Hypoxia Ups Cancer Dx

OSA • *from page 1*

reported in a press briefing at the annual meeting of the American Thoracic Society.

In a separate prospective 5-year study of 5,618 patients who were referred to seven sleep clinics in Spain, severe hypoxemia during sleep was associated with significantly increased incidence of cancer. Patients with OSA who spent more than 30% of their sleep time with an oxyhemoglobin saturation under 90% were more than twice as likely to be diagnosed with cancer during 5 years of follow-up, compared with patients without OSA, Dr. Miguel A. Martinez-Garcia and his associates reported.

"In both studies, when they looked at the amount of low oxygen, that's when the incidence and mortality from cancer went up," said Mary J. Morrell, Ph.D., who moderated the press briefing. "What it suggests is that there's something associated with low oxygen that's triggering the cancer, which would fit with the initial animal work that caused them to look into the two large cohorts" of people, added Dr. Morrell, professor of sleep and respiratory physiology at Imperial College, London.

The U.S. study analyzed mortality data for participants in the Wisconsin Sleep Cohort, a prospective, community-based study of the predictors and natural history of sleep disorders. All underwent polysomnography at the start of the study. Sleep-disordered breathing was defined as an apnea-hypopnea index (AHI) score of 5 or greater, the mean number of apnea and hypopnea events per hour of sleep.

'IN BOTH STUDIES, WHEN THEY LOOKED AT THE AMOUNT OF LOW OXYGEN, THAT'S WHEN THE INCIDENCE AND MORTALITY FROM CANCER WENT UP.'

The mortality risks were associated with the presence and severity of OSA in a dose-response fashion, said Dr. Nieto, chair of the department of population health sciences at the University of Wisconsin, Madison.

Compared with participants who did not have OSA, those with mild OSA (defined as an AHI of 5-14.9) were 10% more likely to die of cancer during the follow-up years. People with moderate OSA (AHI of 15-29.9) were twice as likely and those with OSA (AHI of 30 or greater) were nearly five times as likely to die of cancer, compared with the control group without OSA. The results were adjusted for the confounding effects of age, sex, body mass index, and smoking, Dr. Nieto said.

"The key thing is that it's the amount of low oxygen that the patients are getting, not essentially how many times it occurs, which is the apnea-hypopnea index. It's the amount that they're getting" that matters most, Dr. Morrell noted.

When the results of the Spanish study were analyzed according to the AHI, the increased incidence of cancer in patients with OSA was no longer statistically significant after adjusting for the confounding effects of age, gender, and body mass index, said Dr. Martinez-Garcia of Le Fe University and Polytechnic Hospital, Valencia, Spain. Subset analyses suggest that the association between the AHI and cancer incidence may be limited to males and younger patients, Dr. Martinez-Garcia said.

Dr. Nieto, Dr. Martinez-Garcia, and Dr. Morrell reported having no financial disclosures. ■

Skimping on Sleep May Increase Stroke Risk

BY DIANA MAHONEY
IMNG Medical News

BOSTON – Consistently short sleep duration not only leaves otherwise healthy individuals tired, it also increases their risk of developing stroke, a study has shown.

Previous studies have linked self-reported sleep duration to incident stroke, but none have considered whether sleep-disordered breathing, which itself is associated with adverse cardiovascular outcomes, mediates that risk, said Megan Ruiter, Ph.D., of the University of Alabama at Birmingham. Dr. Ruiter and her colleagues used data from the national, population-based REGARDS (Reasons for Geographic and Racial Differences in Stroke) study to determine whether sleep duration predicts stroke risk among individuals at low risk for sleep apnea or hypopnea.

Funded by the National Institute of Neurological Disorders and Stroke, the ongoing REGARDS study enrolled more than 30,000 black and white volunteers, aged 45 years and older, to track stroke risk and cognitive health.

Based on self-reported stroke symptoms collected at 6-month intervals, Dr. Ruiter and her colleagues identified 5,666 participants who had been followed for up to 3 years without history of stroke, transient ischemic attack, stroke symptoms, or high risk for sleep-disordered breathing according to the Berlin Sleep Questionnaire. The researchers then conducted interval-censored, parametric survival models with exponential distributions to estimate the hazard ratios predicting time from measurement of sleep duration (less than 6 hours, 6-6.9 hours, 7-7.9 hours, 8-8.9 hours, and 9 or more hours) to first stroke symptoms. Data were adjusted for demographic information, cholesterol levels, hypertension, body mass index (BMI), sleep-disordered breathing, depressive symptoms, and anxiety.

VITALS

Major Finding: The hazard ratio for stroke symptoms among healthy, normal-weight adults who report fewer than 6 hours of sleep nightly was 2.93 relative to those who reported 7-8 hours of nightly sleep.

Data Source: Data are from 5,666 adults enrolled in a national, population-based longitudinal study, without history of stroke or stroke symptoms at enrollment.

Disclosures: Dr. Ruiter disclosed no relevant financial conflicts of interest.

"In people with a low risk for obstructive sleep apnea and a BMI in the optimal range of 18.5-24.99 kg/m^2, the risk of stroke symptoms was four times higher in those who had fewer than 6 hours of sleep per night, compared with participants in the same BMI range who reported 7-8 hours of sleep per night," Dr. Ruiter reported at the annual meeting of the Associated Professional Sleep Societies. Specifically, the hazard ratio for stroke symptoms among individuals within the normal BMI range who reported fewer than 6 hours of sleep nightly was 2.93, relative to the reference group. "We didn't find any similar association between short sleep duration and stroke symptoms among overweight and obese individuals," she noted.

The association between shorter periods of sleep and stroke symptoms, including sudden body weakness, numbness, or vision deficits, remained significant after controlling for other known stroke risk factors, Dr. Ruiter said, acknowledging the possibility that "these participants may be late in the development of stroke."

The findings suggest that habitually short sleep duration may independently predispose middle-age adults to develop major stroke risk factors. "We speculate short sleep is precursor to other traditional risk factors and, once these traditional risk factors are present, they may become stronger risk factors than sleep duration alone," Dr. Ruiter hypothesized.

In a separate analysis, the investigators also evaluated the association between stroke symptoms and sleep duration by racial group and found a differential risk, according to Dr. Ruiter. "It is possible that sleep duration might partially explain the relationship between ethnic differences in stroke symptoms. For example, African Americans had a greater prevalence of short sleep and were more likely to have stroke symptoms," she said.

The study is limited by the reliance on self-reporting of stroke symptoms and the potential for recall inaccuracy, Dr. Ruiter said. Further studies are warranted to tease out the specific characteristics of sleep duration that are related to stroke symptoms, she said. For example, "Is it actually sleep fragmentation or one's perception of sleep and factors that contribute to its quality rather than sleep duration itself?" she proposed. Additionally, "we need to see if sleep duration is related to actual stroke events." Many of these factors, she noted, are modifiable through behavioral treatment. ■

COMMENT

Dr. Paul Selecky, FCCP, comments: We are a sleep-deprived nation. The old adage again rings true that "there is nothing better than a good night's sleep."

Insomnia Drug Helps Patients Sleep Sooner, Longer

BY DIANA MAHONEY
IMNG Medical News

BOSTON – The promise of shorter time to sleep, longer sleep duration, and fewer side effects associated with the experimental sleep drug suvorexant has sleep medicine clinicians and their patients eagerly anticipating the approval of the first-in-class agent.

Suvorexant's mechanism of action in targeting the orexin system, which promotes wakefulness, sets it apart from some of the currently available sleep medications, according to Dr. Michael Thorpy, director of the Sleep-Wake Disorders Center at the Montefiore Medical Center in New York. "The effects of the new drug are fairly localized because it targets a more specific receptor than the GABA agonists, which have a more generalized effect and thus more side effects." Importantly, suvorexant does not depress the central nervous system or respiratory function and thus may be a good option for patients with suspected sleep apnea, he noted at the annual meeting of the Associated Professional Sleep Societies.

Two pivotal phase III studies of the drug were presented at the meeting. Both randomized, double-blind, placebo-controlled trials were 3-month studies designed to confirm the safety and efficacy outcomes of an initial 4-week proof-of-concept study in patients with primary insomnia. Each trial evaluated two dose regimens: 40 mg for patients 18-64 years and 30 mg for those older than 65 years in the first trial; and 20 mg and 15 mg, respectively, in the second trial, explained Dr. Andrew D. Krystal, professor of psychiatry and behavioral sciences at Duke University Medical Center, Durham, N.C., and an investigator for both trials.

Efficacy measures were patient self-reported time to sleep onset (sTSO), self-reported total sleep time (sTST), and self-reported wake after sleep onset (sWASO), as well as the polysomnographic end points of latency to onset of persistent sleep (LPS) and wake after sleep onset (WASO), he said.

In the first trial, which randomized 1,021 patients, suvorexant at 40 mg and 30 mg was significantly better than placebo for all end points at 1 and 3 months, Dr. Krystal reported. Specifically, at 3 months, the mean differences from placebo in change from baseline were an increase of 19.7 minutes for sTST and decreases of 8.4 minutes for sTSO, 6.9 minutes for sWASO, 9.4 minutes for LPS, and 22.9 minutes for WASO.

'For optimal efficacy, all medications should be used in combination with behavioral interventions.'

DR. THORPY

Similarly, significant changes were observed in the second trial, with the exception of the drug's effect on LPS at 3 months, which was not significant – a finding the investigators attributed to high placebo response, Dr. Krystal said. In this study, the mean differences from placebo in change from baseline at 3 months were an increase of 25.1 minutes for sTST and decreases of 13.2 minutes for sTSO, 8.9 minutes for sWASO, 3.6 minutes for LPS, and 29.4 minutes for WASO.

Both studies also measured the time it took patients to fall into continuous sleep and the time they spent awake during the first night of use, comparing the results with those reported before starting the drug, Dr. Krystal said. In the first trial, "patients [taking suvorexant] entered into continuous sleep 30.6 minutes faster and spent 58.0 fewer minutes awake during the night, compared to before they started taking the drug," he said. Similarly, in the second trial, the suvorexant patients entered into continuous sleep 34.7 minutes faster and spent 63.3 fewer minutes awake during the night, compared with before they started the drug. The respective placebo group improvements in the two trials were 13.0-20.3 minutes and 19.6-21.3 minutes, he said.

"Over the 3-month period, the overall incidence of adverse events in the higher-dose groups was 25.1%, compared with 13.8% for the placebo group in the first trial, and 22.2%, compared with 16.4%, in the second, and no serious drug-related adverse events were observed in either trial with the high dose of the drug," Dr. Krystal said. The most common adverse events that occurred at least 5% more frequently in the high-dose suvorexant group, compared with placebo, were sleepiness and headache, he noted.

No significant next-day objective residual effects were seen with the study drug relative to placebo, as measured by the Digit Symbol Substitution Test, Dr. Krystal said. At 3 months, incidence of next-day sleepiness was about 10% with high-dose suvorexant and 3% with placebo.

While the drug was well tolerated in two short-term trials, "longer trials will be more telling," Dr. Thorpy said. "The orexin inhibitors were first investigated because of their effect on metabolism, so there is a possibility that, in the longer-term studies, we might see weight changes or other metabolic effects."

Although suvorexant, which has not yet been submitted to the Food and Drug Administration for approval, promises to be a valuable addition to the sleep therapy arsenal, "medications in the management of insomnia can only go so far," Dr. Thorpy stressed. "Some of the more important therapies are behavioral. No sleep pill will work with someone who has bad sleep hygiene or sleep/wake cycle issues. For optimal efficacy, all medications should be used in combination with behavioral interventions."

Dr. Krystal reported serving as a consultant to Merck, which funded the studies. Dr. Thorpy said that he had no relevant conflicts of interest. ■

Thoracic Surgery Possible for Some PAH Patients

BY DAMIAN McNAMARA
IMNG Medical News

SAN FRANCISCO – Although pulmonary artery hypertension is considered a relative contraindication to most thoracic surgery, it may be safe to proceed after careful patient selection, according to the findings of a retrospective study.

"Patients with mild to moderate pulmonary artery hypertension who required thoracic surgery procedures are not at an increased risk of 30-day mortality," said Dr. Julissa E. Jurado, explaining the main finding from an assessment of 96 surgical patients.

VITALS

Major Finding: Postoperative 30-day survival in patients with severe pulmonary artery hypertension was 86%. No patient with mild or moderate PAH died during this postoperative period.

Data Source: Data are from a retrospective study of 96 patients who underwent surgery during 1997-2011.

Disclosures: Dr. Jurado said that she had no relevant financial disclosures.

Dr. Jurado and her colleagues classified the patients into mild, moderate, and severe pulmonary artery hypertension (PAH) groups. Of the 28 patients with severe PAH, 4 died within 30 days of surgery – 3 with end-stage interstitial disease and 1 pericardial window case. One patient in this group died from cardiac arrhythmia, one from respiratory failure, and two from unknown causes. In other words, 30-day survival in the severe PAH group was 86%.

"At 1 year, even in the severe group, survival was 70%," Dr. Jurado said at the annual meeting of the American Association for Thoracic Surgery.

Study discussant Dr. Alexander Krupnick called this a "relevant study." He added, "At some time or other, we are all asked to operate on a patient with pulmonary artery hypertension … and this should help with risk stratification." Dr. Krupnick is a cardiothoracic surgeon at Barnes Jewish Hospital in St. Louis.

The study included patients with PAH who underwent noncardiac surgery during 1997-2011. Mean pulmonary systolic pressure was 27 mm Hg in the mild PAH group, 31 mm Hg in the moderate group, and 45 mm Hg in the severe PAH group.

Surgeries included 64 diagnostic and 32 therapeutic procedures; 70 were minimally invasive, 26 were open. The most common procedure was wedge resection (49% of patients), followed by mediastinoscopy/bronchoscopy with biopsy (14%), lung volume reduction (11%), decortication/pleurodesis/pleural biopsy (11%), pericardial window (6%), lobectomy (5%), Nissen procedure (2%), and pneumonectomy (2%).

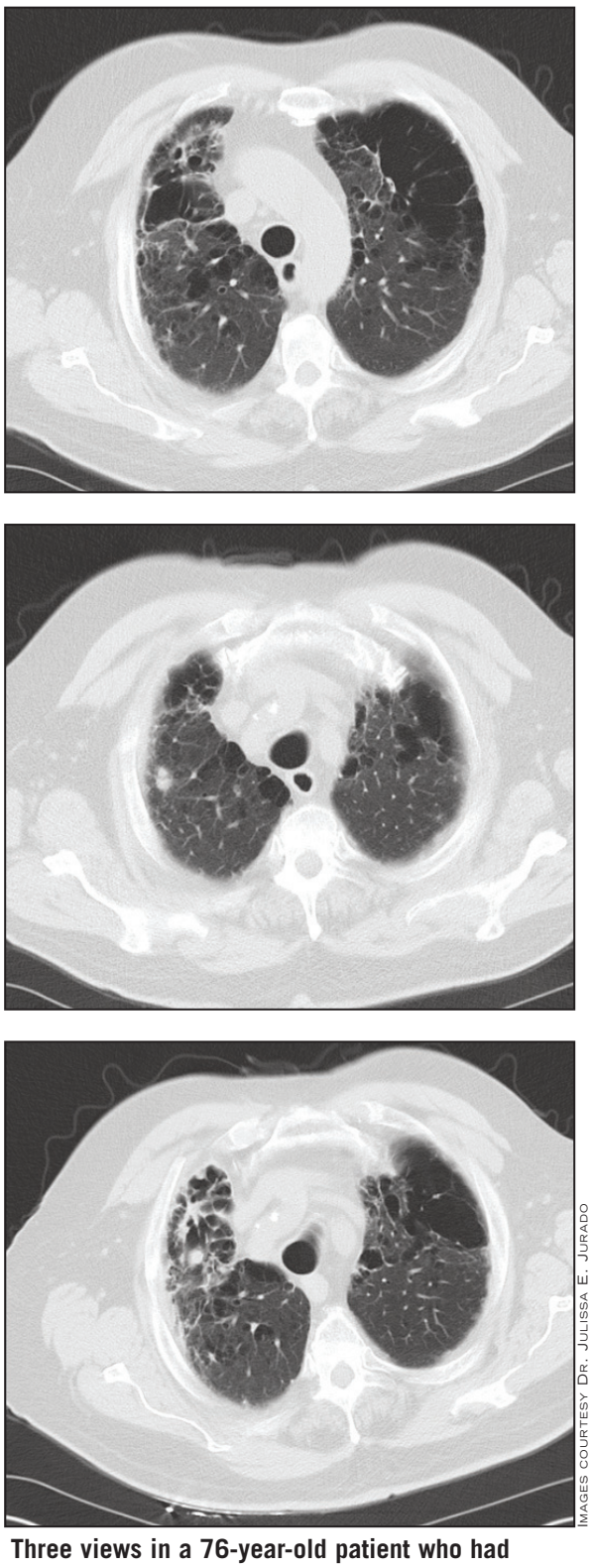
A meeting attendee asked what factors led surgeons to proceed with surgery in patients with severe PAH. "Unfortunately, the study was retrospective and goes back to 1997," said Dr. Jurado, who is a clinical fellow in thoracic surgery at Columbia University/New York–Presbyterian Hospital. "I cannot speak for the surgeons and why they felt it was okay to operate on these patients."

The median ICU stay was 0 days in the mild and moderate groups and 2 days in the severe PAH group. Mean length of hospital stay was 4 days in the mild group versus 10 days in the moderate and 11 days in the severe PAH groups. Overall improvement in forced expiratory volume in 1 second was 23%, with the greatest improvement seen in the moderate group (53%).

Another meeting attendee asked about left heart dysfunction. "We were specifically looking for left ventricular and right ventricular dysfunction and outflow," Dr. Jurado replied. "We did not find any right side lesions or right obstructions."

The retrospective, nonrandomized design is a potential limitation of the study, Dr. Jurado said.

The PAH severity groups were matched for age and gender. The study included 43 men and 51 women with a mean age of 58 years. ■



IMAGES COURTESY DR. JULISSA E. JURADO

Three views in a 76-year-old patient who had moderate pulmonary hypertension before undergoing right-upper-lobe wedge resection.

COMMENTARY

Dr. Lary Robinson, FCCP, comments: The presence of elevated pulmonary artery pressures in a prospective patient is a concern to all lung surgeons. Dr. Jurado's retrospective 14-year review of the results of lung surgery in 96 patients with varying degrees of pulmonary hypertension is reassuring, and gives us more confidence in our risk stratification when approaching lung resections in the patients with mild or moderate pulmonary arterial pressure elevations. Caution is still indicated in those with severe pulmonary hypertension, especially if a major lung resection is contemplated. However, surgeons also need to realize that Doppler echocardiography, which is most commonly used to evaluate pulmonary artery pressures in a prospective lung surgery patient, is fraught with significant, potential technical inaccuracies due to the poor acoustic window frequently encountered in the usual COPD patient. Therefore, care should be exercised before denying a patient surgery because of severe pulmonary hypertension based purely on an echocardiogram alone.

Noninvasive Ventilation Overused for Some Conditions

BY M. ALEXANDER OTTO
IMNG Medical News

SAN FRANCISCO – Clinicians may have become too enthusiastic about using noninvasive ventilation in lieu of intubation and mechanical ventilation, according to a nationwide database study from the Boston University Pulmonary Center.

Noninvasive ventilation (NIV) use tripled during 2000-2009 for acute respiratory failure (ARF) caused by chronic obstructive pulmonary disease, for which there is good evidence of a mortality benefit (Cochrane Database Syst. Rev. 2004;3:CD004104).

But in the same period, use increased 3.4-fold for ARF caused by conditions for which there is little evidence to support its use, including asthma, pneumonia, neurologic diseases, and nonpulmonary sepsis. Currently, about half of ARF patients receiving NIV have COPD, while half have other conditions.

The investigators found that patients are more likely to fail NIV – and subsequently receive mechanical ventilation – when it's used for those conditions instead of COPD (odds ratio, 1.12; 95% confidence interval, 1.08-1.16). Overall, 12% of COPD patients failed NIV, compared with 18% of non-COPD patients (*P* less than .001).

Of the study patients who failed NIV, 37% died, compared with 35% on mechanical ventilation alone ($P = .002$).

The researchers analyzed approximately 11 million hospital records from 2000-2009 coded for ARF in the Agency for Healthcare Research and Quality's Nationwide Inpatient Sample (NIS) database, excluding patients with sleep apnea.

VITALS

Major Finding: Use of noninvasive ventilation grew 3.4-fold during 2000-2009 for conditions that have little evidence to support its use.

Data Source: Data are from the Nationwide Inpatient Sample database.

Disclosures: Dr. Walkey said he had no disclosures.

"People might have a little too much faith in noninvasive ventilation. They see it work really well in COPD, so they think it might work well in everyone," said lead investigator Dr. Allan J. Walkey, director of pulmonary and critical care education at Boston University.

He said the study's take-home message is to "think twice if you are going to put a noninvasive ventilator on someone without COPD or acute cardiogenic pulmonary edema," for which there is also strong evidence of benefit (Cochrane Database Syst. Rev. 2008;3:CD005351). In other patients, "there's generally not good evidence to support use of noninvasive ventilation, and [our study suggests] it may be associated with worse outcomes. [Those patients] need to be monitored closely, and if they are showing signs of failure, they need to be intubated," he said at an international conference of the American Thoracic Society.

It's unclear why NIV might be problematic for some. Perhaps not being able to suction secretions out of an endotracheal tube leads to problems in pneumonia. Maybe fading sensorium in other conditions increases the likelihood of gastric aspiration if there's no tube in place to protect the airway, Dr. Walkey said.

Although the NIS database does not include vital signs, lab reports, and other patient-level clinical data, the researchers used an algorithm to assess and control for disease severity. "There is growing evidence that the adjustment of disease severity using data you do have in large databases" – such as information on comorbidities, billing codes, and demographics – "is actually as accurate as those based on disease severity scores," Dr. Walkey said (Crit. Care Med. 2011; 39:2425-30).

The researchers also found wide regional variations in NIV use, with the heaviest use in the Northeast and the lowest in the Midwest; use was roughly equal in teaching and nonteaching hospitals.

Insurance claims for acute respiratory failure increased from 818,781 in 2000 to 1,531,352 in 2009, with an associated 25% decrease in ARF mortality over that period. ■

COMMENTARY

Dr. Steven Q. Simpson, FCCP, comments: This very large analysis of a national database provides support for what most intensivists have discerned, that noninvasive positive pressure ventilation (NIV) is less effective in non-COPD indications than it is in patients with COPD. However, the authors may overstate their case. In reality, more than 8 out of 10 non-COPD patients tolerate NIV without the need for more invasive ventilation – in other words, the odds of successful ventilation are 4.5:1. The 2% absolute increase in mortality among those who fail NIV over those who are initially intubated equates to an odds ratio of 1.09 for dying. Given these odds, a patient may well opt for NIV, in spite of some increased risk if they fail it. Also, the authors do not explore the increasing use of NIV in patients who do not wish to be intubated but are willing to have noninvasive treatment. The data may be useful in the sense that they should prompt intensivists to make more rapid decisions regarding the effectiveness of NIV or to estimate the likelihood that a patient's respiratory failure will be quickly reversible, but they should not be taken as definitive.

Inpatient Mortality Unchanged by Enoxaparin Prophylaxis

BY M. ALEXANDER OTTO
IMNG Medical News

SAN FRANCISCO – Thromboprophylaxis with enoxaparin did not reduce mortality in acutely ill medical inpatients in a trial funded by the maker of the low-molecular-weight heparin, Sanofi-Aventis.

VITALS

Major Finding: Among 4,171 acutely ill hospitalized medical patients randomized to enoxaparin 40 mg subcutaneously for 10 ± 4 days, all-cause 30-day mortality was 4.9%; among 4,136 randomized to placebo for the same amount of time, it was 4.8%.

Data Source: Data were taken from a randomized, blinded, placebo-controlled trial.

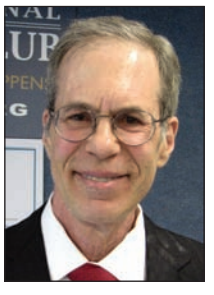
Disclosures: The trial was funded by Sanofi-Aventis, the maker of enoxaparin. The presenter of the findings, also an investigator, disclosed that he is a paid consultant for Sanofi-Aventis, Boehringer Ingelheim, Bristol Myers Squibb, Merck, and several other companies. Dr. Goldhaber disclosed that he is a paid consultant for Sanofi-Aventis, Boehringer Ingelheim, Bristol Myers Squibb, Merck, and several other companies. Dr. Drazen reported having no disclosures.

Among 4,171 patients randomized to enoxaparin (Lovenox) 40 mg subcutaneously for 10 ± 4 days, all-cause 30-day mortality was 4.9%; among 4,136 randomized to placebo for the same amount of time, it was 4.8% (relative risk, 1.0; 95% CI, 0.8-1.2; $P = .83$).

The major bleeding rate was below a half percent in both groups and not statistically different. Minor bleeding was seen in 1.8% with enoxaparin and 1.1% with placebo, a statistically significant difference, Dr. Samuel Goldhaber, FCCP, said at an international conference of the American Thoracic Society.

Commenting on the study, New England Journal of Medicine editor Dr. Jeffrey Drazen, FCCP, noted that, in the United States, the reflex has been to use prophylaxis on even low-risk patients for VTE. "The reason we published these data was that maybe we should rethink this. Maybe we should be making decisions about who should be receiving pharmacologic prophylaxis based on factors other than the fact that they are in the hospital for an acute medical illness," he said.

Patients were hospitalized for acute decompensated heart failure, severe systemic infections, or active cancer. No mortality benefit was found for enoxaparin on subgroup analysis. Both groups wore knee-high elastic graduated compression stockings during the treatment phase of the trial (N. Engl. J. Med. 2011;365:2463-72).



'We were quite surprised' that the all-cause 1-90 day mortality curves 'were absolutely superimposable.'

DR. GOLDHABER

The all-cause 1-90 day mortality curves for the two groups "were absolutely superimposable. We were quite surprised by the results," said Dr. Goldhaber, professor of medicine at Harvard Medical School and director of the venous thromboembolism research group at Brigham and Women's Hospital, both in Boston.

They were surprised because enoxaparin has been shown to reduce VTE in both surgical and medical patients, and to reduce the incidence of fatal PE and all-cause mortality in surgical patients. There was a presumption it would save medical patients' lives, too, although they have a lower PE rate. Current U.S. treatment guidelines recommend pharmacologic prophylaxis in both surgical and acutely ill medical inpatients.

The study was conducted in China, India, Korea, Malaysia, Mexico, the Philippines, and Tunisia because, in those places, enoxaparin prophylaxis for medical patients is "still considered an open question," Dr. Goldhaber said.

About 88% of the subjects were Asian, and 63% were men. Their average age was 65 years. There were no statistically significant baseline differences between the placebo and enoxaparin groups.

Perhaps enoxaparin didn't cut mortality in the trial because "the natural history of deep vein thrombosis differs between medical and surgical patients." It's been assumed that "the natural history would be the same. This assumption may be incorrect," Dr. Goldhaber said.

It's also possible that the elastic stockings used in the trial were enough to prevent fatal PE in the Asian subjects, a group known to have a lower PE risk than Westerners. Just one patient in each group died from a PE in the study; infections were the main cause of death.

Dr. Goldhaber said he still tends to prophylaxis low-risk medical inpatients. "In our world, the quality measures are in place, but I'd be thinking to myself" that they are probably not going to develop a PE, he said. ■

Tips on Cardiovascular Testing Before Cancer Surgery

BY DAMIAN McNAMARA
IMNG Medical News

MIAMI BEACH – When you are called to assess a patient before cancer surgery, how do you know when noninvasive cardiovascular testing is warranted?

Start by asking patients to describe their functional status before they started any treatment to combat their cancer, Dr. Sunil K. Sahai said.

Also assess for any ischemia preoperatively, because its presence might direct a surgeon to prescribe a less cardiotoxic postoperative treatment for your patient, Dr. Sahai said at a meeting on perioperative medicine sponsored by the University of Miami. Occult ischemia might be found if a patient reports shortness of breath during prior chemotherapy administration, he added.

"Everything you've heard about perioperative medicine is true for cancer patients, but they are also unique," Dr. Sahai said. The physiologic burden of cancer and its treatment makes preoperative evaluation challenging, but it's worth doing right to ensure the patient receives the optimal therapy. Also, in some cases, either the patient or surgeon will decide not to proceed with surgery based on your risk assessment, said Dr. Sahai, medical director of the Internal Medicine Perioperative Assessment Center at the University of Texas M.D. Anderson Cancer Center in Houston.

To illustrate some of the challenges, Dr. Sahai described an actual patient, a 60-year-old man referred for assessment 1 week before a scheduled neck dissection and total laryngectomy. He presented with dysphagia and sore throat. A biopsy revealed postcricoid squamous cell carcinoma. He had undergone surgery and radiation for nasopharyngeal cancer 15 years earlier but was otherwise healthy. The current physical exam was unremarkable, except for bilateral carotid bruits. Doppler ultrasound findings led to a diagnosis of radiation-induced carotid stenosis with diffuse, bilateral atherosclerosis and greater than 70% stenosis.

Head and neck cancer patients can have double the risk of transient ischemic attack or cerebrovascular accident, compared with a patient with normal pathologic narrowing of the carotid arteries, Dr. Sahai said. This is a controversial area because "data are not clear on what to do."

A stent was placed in the patient's right internal carotid artery, and cancer surgery was delayed for 1 month while he took clopidogrel and aspirin. "He then went to the operating room on aspirin, and he did well."

Another case, a 70-year-old woman scheduled for a 6-hour cystectomy for bladder cancer, raised issues around preoperative cardiovascular assessment. "She reports fatigue and shortness of breath with exertion," Dr. Sahai said. "Before chemotherapy, she was able to walk eight blocks and up two flights of stairs without stopping. Now she can walk only four blocks and stops to rest between flights." The patient is obese, has diabetes, and is taking a statin for hyperlipidemia. She does not report any angina symptoms. Her history includes an MI 5 years earlier addressed with medical management only.

Cancer can sap a patient's energy, but the precise etiology in this case was unclear, Dr. Sahai said. Was her shortness of breath related to coronary artery disease, heart failure, pulmonary hypertension, or treatment with cardiotoxic chemotherapy? Should the patient be tested, for example, with an echocardiogram for heart function, stress test for ischemia, or both?

"Because this patient had received cardiotoxic chemotherapy … we would do a stress echo on this patient," Dr. Sahai said. "In addition, BNP [B-type natriuretic peptide] levels may be helpful to detect cardiomyopathy. I would also optimize cardiac function and heart rate and send her to the operating room with the statin on board."

Patients with no cardiovascular symptoms can generally go to the operating room. If a patient is symptomatic, however, especially if the symptoms are new since cancer therapy was begun, Dr. Sahai said he generally considers further testing and work-up.

Dr. Sahai said that he had no relevant financial disclosures. ■

COMMENTARY

Dr. Jun Chiong, FCCP, comments: Cancer surgery poses a unique challenge to cardiologists. First of all, most cancer patients belong to the age group that also has a high incidence of coronary artery disease. Second, the functional capacity of many cancer patients is limited, which makes it necessary to do pharmacologic testing. Third, their bleeding risk is higher as malignant tumors are highly vascular. These factors require special attention during the preoperative evaluation for cancer surgery.

Daily Aspirin Reduced Recurrent Venous Thromboembolism

BY JANE SALODOF MACNEIL
IMNG Medical News

Daily aspirin reduced the risk of recurrent blood clots significantly for patients who had stopped anticoagulant therapy after a first unprovoked venous thromboembolism, investigators reported.

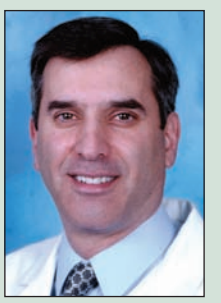
About a 40% reduction was accomplished without an increase in major bleeding, in the 402-patient Aspirin for the Prevention of Recurrent Venous Thromboembolism study. Adverse events were similar whether patients were randomized to 100 mg of aspirin daily or placebo.

New blood clots occurred at a rate of 6.6% per year in patients randomized to aspirin, compared with 11.2% per year in those given placebo, Dr. Cecilia Becattini and her associates reported. At a median treatment period of 23.9 months, the recurrence rates while taking the study drug were 5.9% and 11.0% per year, respectively, with one patient in each group having a major bleed (N. Engl. J. Med. 366;21:1959-67).

All patients had completed 6-18 months of oral anticoagulant treatment with a vitamin K antagonist before randomization in the multicenter, double-blind trial. Patients were not enrolled if they had cancer, thrombophilia, or bleeding during the period of anticoagulant treatment, but the authors wrote that they "estimate that a substantial proportion (probably the majority) of patients with an initial episode of venous thromboembolism would be eligible for aspirin therapy as secondary prevention."

The trial had support from the University of Perugia, a grant-in-aid from Bayer HealthCare, and an Aventis Fellowship for Clinical Research from the International Society of Thrombosis and Haemostasis. Dr. Becattini and several coauthors disclosed relationships with various drug companies, including Bayer. ■

COMMENTARY



Dr. Carl Kaplan, FCCP, comments: This study will likely influence clinical practice with the use of an inexpensive, low-risk, familiar medication (daily 100-mg aspirin) without the need for monitoring. This regimen has resulted in a significant reduction in recurrent VTE in patients with a history of unprovoked thromboembolism with no increase in major bleeding events.

PRESIDENT'S CORNER: THE MEMBERSHIP SPEAKS

Preparing for Change: A Practitioner's Top 10

BY DR. ROBERT DE MARCO, FCCP; DR. SCOTT MANAKER, FCCP; AND DR. CLAYTON COWL, FCCP

The changes in health-care policy have a direct effect on the art and the science of the practice of medicine. We have compiled a list of topics that will give you some insight into navigating these complex regulations. Plan ahead, now is not too late. With both financial incentives and penalties looming from Medicare, start preparing for 2014.

1. Electronic Health Record (EHR). Proceed with implementing an EHR in your office practice. Many commercially available, stand-alone versions are designed for small to medium practices. You may need to supplement an office EHR with a handheld device to e-prescribe. Alternatively, consider partnering with a local hospital or health system. A safe harbor under the Stark Law allows a facility to underwrite up to 85% of the cost of an office-based EHR (excluding hardware including printers and monitors, as well as desktops and laptops) for medical staff.

2. Meaningful Use. Once your EHR is implemented, strive to meet the Meaningful Use criteria. Even if unable to implement and attest to Medicare by the end of 2012 to receive the maximum $44,000 over 5 years, by beginning the process and attesting in 2013, you will be eligible for Medicare incentive payments over 5 years totaling $39,000. Alternatively, physicians receiving 30% of their revenue from Medicaid can attest beginning at any time through 2016 and receive $63,750 over the subsequent 6 years.

3. e-Prescribing. For 2014 incentive payments from Medicare, you need to report on 25 claims (ie, individual patients, not 25 e-prescriptions) by December 31, 2012. You may also report by registry or direct data submission, often a service from your EHR vendor. If not e-prescribing because you practice in an area with few participating pharmacies, or in a rural area with limited high-speed Internet access, apply for an exemption by June 30, 2013, to avert penalties that begin in 2014.

4. Accountable Care Organization (ACO). An ACO is a group of physicians, hospitals, and other health-care providers who create a group to provide care to Medicare patients. It is voluntary for the provider, and failing to join does not affect your Medicare patient's ability to continue to see you. Once the group achieves 33 predefined quality measures, it will be able to share in the savings achieved by Medicare. For more information, go to http://www.cms.gov/ACO.

5. Physician Quality Reporting System (PQRS). PQRS is also a voluntary program where a physician and/or group can report on quality measures delivered to their Medicare patients. Once this quality measure is reported for 50% of the appropriate ICD-9 diagnoses (you need to report three measures to qualify) that match this measure, you will receive an incentive of 0.5% of all your Medicare Part B Physician Fee Schedule (PFS) charges. For further information, go to http://www.cms.gov/PQRS.

6. Repeal of the Sustainable Growth Rate (SGR). The SGR is an index used to determine the PFS under Medicare, which is governed by changes in the gross domestic product (GDP) and has not kept pace with the costs of providing care. For over a decade, Congress repeatedly delayed the decrease in Medicare fees, leaving us with a 30% cut in the PFS scheduled for January 2013. Congress agrees that the SGR needs to be repealed, but the present replacement proposal is also fraught with problems: primary care would receive a 10-year PFS freeze, with subspecialists getting a 5.9% fee reduction for 3 years and then a 7-year freeze. The ACCP will keep you updated on progress as it occurs.

7. Hospitalist Models. As health care continues to evolve, an alternative to private practice is the hospitalist model. These physicians provide only inpatient care and are employed by the hospital or by a group. The physician has a secure income, benefits, and a predefined work schedule but risks the contractual whims of the hospital. The contracted groups are self-employed but face stiff competition from the employed groups of the larger health-care systems.

8. New Technologies. Advances in new technology can be applied to a variety of applications to assist in streamlining tasks in order to maximize efficiency—from scheduling appointments, to marketing, to performing remote monitoring of patients with chronic diseases. The ability to identify useful technologies that create value (and not just cost) will be a key factor in practice sustainability and growth.

9. Optimizing Business Strategies. Practices in rural areas or in solo practice environments appear to be hardest hit in terms of effects of legislation passed into law. Unfunded mandates, such as EHR implementation and electronic billing paradigms, are expensive and many times difficult to service from an information technology perspective. The ability to minimize overhead and find business strategies to address these issues will become more critical over time.

10. Manage Patient Expectations. As the national health-care delivery model continues to evolve, patient expectations have also changed—frequently in ways that result in delivery of data in a much shorter timeframe and with the expectation of contact with their providers via electronic or other methods that require more provider time at less convenient hours. Some of these expectations will need to be managed, in order to preserve quality of care while balancing costs of providing additional services.

This list is not all inclusive but just a glimpse of suggested changes we believe can help ease the burden of our present regulatory environment. Each month since March, topics of relevance to practice operations are presented in *CHEST Physician* in hopes of staying in front of changes we need to make in our practices. ■

DR. DE MARCO *is Chair of the Practice Management Committee;* DR. MANAKER *is Regent-at-Large and BOR Liaison to the Practice Management Committee; and* DR. COWL *is Regent-at-Large.*

Health-care Reform: Is Anyone Listening?

This month's article on health-care reforms enumerates the top 10 changes that physicians should consider implementing in their medical practices to prepare for the imminent changes. The authors-Dr. Robert DeMarco, chair of the Practice Management Committee, and Drs. Scott Manaker and Clay Cowl, Regents-at-Large, have joined hands to bring their in-depth perspectives to our members. They have distilled the more than 1.000 pages of fine print of the bill to what is important and what needs to be prioritized. They focus on the electronic medical platforms and e-billing, on various models of practicing medicine, and how overhead costs can be curtailed. I think our readers will find this article very timely and useful.

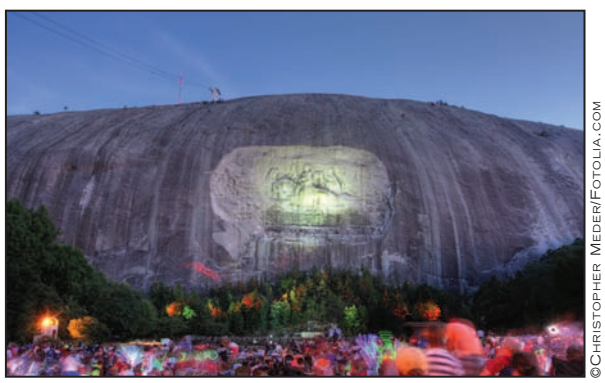
–Dr. Suhail Raoof, FCCP

Note: The views expressed in these articles are those of the authors and do not represent the views of the ACCP, its leadership, members, or staff.

CHEST 2012: Destination Atlanta

CHEST 2012 is taking place October 20-25 in Atlanta. Plan now to attend for essential updates on patient care and practice management strategies. In addition to more than 300 general sessions, many new and exciting education opportunities are being planned. Be sure to read the article highlighting some new features at CHEST 2012, written by ACCP President Suhail Raoof, MBBS, FCCP, on page 19 in this issue.

Atlanta is a world-class, modern city with a rich, passionate history, so explore while you're in town for CHEST 2012. To help you find your way, ACCP members who live in Atlanta have suggested places to visit near the Georgia World Congress Center, site of CHEST 2012, as well as other places to check out if you have some extra time.



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Stone Mountain is the site of the multidimensional Lasershow Spectacular in Mountainvision™.

Recommended Attractions Near the Convention Center

► **Georgia Aquarium.** Dive into a one-of-a-kind aquatic experience at the world's largest aquarium, featuring graceful beluga whales, spectacular whale sharks, playful penguins, and aquatic animals from around the globe. Sign up for the The OneBreath® Evening at the Georgia Aquarium at accpmeeting.org.

► **Inside CNN.** Tour the core of CNN Worldwide for an up-close look at global news in the making. A 55-min guided walking tour offers behind-the-scenes views of the CNN studios and an exclusive glimpse of news and broadcasting in action.

► **Martin Luther King Jr. National Historic Site.** Explore the birth home of MLK and The King Center, where Dr. King's Nobel Peace Prize is displayed. The crypt and grave site of Dr. King and his wife are also here.

► **Underground Atlanta.** Visit historic Underground Atlanta for a complete family experience with retail, specialty shops, fast food, food trucks on Wednesdays, entertainment, special events, and plenty of restaurants.

► **World of Coca-Cola.** Experience the intriguing World of Coca-Cola, featuring an 1880s soda fountain, live-action bottling line, and samples for nearly 60 different beverages from around the world.

Other Recommended Attractions

► **Atlanta Botanical Garden.** With more than 30 acres of gardens, forest, wildflower trails, and the Fuqua Orchid Center, the Atlanta Botanical Garden is one of Atlanta's most beautiful attractions. Be sure to enjoy the Edible Garden Outdoor Kitchen and soothing sanctuary of the Cascades Garden.

► **City Segway Tours.** Tour Atlanta in a unique, innovative, and exciting way—by Segway! Imagine cruising effortlessly through parks and along sidewalks while hearing informative, historical, and current-day information. You'll hear heaps of unique and fascinating stories and have a chance to snap fantastic photos.

► **Piedmont Park.** Visit Piedmont Park for lush woods, Lake Clara Meer, picnic spots, skating paths, and many annual events.

► **Stone Mountain Park.** Stone Mountain Park is Georgia's most-visited attraction, featuring more than 3,200 acres of natural beauty and family-oriented recreational activities. The Lasershow Spectacular in Mountainvision™ has graphics and awe-inspiring effects that create multidimensional magic on one of the world's largest screens—Stone Mountain. Visit the 1870s town of Crossroads® for craft demos, shopping, and dining, or enjoy the Great Locomotive Adventure, Scenic Railroad, and Antebellum Plantation & Farmyard. Other family favorites are Sky Hike, the largest treetop adventure course, and Geyser Towers, a multilevel ropes course combining the challenge of climbing with the thrill of a water park.

► **Zoo Atlanta.** Zoo Atlanta features more than 200 species of animals from the African plains and Asian forests. Visit the giant pandas and other mammals, reptiles, and amphibians. The Ford African Rain Forest houses 24 gorillas, one of North America's largest captive populations.

© jedphoto/Fotolia.com

Atlanta Botanical Garden has more than 30 acres of plant life, including the Fuqua Orchid Center.

Recommended Activities

► **Bike.** If you like to bike, be sure to check out the Silver Comet Trail or the Big Creek Greenway.

► **Golf.** If golf is your thing, check into these courses: East Lake Golf Club (in Atlanta), Reynolds Plantation (1.5 hours east, featuring golf and lake fun), Callaway Gardens (1 hour south, featuring golf and outdoor fun), North Georgia Mountains (2 hours north, featuring lots of golf, fun towns, and hiking).

Thanks to ACCP members Dr. Salim Harianawala, FCCP; Ms. Ellen Hillegass; Dr. Saeid Khansarinia, FCCP; Dr. Burt Lesnick, FCCP; Dr. Greg Martin, FCCP; Dr. Jonathan Popler, FCCP; and Dr. David Schulman, FCCP, for sharing recommendations on what to do in Atlanta. Learn more about the city at atlanta.net. And, keep watching for developing details on CHEST 2012 at accpmeeting.org. ■

Purchase Your Tickets Today for The OneBreath® Evening at the Georgia Aquarium

During all of the extraordinary learning and networking opportunities at CHEST 2012, attendees can also take an exciting, aquatic trip with friends and colleagues and support a phenomenal cause. The OneBreath® Evening at the Georgia Aquarium will be held on Sunday evening, October 21, in support of The CHEST Foundation's OneBreath initiative.

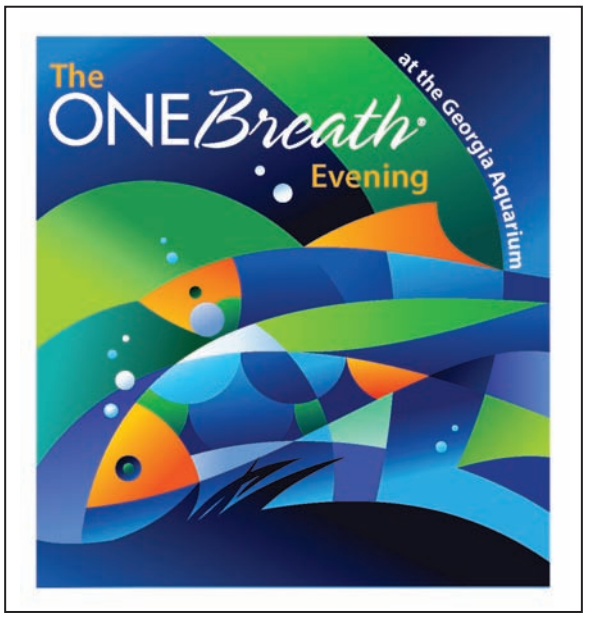
OneBreath inspires people to take care of their lungs and heart and never take their next breath for granted. Drawing from the professional expertise of the American College of Chest Physicians and ACCP members, the initiative aims to improve lung and heart health by providing valuable prevention resources, raising public awareness, and encouraging healthy behaviors.

The Georgia Aquarium is the world's largest aquarium, with more than 8.5 million gallons of marine and fresh water housing more than 120,000 animals from 500 species. The notable marine life at the aquarium includes whale sharks, beluga whales, bottlenose dolphins, great hammerhead sharks, and manta rays.

Guests will feast on sumptuous food prepared in the kitchens of Wolfgang Puck and have access to exhibits throughout the aquarium. Individuals who purchase the VIP Pass will enjoy the additional benefits of an exclusive welcome celebration, entry to the phenomenal Dolphin Tales show, and a delectable dessert reception.

VIP Pass tickets are $300; children (aged 3-11) are $50. Gallery Tour admission tickets are $150; children (aged 3-11) are $35.

Donors to The CHEST Foundation and OneBreath who have contributed $500 between January 1, 2012, and September 30, 2012, are entitled to one free VIP ticket. Donors who have contributed $1,000 in this same time frame are entitled to two free VIP tickets.



OneBreath is also offering chances to win an opportunity to swim with the whale sharks while visiting Atlanta during CHEST 2012. Two, four-person prize packages are available. Raffle tickets are $100 each or three for $250. Only 500 tickets are available, making your chances of winning quite good!

Secure your admission and raffle tickets now through the CHEST 2012 registration page at accpmeeting.org. To make a donation to OneBreath, visit onebreath.org. ■

A Special CHEST 2012 Note From Our President

BY SUHAIL RAOOF, MBBS, FCCP
ACCP President

Under the stewardship of Doreen Addrizzo-Harris, MD, FCCP, Chair, and her program committee, an exceptional clinical education program has been developed for CHEST 2012.

Approximately 300 general sessions covering pulmonary, critical care, and sleep medicine will be complemented by hands-on simulation opportunities, case- and problem-based presentations, small-group interactive discussions, and enhanced self-study sessions.

Headlining several special events held during CHEST 2012 is The OneBreath® Evening at the Georgia Aquarium, where you, with your colleagues and friends, can experience the world's largest aquarium and show your support for the OneBreath initiative.

This event is an opportunity not to be missed, and you can get more information and purchase tickets at accpmeeting.org/program/onebreath-evening. Find details also on page 18 in this issue of *CHEST Physician*.

And there will be plenty of new experiences at CHEST 2012, including:

- Daily opening sessions will feature some internationally renowned speakers: Emmanuel Gobillot will speak on leadership; and Marilyn Tam will present on diversity; and Aneesh Chopra will talk about innovations in health care.
- A "pulmonary practitioner track," is being designed for Saturday and Sunday for those who might have limited time at CHEST.
- Special sessions on chest infections will be delivered in partnership with members from the Centers for Disease Control and Prevention (CDC), which is headquartered in Atlanta.
- Clinical Care-Focused Tracks on Thursday will focus on the newly published antithrombotic guidelines, bronchiectasis, COPD and asthma, critical care medicine, thoracic oncology, and interventional bronchology.
- The popular problem-based learning sessions will be offered. Some sessions covering radiologic cases will be available as an app, so you can continue a self-study experience through systematic interpretations of chest radiographs and CT scans and critical care radiology.
- Other sessions will focus on radiology and highlight clinical-radiologic algorithms on the diagnosis of disease entities, such as multiple pulmonary nodules, bronchiolar diseases, pleural diseases, lung cancers, and others.
- The ACCP Simulation Center will offer half-day comprehensive simulation sessions in airway management, bronchoscopy, mechanical ventilation, and ultrasonography.
- Find out more about ACCP's Certificate of Completion for advanced training in ultrasonography and bronchology while attending CHEST 2012.
- Several symposia will be set up to enhance learning in leadership development and education.
- Poster presentations will showcase original science and research. An electronic presentation format will allow you constant access to select studies.
- The Clinical Resource Center will showcase diagnostic and treatment solutions, and the Centers of Excellence, a dedicated area for showcasing programs and practices that advance outcomes, will exhibit practices that have made the selected programs exceptional.
- Reaching outside of the exceptional meeting, there are many medical institution and general community outreach opportunities being planned.

CHEST 2012

October 20 - 25
Atlanta, Georgia

Come and join us at CHEST 2012, and experience the innovation and clinically relevant sessions being offered. The host city of Atlanta will charm you with its southern hospitality and abundant attractions. Register for CHEST 2012 today! ■

NETWORKS
Asbestos, Diversity, e-Community, LTOT

Clinical Pulmonary Medicine

Shattered Lives: Asbestos-Related Diseases

Just this week, I saw a half-dozen patients with asbestos-related diseases in my pulmonary clinic. One would think that asbestos was phased out of industrial use since the 1980s. However, this statement is far from true. Asbestos has been used in more than 3,000 different applications in most industrial sectors; chrysotile or white asbestos is the most widespread. In addition to its fibrogenic properties, asbestos is a first-level carcinogen, and there is a long latency period between inhalation and clinical disease. Asbestos-related diseases are a group of 10 conditions that affect mainly the respiratory system, and they are divided into malignant (pleural mesothelioma, peritoneal mesothelioma, asbestos-related bronchopulmonary carcinoma, and other neoplasms) and nonmalignant. The nonmalignant asbestos-related diseases comprise diseases of the lung parenchyma (asbestosis or interstitial lung fibrosis), pleura (isolated pleural plaques, diffuse pleural fibrosis or pleural thickening, and benign pleural effusion), and bronchi (chronic bronchial obstruction and round atelectasis). The World Health Organization estimates that 125 million people worldwide remain exposed to asbestos in the workplace, and more than 107,000 people die each year of asbestos-related diseases.

In Canada and the United States, industrial use of asbestos is regulated but not banned, even though the US Environmental Protection Agency has repeatedly stated that there is no safe level of asbestos exposure. The World Health Organization recognizes that the most efficient way to eliminate asbestos-related diseases is to stop the use of all types of asbestos. The physician community must strongly advocate that asbestos in all forms is deadly.

Dr. Satyendra Sharma, FCCP
Steering Committee Member

Cultural Diversity in Medicine

Addressing End-of-Life Issues Across the Diverse Cultural Spectrum: Cultural Competence Is Key

Muni and colleagues, in a recent study in *Chest* (2011;139[5]:1025), came up with some very interesting observations regarding the influence of race/ethnicity on end-of-life-care in the ICU. According to this study, compared with white patients, nonwhite patients consisting of a diverse group of racial minorities were less likely to have documentation of advance-care planning. They also were less likely to have life-sustaining therapies withdrawn, less likely to have do not resuscitate orders, and were more likely to die in the setting of full support. Family conferences involving nonwhites were more likely to conclude with only discussions of prognosis, physician recommendations for withdrawal of life support, and lack of consensus regarding goal-of-care. Although the results of this study do not match earlier smaller observations, this study stresses the importance of a culturally competent approach to end-of-life issues. In an earlier observation, Searight and Gafford (*Am Fam Physician*. 2005;71[3]:515) stated that cultural factors shape preferences around decision making, receiving bad news, and end-of-life-care. The emphasis by the developed world on patient autonomy, informed consent, and truth-telling is often at odds with the beliefs of some groups who may place greater value on family involvement in decision making than individual autonomy. Discussing death with the patient is actively discouraged in some cultures.

The above discussion emphasizes cultural competence that will not only help physicians appreciate alien values but also ensure the skills to communicate appropriately with patients outside their cultural groups. Crawley and colleagues (*Ann Intern Med*. 2002;136[9]:673) recommend asking a series of respectful, open-ended questions to provide critical insights about an individual's culture.

Dr. Ahmed Khan, FCCP
Steering Committee Member

e-Community Update

The Critical Care NetWork e-Community was launched in February 2012 and is evolving into a powerful tool thanks to its ease of use and functionality. However, it only works if you use it. Dive in to see what it can do for you.

There are currently 4,990 members within the Critical Care NetWork e-community group and 21 different discussion threads. There are also 13 resources available for use by members. For example, a PowerPoint presentation for incoming house staff rotating into a medial ICU and a VA orientation by Dr Marcos Restrepo, FCCP, can be found in the resources section. Timely discussion topics include 24-hour intensivist staffing, ventilator maneuvers to counteract dyssynchrony, checklist implementation, nocturnal intensivist staffing, early mobilization program, and the Society of Critical Care Medicine and the Society of Hospital Medicine critical care training statements.

The potential of an online platform is huge. It can be used simply to communicate with peers, as was done recently when the Society of Critical Care Medicine published their white paper on a single-year fellowship track for hospitalists in critical care. It also can be used for near real-time collaboration and revision of guidelines and protocols; sharing of clinical protocols, presentations, and educational materials; and distribution of events and surveys and other value-added information sharing.

With nearly 5,000 members, the Critical Care NetWork e-Community is more than just "Facebook for physicians." It is a powerful tool for collaboration and care improvement.

Dr. John McIlwaine, FCCP
Vice-Chair
Dr. Christopher Spradley, FCCP
Steering Committee Member

Prescribing Long-term Oxygen Therapy

Data confirming the effect of supplemental oxygen on survival in COPD were published in the early 1980s. However, despite what appears to be a long history of the benefit of oxygen, and more recent evidence suggesting the benefit of long-term oxygen therapy (LTOT) in the management of lung diseases, deficits remain in the knowledge of clinicians regarding indications for prescription.

Moreover, rapidly changing technology and the availability of a myriad of oxygen delivery equipment makes it difficult for practicing pulmonologists to maintain their knowledge. Some issues may arise, such as physicians prescribing oxygen as liters per minute or failing to take into account increased oxygen demands during exercise and, perhaps, sleep. On the other hand, patients generally express preference for portable oxygen devices, and while such devices perform well at rest, they may not do so upon exertion when minute ventilation increases. Portable devices use different oxygen delivery methods, so some will not be adequate for use with exertion.

The Airways Disorders NetWork and the Respiratory Care NetWork assembled a task force to review LTOT, its indications, prescribing requirements, the multiple devices available, and portability. The following online documents explain what clinicians should take into account when prescribing LTOT. The online availability should make it easier to update the information as LTOT technology continues to change.

Download the guide: summary version at www.chestnet.org/downloads/patients/guides/LTOT-summary-2012.pdf. Download the guide: full version at www.chestnet.org/downloads/patients/guides/LTOT-full-2012.pdf.

Dr. Rubin Cohen, FCCP
Vice-Chair

Centers of Excellence: An Incredible Opportunity

BY DR. LEROY M. GRAHAM, FCCP

Our not-for-profit, Not One More Life, Inc. (www.notonemorlige.org) was honored to have been selected as a participant in the American College of Chest Physicians inaugural Centers of Excellence at CHEST 2011.

Not One More Life joined 11 other organizations in a unique opportunity to showcase innovative educational and clinical activities among our colleagues. The 3-day event allowed over 500 visitors to meet with Not One More Life staff and view multimedia presentations of our innovative model of community-based patient education, screening, counseling, referral, and outcome monitoring in the areas of asthma and COPD. Many visitors were intrigued by our uniquely effective model that partners with communities of faith to offer programming to populations characterized by disparate morbidity and mortality attributable to asthma, COPD, and other respiratory diseases.

As a direct result of this incredible opportunity, Not One More Life has brought its model to two new cities since CHEST 2011.

We currently have 10 additional cities in the formation process for future expansions.

Not One More Life, Inc., is so very grateful to the ACCP for this opportunity and in particular to David Eubanks, EdD, FCCP(Hon), for his incredible vision and expertise in developing and implementing the Centers of Excellence concept at CHEST 2011. This activity should remain an integral and expanding part of all future CHEST meetings. ■

This Month in *CHEST*: Editor's Picks

BY DR. RICHARD S. IRWIN, MASTER FCCP
Editor in Chief

EDITORIAL

▶ **Managing Information Overload: The Evolution of *CHEST*.**
By N. Augustyn; S. J. Welch; and Dr. R. S. Irwin, Master FCCP.

ORIGINAL RESEARCH

▶ **Subtherapeutic Initial ß-Lactam Concentrations in Select Critically Ill Patients: Association Between Augmented Renal Clearance and Low Trough Drug Concentrations.**
By Dr. A. A. Udy et al.

▶ **Mast Cell-Airway Smooth Muscle Crosstalk: The Role of Thymic Stromal Lymphopoietin.**
By Dr. D. Kaur et al.

▶ **Challenges of Interferon-Gamma Release Assay Conversions in Serial Testing of Health-care Workers in a TB Control Program.**
By Dr. K. S. Fong et al.

CHEST Challenge 2012 Semifinalists Announced

Nine teams will compete in play-off rounds held August 21, in Phoenix, Arizona, during the ACCP Board Review courses. After months of competing in the CHEST Challenge online test of knowledge, the following semifinal teams now move on:

▶ Albert Einstein College of Medicine
▶ Baylor College of Medicine
▶ Maimonides Medical Center
▶ Massachusetts General Hospital
▶ Ohio State University Medical Center
▶ University of Arkansas for Medical Sciences
▶ University of California Fresno
▶ University of Missouri Columbia School of Medicine
▶ University of Toronto

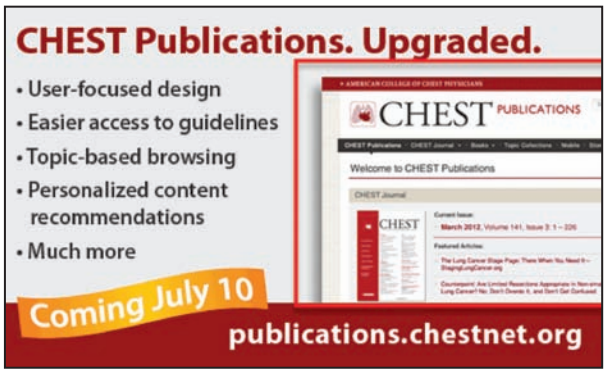
The three, top-scoring programs from the Phoenix play-off rounds will be invited to compete in the CHEST Challenge Championship during CHEST 2012, October 20-25, in Atlanta, Georgia.

Learn more about the CHEST Challenge semifinal rounds. Register now for ACCP Board Review courses. ■

CHEST Publications: Redesigned and Reimagined

This month, the revamped CHEST Publications website launches at publications.chestnet.org. Not only will you find an eye-pleasing new design with tabbed article layout and a figure previewer, but you will also find new and improved functionality, such as related article recommendations from *CHEST*, CHEST Books, PubMed, and National Guideline Clearinghouse. The goal is to put the most relevant information front and center, no matter where you are on the site. The journal and CHEST Books are more fully integrated, allowing you to view search results from either source on a single page. Whittle down search results further by topic areas, such as COPD or sleep medicine, or use these same topic areas to browse, using the new CHEST Collections feature to view the latest information in a particular subject.

Let the information come to you by signing up for e-mail alerts or RSS feeds to Topic or Subject Collections, the *CHEST* Current Issue, Online First articles, and more. The CHEST Publications site itself is now portable; all pages are mobile optimized for easy reading on your smartphone. Not to be left out, the *CHEST* Journal app for iPad® and iPhone® has received an upgrade, too: the entire *CHEST* archive is now accessible through the app, and podcasts are included for instant listening. Connect to the new CHEST Publications site today, and give these new features a test ride. ■



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Critical Care or Pulm/CCM Physician

St. Barnabas Hospital in the Bronx, NY is searching for a Critical Care or Pulm/CCM physician to practice in our multi-disciplinary ICU. To work in such a collegial group with flexible hours is truly unique. H1 Visa's are welcome. Fax CV to: 718-960-6122.

Chief of the Division of Pulmonary, Critical Care and Sleep Medicine

Beth Israel Medical Center, University Hospital and Manhattan Campus of the Albert Einstein College of Medicine, invites applications for the position of Chief of the Division of Pulmonary, Critical Care and Sleep Medicine. This is a unique opportunity to direct an outstanding group of physicians and an active fellowship program. The Division is responsible for the Medical Intensive Care Unit, a Respiratory Care Stepdown Unit, a busy outpatient practice, the pulmonary function laboratory and a sleep laboratory. Candidates must be Board Certified in Pulmonary Medicine and/or Critical Care Medicine. Compensation and academic appointment will be commensurate with the candidate's experience.

Candidates should send a CV and the names of 3 professional references by e-mail to Steven Bergmann, MD, PhD, Chair, Pulmonary Search Committee, (sbergman@chpnet.org).

Beth Israel Medical Center is committed to diversity and equal opportunity.

Assistant or Associate Professor in the Pulmonary and Critical Care Division, University of Rochester, Rochester, New York

Full-time positions

The University of Rochester Medical Center (URMC), a leading academic institution, seeks outstanding candidates to join the Division of Pulmonary and Critical Care Medicine in the Clinician-Educator Pathway. Clinical practice opportunities include the medical and medical/surgical intensive care units, inpatient pulmonary consultation services, outpatient general pulmonary or pulmonary subspecialty practices, a comprehensive bronchoscopy program (including endobronchial ultrasound and navigational bronchoscopy) and an active sleep medicine program. Ample opportunities and resources for teaching and clinical research are available and welcome. We have competitive fellowships in Pulmonary/Critical Care and Critical Care Medicine, with long-standing continuous support provided by a NIH T32 training grant. The University of Rochester is a national leader in translational research and lung biology research, and maintains a strong and active program in faculty development. The Rochester area affords the best in stress-free living, including affordable housing; easy commutes; highly ranked public schools and varied cultural, recreational and outdoor activities.

We seek individuals with a passion for academic medicine who are board eligible or board certified in Pulmonary Diseases and/or Critical Care Medicine to join our diverse and collegial faculty group. Interested candidates should send their CV, a letter of interest and the names of three references to Ann Bauman, Pulmonary and Critical Care Division, 601 Elmwood Avenue, Rochester, NY 146428692 or ann_bauman@urmc.rochester.edu. URMC is an equal opportunity employer. Minority and women candidates are encouraged to apply.

Pulmonary/Critical Care Physicians

OSF Medical Group seeks two Pulmonary/Critical Care physicians to join growing group, two hours from Chicago and St. Louis, in Bloomington, Illinois. Call 1:5. OSF Saint Joseph Medical Center, a Level II Trauma Center, houses a state-of-the-art Comprehensive Care Unit of 32 beds, which includes Critical Care and Step Down, growing ambulatory pulmonary practice, sub-specialty clinics in pulmonary hypertension and lung nodules, and six bed accredited sleep center. Come be part of the OSF Healthcare, ranked # 1 in Integrated Healthcare Networks in Illinois. Call or send CV to: Rachel Reliford Kloter, Phone: 309-683-8352
Email: **rachel.kloter@osfhealthcare.org**
Web: **www.osfhealthcare.org**

Director of Hospital Intensivist Service Position

Applicant sought to build Intensivist Critical Care Platform Program at Community Hospital. Work with existing pulmonary group to build on site unit based program in exciting Long Island location one hour from NYC. Excellent competitive compensation package with bonus potential which includes full malpractice coverage and comprehensive benefits. Applicant MUST be fellowship trained and be BC/BE in Pulmonary and Critical Care Medicine and have strong communication procedural and leadership skills.

Interested applicants should send CV in confidence to:

Patrickm.O'Shaughnessy@chsli.org
or call 631.862.3100. EOE

Outstanding Partnership Opportunity

Pulmonary/Critical Care West Suburbs of Chicago

Successful Pulmonology/Critical Care & Sleep group is currently seeking an additional pulmonary physician for a Partnership or Associate Opportunity. The Practice currently has ten other Pulmonologists and 16 Hospitalists, serving 4 regional hospitals with four clinic locations. Applicants must be Board Certified or Eligible in Pulmonary Medicine and Critical Care Medicine as well. Please send CV to: Fred Martinez, Practice Administrator, Suburban Pulmonary & Sleep Assoc. LTD, 700 E. Ogden Avenue, Suite 202, Westmont, IL. 60559, Phone: 630-789-9785 x 350, Fax: 630-789-9798,
Email: fmartinez@spasamed.com

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Pulmonary, Critical Care and Sleep

Southern New Jersey Pulmonary Medicine: Three-doctor pulmonary, critical care and sleep group seeking fourth associate because of growth of practice. Over 30 new patients seen per week. This practice is within 30 minutes of Philadelphia and is the most recognizable practice in the area. Very good payor mix. Partnership in under two years. Wanda Parker, The HealthField Alliance, 866-232-2333, 203-778-3333, **healthfield@mindspring.com**

Pulmonary/ Critical Care

Busy Pulmonary /Critical Care Practice, located in the Phoenix metropolitan area is looking to add a physician to our group. We offer an excellent salary, a benefits package and the opportunity to become a partner in 1-2 years. Call is 1:4 nights and weekends. Weekday call is covered by a well-run hospitalist group. We work in a single hospital with a busy open heart program and a 31 bed critical care complex. Interested Candidates please e-mail CV to **b.blanchard@cox.net**

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SLEEP STRATEGIES

United States Army Sleep Medicine: I Want YOU

James Montgomery Flagg's iconic poster of Uncle Sam pointing a finger at America with the title, "What Are You Doing for Preparedness?" for World War I was originally published in 1916. In 1917, Uncle Sam was put to work recruiting for the US Army (http://tinyurl.com/777pow8. Accessed June 18, 2012). The United States is again at war; we are currently engaged in conflicts that have lasted more than a decade. Over that same period of time, there has been a steady rise in sleep disorders diagnosed in active duty (AD) service members. Many service members receive sleep services outside of the military health system, so it is likely that many of you are involved in their care. This article provides background about military sleep medicine and the unique characteristics of the patient population that will allow you to be prepared to help "Conserve the Fighting Strength."

Rise in Sleep Disorders Diagnosis

The US Army has a growing sleep medicine community. Over the last decade, it has grown from one board-certified sleep medicine specialist to 32, including neurologists, pediatricians, internists, family medicine providers, psychiatrists, and otolaryngologists. Our mission is to provide evidence-based, state-of-the-art sleep medicine evaluations and treatments for our AD service members, retired beneficiaries, and their family members. Sleep disorder centers (SDCs) are not only staffed with AD providers but also civilian Department of Defense employees. The Army SDCs are located within community hospitals and teaching medical centers. Each of the Army's teaching medical centers and a handful of affiliated community hospitals has a SDC.

The military has two Accreditation Council for Graduate Medical Education-accredited sleep medicine fellowships that train AD service members of the Army, Navy, and Air Force. The seven accredited training slots are divided between the fellowships at Walter Reed National Military Medical Center in Bethesda, Maryland, and San Antonio Military Health System in San Antonio, Texas. We are proud to brag that our graduates have a 100% board pass rate among first-time test takers. While these training programs allow the number of military sleep medicine providers and sleep centers to grow, our patient population requiring sleep services is outpacing this growth, necessitating referral to civilian network providers. In 2011, the 10-bed sleep disorders laboratory of the San Antonio Military Health System received more than 5,700 sleep referrals but was able to service only 40% of those patients.

According to the Medical Surveillance Monthly Report (Armed Forces Health Surveillance Center. *MSMR*. 2010; 17[5]:) by the Department of Defense, there were 3,563 (25.6/10,000 person-years) AD service members diagnosed with obstructive sleep apnea (OSA) and 1,013 (7.2/10,000 person-years) diagnosed with insomnia in 2000. Those numbers dramatically increased to 20,435 (145.3/10,000 person-years) and 19,631(135.8/10,000 person-years), respectively, in 2009. Of the military branches, the prevalence of both diagnoses was highest in the Army. In contrast, the service with the least amount of people with OSA was the Marines (at about one-third the rate of OSA in the Army), and insomnia was least often seen in the Navy (at one-fourth the rate of OSA in the Army). In general, the demographics of AD patients with OSA are similar to that of civilians with OSA. The annual rate is higher for men (158.3/10,000 compared with 68.2/10,000 for women), those who are black (230.2/10,000 compared with 126.9/10,000 for those who are white), and those who are older than 40 years (736.8/10,000 compared with 32.9/10,000 for those aged 20-24 years).

Obesity and OSA in AD Personnel

One big difference in the OSA seen in AD service members is that the disease occurs in patients who are not obese. The weight and physical fitness requirements by the Army make the patient population different from the civilian populations. LTC Chris Lettieri, MC, USA, FCCP, reported a comparison study of AD service members, National Guardsmen (NG), and civilians (Lettieri et al. *J Clin Sleep Med*. 2005;1[4]:381). The prevalence of severe OSA (apnea-hypopnea index = 30/h) did not differ significantly between the groups, with 37.5% of AD service members, 42.5% of NG, and 45.7% of civilians having severe disease (P=.18 and P=.09, respectively). Evaluating the prevalence of obesity in these populations, 19.2% of AD service members had a BMI = 30 kg/m^2 whereas 64.3% of civilians and 48.8% of NG were obese (P= <.001). The AD service member population did not show a correlation between disease severity and BMI (P=.33), leading to the conclusion that OSA should be considered in AD service members who have excessive daytime sleepiness (Epworth sleepiness scale score =10) and symptoms of obstructed breathing during sleep (snoring, witnessed apneas, choking, gasping) even in the absence of obesity.

Sleep Duration

Short sleep duration (SSD), defined as habitual total sleep time < 6 h, either volitional or due to a disorder such as insomnia, is a very common characteristic of the sleep patterns of AD service members. In 2008, the Office of the US Army Surgeon General's Mental Health Advisory Team V (http://tinyurl.com/7bvlplq. Accessed June 18, 2012) surveyed more than 2,200 soldiers deployed in Iraq and Afghanistan. The report revealed an average total sleep time of only 5.6 h per night. Sleep-deprived soldiers were more likely to have a positive screen result for a mental health disorder (about 10% without sleep deprivation compared with more than 40% with 4 h time in bed) and have a mission-impacting mistake or accident (<5% without sleep deprivation compared with more than 10% with 4 h time in bed). In the deployed setting, the sleep deprivation is often a mission-specific requirement due to 24-h operations, but the SSD continues upon return from deployment. A group of investigators led by LTC Vince Mysliwiec, MC, USA, FCCP, reported on the prevalence and impact of SSD in redeployed soldiers from Operation Iraqi Freedom (Luxton et al. *Sleep*. 2011;34[9]:1189). This study surveyed more than 3,100 soldiers between 90 and 180 days postdeployment. Mean total sleep time was 5.8 h ± 1.2 h, with 72% of soldiers sleeping = 6 h per night. The conclusion of the study was that combat exposure increased the risk for SSD, which, in turn, was a risk factor for the comorbidities of depression, post-traumatic stress disorder, high-risk behaviors of abuse of alcohol and tobacco, and suicide attempts. It is therefore very important to screen for SSD in AD service members. A recent revision to the Army regulations for the evaluation of a possible hypersomnia of central origin requires the use of actigraphy to estimate the objective total sleep time and document adequate total sleep time before proceeding with other diagnostic testing.

Deployment With a Sleep Disorder

It is important to take a patient history of travel and sleeping quarters when evaluating a deploying AD service member with OSA. Military regulations permit deployment with positive airway pressure (PAP) devices with certain restrictions. Many areas of operation have an inconsistent source of power that requires AD service members to deploy with a battery backup for the PAP device. If the deployment is to a dusty location (eg, Afghanistan), AD service members will need living quarters that have an additional filter to that of the PAP device (eg, an air conditioner filter). Even then, the PAP filters become clogged quickly and require replacement on a weekly basis. It is also important to have AD service members deploy with enough PAP supplies (interfaces, tubing) for the entire deployment because it often takes weeks for mail delivery. Drinking water can be used in the humidifier. There are certain military occupations that do not allow sleeping arrangements with power or filtered air; affected AD service members will need an alternate therapy to PAP (dental appliance, positional therapy, surgery) for the deployment.

Hypnotics are allowable but restricted in the deployed setting and need to be used with extreme caution. A trial of therapy before deployment is recommended to assess for potential side effects (residual daytime sleepiness or parasomnias). While deployed, AD service members often will have to immediately seek shelter from indirect fire. Therefore, cognitive and behavioral therapy is the preferred therapy for insomnia, if clinically appropriate. AD service members with behavioral health disorders are screened thoroughly and often require special permission for deployment.

Summary

The number of AD service members who need sleep medicine evaluations has dramatically increased over the last decade and continues to escalate. Although sleep medicine in the Army is growing, the rate of growth has not kept up with demand. We rely heavily upon you, our civilian colleagues, to contribute to the care of AD service members. Thank you for your dedication to this mission, and keep in mind the unique characteristics of this population.

Army Medicine: Serving to Heal… Honored to Serve.

LTC(P) William C. Frey, MC, USA, FCCP
Brooke Army Medical Center
San Antonio, Texas

The views expressed in this article are those of the author and do not reflect the official policy of the Department of the Army, the Department of Defense, or the US government.

Editor's Comment

This month's column focuses on the practice of sleep medicine in the military; as Dr. Frey points out, the magnitude of sleep disorders has required a growing number of military patients to be seen outside of military facilities. By learning how to screen and treat this population effectively, we can honor and begin to repay them in a small way for their dedication and service to this country.

Dr. David Schulman, FCCP
Section Editor

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