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INSIDE

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Anemia and Limited-stage Small Cell Lung Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *By analysis of two National Cancer Institute of Canada clinical trials for limited-stage small cell lung cancer, it was found that anemia was present in approximately one-third prior to treatment and was associated with other negative prognostic factors but by itself was not significant with regard to overall survival. When anemia occurs as a consequence of therapy, the data indicates an interesting trend towards improved local control; a finding that runs counter to expectations. This, however, was not associated with improved overall survival.*

Source: Laurie SA, et al. The impact of anemia on outcome of chemoradiation for limited small cell cancer: a combine analysis of studies of the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol.* 2007;18:1051-1055.

THERE HAS BEEN MUCH WRITTEN ABOUT THE IMPORTANCE and management of anemia in cancer patients this past year. For certain tumors, it is clear that the appearance of anemia prior to therapy confers adverse prognostic implications.[1-3] One aspect of the controversy surrounding anemia is whether directed intervention (ie, by recombinant erythropoietin or transfusion) results in favorable or unfavorable outcomes; an issue not directly addressed in this report. Dr. Laurie and colleagues provide an analysis of the importance of anemia in limited small cell lung cancer, derived from two National Cancer Institute of Canada (NCIC) clinical trials. In these trials, the relationship between the presence of anemia prior to therapy or the development of anemia during therapy was related to outcomes such as local control and overall survival.

The two clinical trials involved patients with previously untreated limited stage small cell lung cancer. In the first trial (BR.3), patients were randomized to receive six cycles of

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chemotherapy with cisplatin and etoposide (EP) and cyclophosphamide, doxorubicin, vincristine (CAV) given either sequentially (three cycles of CAV followed by three cycles of EP) or alternating. In this trial, thoracic radiotherapy (either 37.5 Gy in 15 fractions or 25 Gy in 10 fractions) was administered to all patients following the completion of the chemotherapy while prophylactic cranial radiation (20 Gy in 5 fractions) was administered to all patients during week seven. The second trial (BR.6) was designed to evaluate the importance of early vs late concurrent thoracic radiotherapy. All patients in this trial received six cycles of alternating CAV/EP with thoracic radiotherapy (40 Gy in 15 fractions) administered concurrently with either cycle two or six of chemotherapy. Prophylactic cranial irradiation (25 Gy in 10 fractions) was administered following the completion of chemoradiation. Three hundred twenty-two patients were enrolled in BR.3 and 330 in BR.6. Thus, there were a total of 652 patients available for this review.

Of the 652 patients enrolled, anemia, defined as a hemoglobin concentration of less than 13.6 g/dL for men and less than 12 g/dL for women, was present in 32%. Males, patients over the age of 65, those with ECOG Performance Status of > 2, and those with increased LDH were most likely to present with a low baseline hemoglobin concentration. During therapy grade 2 anemia (hemoglobin less than 10 g/dL) occurred in 55% of patients. Female gender, the presence of a low baseline hemoglobin concentration, age > 65 years, and a BSA < 2 all were associated with the development of anemia during therapy.

Baseline anemia was not statistically associated with either overall survival or progression-free survival in univariate analysis. In the multivariate COX regression model, male gender, a performance status greater or equal to 2, and an elevated LDH were associated with poorer overall survival and progression-free survival while baseline hemoglobin remained nonsignificant. Additionally, the baseline hemoglobin concentration had no impact on the rate of local progression and relapse. The evaluation of the implications of anemia occurring during therapy also revealed that the nadir hemoglobin was not independently associated with overall or progression-free survival. Those with nadir hemoglobin of less than 10 g/dL, however, had a longer duration of freedom from local recurrence (hazard ratio = 0.70, 95% confidence interval 0.54-0.90, $P = 0.005$). By multivariate analysis, males had a higher risk of local progression and the nadir hemoglobin of less than 10 remained marginally significant ($P = 0.06$).

COMMENTARY

This comprehensive analysis of limited stage small cell lung cancer demonstrates that anemia is common in this clinical setting and that it is associated with adverse outcomes. However, in this series, anemia was not independent of other adverse factors such as poor performance status and elevated LDH. Thus, the association between baseline anemia and poor outcome is more likely an indicator of increased disease burden and possibly the presence of comorbidities. The current study demonstrated that the majority of treated patients (55%) developed grade II (hemoglobin < 10 g/dL) anemia. It was of some interest to note a trend towards improved local control in those who had the greatest drop in hemoglobin during therapy. This, however, does not translate into improved overall survival. Thus, it might seem that the development of anemia enhanced local measures such as radiotherapy; a concept that runs counter to the premise that hypoxia would favor radioresistance and thereby less adequate local control.

With the widespread use of recombinant erythropoietin in anemic cancer patients, concerns have been raised lately about the efficacy and safety of correcting anemia. This report will do little to settle the issue. What we do take from the analysis is that anemia is common both at presentation for which it is a marker for poor prognosis and during therapy for which the implications are less clear. One of the

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many unanswered questions is whether correction of anemia either prior to or during treatment is of value or detriment to the patient. A study in which erythropoietin, transfusion, and observation alone are compared would seem warranted at this time. ■

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Establishing 'Standard Treatment' for CLL

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Fludarabine combined with cyclophosphamide was compared to fludarabine alone or chlorambucil as initial treatment for chronic lymphocytic leukemia (CLL) in a randomized multi-site trial. The combination proved superior with regard to response rate and time to progression, but overall survival was not different. Response to any of the treatments was associated with improved quality of life.*

Source: Catovsky D, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia (the LRF CLL4 Trial): a randomized controlled trial. *Lancet.* 2007;370:230-239.

Since the first publication of the combination fludarabine-cyclophosphamide use in chronic lymphocytic leukemia (CLL),[1] there has been considerable interest in this combination. Catovsky and colleagues present data from a randomized controlled trial (LRF CLL4 trial) in which the combination was compared with fludarabine alone or chlorambucil in previously untreated patients with CLL. There were 136 participating centers primarily in the United Kingdom but also in Argentina, Croatia, Greece, Ireland, Italy, New Zealand, and Russia. The 777 patients with CLL requiring treatment were randomly assigned to fludarabine, fludarabine plus cyclophosphamide, or chlorambucil. Those randomized to fludarabine received the drug either intravenously (25 mg/m2 per day intravenously for five days) or orally (40 mg/m2 per day given orally). Those who received the combination fludarabine and cyclophosphamide received a fludarabine dose of 25 mg/m2 per day and plus cyclophosphamide 250 mg/m2 for three days. The combination could also be administered orally and the dose of fludarabine was 24 mg/m2 per day and cyclophosphamide 450 mg/m2 per day for a five day treatment. Those that received chlorambucil were given 10 mg/m2 per day for a total of seven days. All three of the treatment schedules were repeated every four weeks. Fludarabine and fludarabine plus cyclophosphamide were given for a total of six courses and chlorambucil for a total of 12 courses.

At the time of this report, the median follow-up was three years and five months (range one year and nine months to seven years and six months). There was no significant difference in the randomization with regard to stage of disease, risk group, or age. Approximately one-third of patients were older than 70 years.

For those receiving fludarabine or fludarabine plus cyclophosphamide the oral route was given in approximately two-thirds of the cases.

Complete remission and overall response rates were significantly higher with fludarabine plus cyclophosphamide when compared with fludarabine alone or with chlorambucil. This was true for all age groups. There was no evidence that the response rates or adverse effects were different between earlier stage or more advanced stage CLL. There was no significant difference in overall survival between patients given any of the three therapies. However, in terms of treatment response, the fludarabine cyclophosphamide combination was most effective for each of the prognostic groups including those defined by immunoglobulin heavy chain (VH mutation status) and cytogenetic analyses, which were tested in 533 and 579 cases respectively.

Patients had more neutropenia and days in the hospital with the combination fludarabine cyclophosphamide or fludarabine alone when compared to chlorambucil. There was less hemolytic anemia with fludarabine plus cyclophosphamide (5%) than with flu-

darabine (11%) or chlorambucil (12%). Quality of life measures indicated a decline in all three treatment arms, but there was no significant difference between the treatments, and the quality of life improved for those who had responses.

COMMENTARY

This study marks the third large-scale investigation of the combination of fludarabine cyclophosphamide vs fludarabine alone for treatment of CLL. The German Chronic Lymphocytic Leukemia Study Group investigated 375 patients who were 65 years or younger with intravenous fludarabine and observed a higher complete remission and overall response rate with fludarabine plus cyclophosphamide, and a longer progression-free survival than when fludarabine was used alone, but no differences in overall survival were recorded.[2] The second study came from US intergroup trial (E2997) which reported on 278 patients between the ages of 33 and 86, and once again a significantly higher complete remission, overall response rate and longer progression-free survival were observed in those who received fludarabine plus cyclophosphamide compared to those who received fludarabine alone.[3] The current study confirms these findings in a large, well-conducted multisite clinical trial.

Furthermore, there were some important additions. The molecular markers including immunoglobulin gene mutation status and non-random cytogenetic defects probed by fluorescence in situ hybridization (FISH) were performed and identified high risk individuals. Thus, it was determined that although fludarabine and cyclophosphamide combination was superior to the other treatments in producing remissions in patients with a 17p13 deletion, these were of short duration. Accordingly, this type of analysis may prove useful in future clinical trials to identify those warranting more aggressive treatment.

Another feature of this trial was the attention paid to quality of life. All three treatments were associated with some negative impact; however, there did not seem to be a difference among the treatments. Furthermore, for those who did respond, quality of life improved. Additionally of note, approximately one-third of the patients on the study were elderly (over the age of 70) and these patients tolerated each of the treatment arms comparably.

As with the German and North American study, there was no overall survival advantage. However, the median followup of only two to three years suggest that an additional assessment be undertaken in time. Yet, the question of overall survival is difficult because those who show evidence for disease progression are most frequently treated with additional agents in sequence, and differences in overall survival on the basis of initial therapy may be impossible to discern. ■

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Coffee Consumption, Hepatitis C and Liver Cancer Risk

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a nested cohort analysis of a large Japanese sample, coffee drinking was associated with a decreased risk of death from hepatocellular carcinoma in all subjects, and specifically, those infected with hepatitis C virus.*

Source: Wakai K, et al. Liver cancer risk, coffee, and hepatitis C virus infection: a nested case-control study in Japan. *Br J Cancer.* 2007;97:426-428.

Recently, an inverse association of coffee consumption and risk for hepatocellular carcinoma has been identified, based upon case-control[1-3] and cohort studies.[4-6] In Japan, where hepatocellular cancer is more common, hepatitis C virus (HCV) infection is a known risk factor.[7] To determine whether coffee consumption might mediate a protective effect on a high risk for HCC population (ie, HCV positive individuals), Wakai and colleagues

conducted a nested case-control study capitalizing on the Japan Cohort Study for Evaluation of Cancer Risk. This cohort includes 110,792 individuals, aged 40-79 at baseline, from 45 areas throughout Japan who answered a questionnaire on lifestyle and medical factors during the years 1988-1990. Among the questions were those relating to habitual coffee consumption, with possible responses including "scarcely any," "1-2 cups per month," "1-2 cups per week," "3-4 cups per week," and "almost every day." Those who answered "almost every day" were asked to report the number of cups consumed per day. Of the entire sample, 39,242 agreed to donate blood as a component of the health assessment phase of this study.

Of the cohort, there were 96 subjects who died with HCC, and 60% of these were HCV positive. For controls, age, sex, HCV status, and geographic region-matched individuals were selected. There were 7 controls for each HCV+ and 84 controls for each HCV-HCC patient. Former alcohol consumption, a history of diabetes mellitus and a history of liver disease were more common among the HCC cases than controls.

Drinking one or more cups of coffee per day was inversely associated with HCC mortality among all subjects (multivariate odds ratio [OR], 0.49; 95% confidence interval [CI], 0.25-0-96). When examined in the context of HCV status, it was apparent that the association was more robust for those who were HCV positive. The OR for HCC among HCV positive individuals consuming one or more cups of coffee per day was 0.31; 95% CI, 0.11-0.85. Although daily coffee consumption in the HCV negative group had a similar trend there was overlap with unity and thus, the association did not reach statistical significance.

COMMENTARY

The results of this prospective cohort study support the earlier observations of a protective effect of coffee with regard to hepatocellular carcinoma in the general population[3] and particularly among individuals considered at high risk for HCC including heavy drinkers and those with HCV infection.[2-8] However, the protective effect has not been universally observed for those at high risk. For example, Montella and colleagues[3] in Italy performed a hospital-based case-control analysis including 185 patients with HCC and 412 matched controls and although they also found an association of coffee and reduced HCC risk, it was most noticeable in those without HCC risk factors.

Why would coffee have such an effect? First, it is notable that the favorable effect of coffee drinking on HCC parallels the inverse association with liver cirrhosis[9,10] and chronic liver disease.[11] An Italian study[12] investigated the role of caffeine in cirrhosis onset and found a protective effect of caffeine intake from coffee, but not from other beverages. This would argue that the protective effect is not from caffeine directly. Coffee itself is rich in antioxidants and other components which may have molecular consequences. For example cafestol and kahweol are two coffee-specific diterpenes with anticarcinogenic activity,[13] and it is likely that others exist. These coffee components may act by modulation of enzymes involved in carcinogen detoxification, as has been suggested in various experimental models.[14]

Thus, it appears that coffee consumption has some protective effect against the development of HCC. Additional studies are warranted to establish a mechanism and hopefully derive an effective prevention strategy for those at high risk. ■

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Endogenous Hormones and Breast Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Circulating levels of sex steroids (estradiol, testosterone) and breast density (as determined by mammography) are known risk factors for the development of breast cancer. In a nested case-control analysis of a subset of postmenopausal participants in the Nurses' Health Study, circulating levels of estradiol and mammographic density were shown to be strong and independent risk factors for breast cancer development.*

Source: Tamimi RM, et al. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* 2007;99:1178-1187.

Both mammographic density and circulating sex hormones are established predictors of breast cancer risk.[1,2] It has been unclear whether mammographic density is just a reflection of the level of sex hormone or an independent indicator of risk. Tamini and colleagues conducted a nested case-control study within the Nurses' Health Study cohort of 253 cases with breast cancer and 522 control subjects. The Nurses' Health Study, originally initiated in 1976 includes 121,700 registered nurses in the United States who were between the ages of 30 and 55 years at that time. During the period from January 1, 1989, through December 31, 1990, blood samples were collected from 32,826 of these subjects. From this group, 322 were diagnosed with breast cancer in the subsequent years (through June 1, 1998). From this, a complete assessment was possible on 253 case subjects and these were closely matched with 522 controls on the basis of age and blood sample availability. Mammograms from the same time period were made available for this analysis. The median time between mammography and blood draw was eight months. Because menopausal status and postmenopausal hormone use were potential confounders in the determination of hormone level and mammographic density, the analysis was restricted to women who were postmenopausal and who were not using exogenous hormones at the time of mammography.

The laboratory assays included the measurement of estradiol and testosterone. The assessment of mammographic density involved a computer-assisted determination based upon optical density in uniform craniocaudal views of both breasts. The results were reported as percent density and these values were highly reproducible.

Those who developed breast cancer were more likely to have had a family history of breast cancer and to report prior breast disease than control subjects. They were also found to have a slightly higher body mass index and a higher mammographic density.

With regard to mammographic density, those within the highest quartile were younger, thinner, and had fewer children. They were also more likely to have a history of benign breast disease and to have used postmenopausal hormones than women in the lowest quartile of mammographic density. Those within the highest quartile of mammographic density had the greatest risk of breast cancer when compared to those in the lowest quartile (relative risk [RR] = 2.7, 95% confidence interval [CI] = 1.7 to 4.3; $P < 0.001$).

When the analyses were adjusted for matching factors (ie, age, month of blood draw, fasting status, and time of blood draw) the highest quartile of circulating estradiol was also associated with an increased risk of breast cancer compared with the lowest quartile (RR = 2.3, 95% CI = 1.5 to 3.5; $P < 0.001$). Circulating testosterone was also associated with an increased risk of breast cancer, comparing

the highest quartile with the lowest (multivariable RR equals 1.8, 95% CI equals 1.2 to 2.9). Thus, circulating levels of estradiol and of testosterone were both associated with breast cancer risk after adjusting for a mammographic density. Further analysis demonstrated that mammographic density and circulating steroids remained statistically significantly associated with breast cancer risk when neutrally adjusted for one another, providing evidence that both are strong breast cancer risk factors independent of each other.

COMMENTARY

This very thorough and careful analysis demonstrated the independent association of circulating hormone levels and mammographic density with regard to breast cancer risk in postmenopausal women. The circulating sex steroid hormones were associated with a two-fold increased risk of breast cancer when comparing the highest and lowest quartiles and mammographic density was associated with an approximate four-fold increased risk by comparable analysis. Both circulating sex steroid and mammographic density had been demonstrated previously to be risk factors for breast cancer, but there had been a sense that the two were directly linked. Previously, data derived from randomized control trials examining the use of hormone replacement therapy demonstrated both increased mammographic density and breast cancer risk.[3] A natural interpretation was that mammographic density appeared to reflect at least in part cumulative exposure to estrogens and an association between the levels of estrogen and breast density were suspected. There have been, however, a number of studies that raised questions regarding this hypothesis. For example, Boyd and colleagues[4] observed an inverse association between levels of circulating estradiol and mammographic density among 189 postmenopausal women, after adjusting for age and waist measurements. Indeed, even the Nurses' Health Study and inverse association between estradiol and mammographic density had been reported.[5] Thus, there was some reason to suspect that mammographic density and circulating hormone levels were both risk factors for breast cancer, but by independent mechanisms. This would certainly be the conclusion from the current report as well.

The mechanism by which mammographic density confers an independent risk for breast cancer is not intuitive and remains to be determined. However, it is notable that in twin studies[6] mammographic density has been shown to be a heritable trait. Thus, the genetic determinants of mammographic density may mediate the association between mammographic density and breast cancer risk.

Epidemiologic studies often raise additional questions that need resolution. The current report shakes the notion that circulating hormones and mammographic density are linked with regard to breast cancer risk. Now, the factors that associate mammographic density as a breast cancer risk need elucidation. ■

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CME Questions

37. From the National Cancer Institute of Canada analysis of their two limited-stage small cell lung cancer trials, which of the following factors was not independently associated with reduced overall survival:

a. age > 65 years
b. male gender
c. performance
d. anemia prior to therapy
e. none of the above

38. In the initial treatment of chronic lymphocytic leukemia, the combination of fludarabine plus cyclophosphamide was superior to fludarabine alone by which of the following parameters:

a. overall response rate
b. quality of life measures
c. overall survival
d. all of the above

39. In the Japanese case/control analysis, it was apparent that approximately how many cups of coffee per day was shown to have a protective effect against the development of hepatocellular cancer.

a. 1 cup per week
b. 1 cup per day
c. 3 cups per day
d. 7 cups per day

40. Which of the following are independent risk factors for breast cancer development:

a. circulating (endogenous) estradiol
b. circulating (endogenous) testosterone
c. breast density determined by mammography
d. all of the above
e. none of the above

Answers: 37 (d); 38 (a); 39 (b); 40 (d)

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- to describe new advances in the field of oncology.

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Treatment of Cancer of Unknown Primary

PHARMACOLOGY WATCH

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

Oral Anticoagulant + Antiplatelet Therapy = Danger

In this issue: *Adding an anticoagulant to aspirin is of no value in patients with peripheral artery disease, older adults with coronary disease benefit from aggressive statin therapy, simvastatin may reduce the risk of dementia and Parkinson's disease by as much as 50%, MiraLAX is safe for long-term use in patients with chronic constipation, the FDA greenlights Avandia, brings back Zelnorm for limited use, and recommends approving Evista for breast cancer prevention.*

Patients with peripheral artery disease are at high risk for cardiovascular complications. Antiplatelet drugs are routinely prescribed for these patients, but is adding an oral anticoagulant of value? No, according to a new study. In fact, the combination may be dangerous. More than 2,100 patients with PAD were randomly assigned to antiplatelet therapy with an oral anticoagulant or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes. The second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention or death from cardiovascular causes. After an average followup of 35 months, the first coprimary outcome occurred in 132 of 1080 patients receiving combination therapy (12.2%) and 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (RR 0.92; 95% CI, 0.73 to 1.16; $P = 0.48$). The second coprimary outcome occurred in 172 patients receiving combination therapy (15.9%) compared to 188 patients receiving antiplatelet therapy alone (17.4%) (RR 0.91; 95% CI, 0.74 to 1.12; $P = 0.37$). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared to 13 patients receiving antiplatelet therapy alone (1.2%) (RR 3.41; is 95% CI, 1.84 to 6.35; $P < 0.001$). The authors conclude that adding an oral anticoagulant to antiplatelet therapy in patients with PAD was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications, but was associated with an increase in life-threatening bleeding (*N Engl J Med* 2007; 357: 217-227). ■

High-Dose Statin Therapy, Value for Older Adults

Aggressive lipid lowering with high-dose statin therapy may be of value in older adults with stable coronary disease. The multicenter study from the United States included 3,809 patients 65 years or older with coronary artery disease and cholesterol levels less than 130 mg/dl who were randomized to receive atorvastatin 10 mg or 80 mg. Patients on low-dose atorvastatin achieved average cholesterol levels of 100 mg/dl versus 70 mg/dl for high dose therapy. The primary endpoint was occurrence of first major cardiovascular event such as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke. Patients treated with high-dose atorvastatin were found have a 2.3% absolute risk reduction and a 19% relative risk reduction for the primary endpoint (hazard ratio 0.81 [95% CI, 0.67 to 0.98]; $P = 0.032$). Mortality rates were

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lower for CHD, nonfatal non--procedure-related myocardial infarction, and stroke in the high-dose group. High-dose therapy was not associated with elevated creatine kinase levels. The authors conclude that treating older patients with coronary heart disease more aggressively to reduce low-density lipoprotein cholesterol levels provides additional clinical benefit (*Ann Int Med* 2007;147: 1-9). ■

Simvastatin, Best for Parkinson's Disease

Simvastatin, not atorvastatin or lovastatin, is associated with a dramatically reduced risk of dementia and Parkinson's disease (PD) according to a study from Boston University and VA database of 4.5 million individuals (95% men). In the observational study, over 700,000 subjects took simvastatin, nearly 54,000 took atorvastatin, and over 54,000 patients were prescribed lovastatin. Three models were used to evaluate the data, adjusting for covariates associated with dementia or Parkinson's disease. The first model was adjusted for age; the second model adjusted for 3 known risk factors for dementia: hypertension, cardiovascular disease, or diabetes; and the third model adjusted using the Charlson index, an index that provides broad assessment of chronic disease. Using the third model, the hazard ratio for dementia was 0.46 for simvastatin (CI 0.44-0.48, $P < 0.0001$) and 0.91 for atorvastatin (CI 0.80-1.02, $P = 0.11$). Lovastatin was not associated with a reduction in the incidence of dementia. The hazard ratio for newly acquired Parkinson's disease was 0.51 for simvastatin (CI 0.49-0.55, $P < 0.001$). There was no reduction in PD with atorvastatin or lovastatin. The degree of risk reduction utilizing the other models was similar with simvastatin. The authors conclude that simvastatin is associated with a strong reduction in the incidence of dementia and PD, while atorvastatin is associated with a modest reduction in incidence of dementia and Parkinson's disease that shows a trend toward significance (*BMC Med* published online July 19, 2007). The surprising finding suggests a difference between simvastatin and atorvastatin out of proportion to their cholesterol lowering effects, which the authors suggest may be due to the ability of simvastatin to cross the blood brain barrier more readily than other statins. ■

Polyethylene Glycol for Chronic Constipation

Long-term use of polyethylene glycol is safe and effective for chronic constipation according to the results of a new study from Alabama. More than 300 patients were randomized to receive polyethylene glycol 3350 (MiraLAX) in a single 17 g dose per day or placebo for 6 months. The primary endpoint of improvement of constipation on an objective scale was reached in 52% of the PEG patients and 11% placebo patients ($P < 0.001$). Similar efficacy was seen in a subgroup of 75 elderly patients. There were no significant adverse events other than diarrhea, flatulence and some nausea associated with PEG. The authors conclude that PEG laxative is safe and effective for use in patients with chronic constipation for up to 6 months (*Am J Gastroenterol* 2007;102:1436-1441). The study is particularly important because MiraLAX is now available over-the-counter and long-term use by patients with chronic constipation is likely. ■

FDA Actions

The FDA's Oncologic Drugs Advisory Committee, on a narrow vote, recommended approval of raloxifene (Evista) for the indication of breast cancer prevention in high risk women. The approval was based on data from the Study of Tamoxifen and Raloxifene (STAR) trial, which showed a reduction of 4 cases of breast cancer per 1,000 women (50% relative risk reduction), although it was not as effective as tamoxifen in preventing noninvasive breast cancers. Similar findings were seen in the Raloxifene for Use for The Heart (RUTH) trial although this trial revealed a higher risk of fatal stroke and blood clots with raloxifene. The FDA generally follows its advisory committee recommendations. Raloxifene is already approved for the prevention of osteoporosis.

The FDA has approved restricted use of tegaserod (Zelnorm) for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in women under the age of 55 who meet certain criteria. The drug was taken off the market earlier this year when it was linked with a higher risk of cardiovascular events including heart attack, stroke, and unstable angina. Patients must have no history of heart disease and must be in critical need of the drug. Prescribing will be under an investigational new drug protocol program that has been set up by the FDA.

Rosiglitazone (Avandia-GlaxoSmithKline) is associated with an increase risk of heart failure and myocardial infarction. Despite this, the FDA's Endocrinologic and Metabolic Drugs Advisory committee along with the Drug Safety and Risk Management Advisory Committee has advised that the drug stay on the market, albeit with increased warnings. Type 2 diabetes patients who are on insulin for those with heart disease are not the candidates for the drug. The FDA will render a final decision on the drug this fall. ■