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INSIDE

Breast Cancer in Men: Similarities and Differences

ABSTRACT & COMMENTARY

Synopsis: *Breast cancer is uncommon in men. In the current report, the NCI SEER database was examined to provide much needed epidemiological data on the similarities and differences of breast cancer in males and females. In general, men with breast cancer are older and present with more advanced disease. Yet, when matched for age and stage at presentation, overall survival is quite similar between men and women with this disease.*

Source: Giordano SH, et al. *Cancer*. 2004;101:51-57.

Male breast cancer remains an uncommon disorder and data about clinical and biological features have, by necessity, been derived from relatively small clinical series. Furthermore, men with breast cancer are typically excluded from large clinical trials, and therefore any sex-specific feature with regard to treatment response has not been adequately addressed. To help fill in the gaps with regard to clinical and biological features of breast cancer and men, Giordano and colleagues utilized the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) 1973-1998 database. This is a population-based cancer registry that has become the authoritative source of information concerning cancer incidence and survival in the United States. The areas included in the registry are the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah, as well as the metropolitan areas of San Francisco, Oakland, Detroit, Seattle and Atlanta. Overall, the SEER database represents approximately 14% of the US population.

For the purpose of the current analysis, from the 2537 men and 383,146 women with breast cancer, on whom data was captured in SEER, age-adjusted incidence rates were calculated and clinical/biological features were compared. Over the years of the study, the incidence rates of male breast cancer increased significantly from 0.86 to 1.08 per 100,000 ($P < 0.001$). Men had a higher median age at diagnosis ($P < 0.001$) and were more likely to have lymph node involvement ($P < 0.001$), a more advanced stage at diagnosis ($P < 0.001$), and tumors that were positive for estrogen receptor (ER) ($P < 0.001$) and progesterone receptor (PR) ($P < 0.001$). In multivariate analysis, larger

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tumor size and lymph node involvement were associated with shortened survival. Tumor grade and ER/PR status did not appear to independently influence survival. Finally, the relative survival rates, by stage, were comparable for men and women.

COMMENT BY WILLIAM B. ERSHLER, MD

Breast cancer in men remains uncommon, but not rare. Most active medical oncologists have had some experience, as it remains that approximately 1% of all breast cancer occurs in men. Yet, it is a bit surprising that the sum total of our understanding has been derived from relatively small retrospective reviews. The current investigation of the SEER database reflects the best information to date on this topic. The data clarify features that are similar in male or female patients and those that are different. Furthermore, the analysis indicated a clearly rising incidence in male breast cancer (from 0.86 to 1.08 cases per 100,000 population over the 25 years that spanned 1973-1998).

When compared to women patients, men present with disease at a more advanced age (67 vs 62 years; $P < 0.001$), with larger tumors and more likely regional lymph node involvement. Overall, survival is worse for men, but when analyzed by age and stage this difference disappears. Histological features are also somewhat different for men, with a relative greater percentage of papillary histologies and a nearly absent number of patients with lobular pattern. Curiously, a higher percentage of men presented with ER positive tumors (approximately 90% vs 76% for women). Evaluation also revealed the relative survival rates, when adjusted for race, gender, age and stage, were actually quite comparable for males and females. This latter observation runs counter the commonly held notion that survival was worse for men.[1]

By examining a large database, the authors have contributed a solid reference on the epidemiology of breast cancer in men, with a highlight on the differences with the same disease in women. What can be said with confidence is that the disease appears later and at a more advanced stage in men, and that its incidence is increasing. Yet, there are also differences in histology and hormone receptor positivity, implying the presence of poorly understood biological differences. It would take global efforts to construct clinical trials directed at determining optimal management of breast cancer in men, and short of that, clinical oncologists are likely to fall back to the evidence obtained from clinical trials in women.

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Treatment of Advanced Non-Small-Cell Lung Cancer Patients with ECOG Performance Status 2

ABSTRACT & COMMENTARY

Synopsis: *Single-agent chemotherapy should be the standard arm against which experimental treatments are tested in randomized trials didicated to PS 2 patients.*

Source: Gridelli C, et al. *Ann Oncol*. 2004;15:419-426.

Lung cancer is the most common cancer in the world and the leading cause of cancer-related

deaths in Europe and in other Western countries. Non-small-cell lung cancer (NSCLC) represents approximately 80% of all lung cancers. The majority of patients have metastatic disease at the time of diagnosis. Palliative treatment is the only therapeutic option. Performance status (PS) is a global, but rough measure of the patient's functional status. Several PS scales are available for clinical use: among them, those most commonly used are the Karnofsky scale and the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS). ECOG PS is a five-point scale (worsening from 0 to 5) based on the level of symptoms interference with normal activity and on the proportion of waking hours spent in bed. According to the latter scale, patients are classified as PS 2 if they are restricted in physical activity, still ambulatory and capable of self-care but needing rest in bed, although for < 50% of waking hours. PS 2 patients usually account for a very small proportion of patients enrolled in trials of first-line treatment for advanced disease but represent a significantly higher proportion (up to 30 40%) when population-based surveys are conducted.[1-3]

In a meta-analysis evaluating chemotherapy in patients with NSCLC, cisplatin based chemotherapy has shown a slight survival advantage over best supportive care. Chemotherapy can improve quality of life and can control symptoms. It is recommended as the standard approach for patients with advanced disease. The benefit is almost entirely limited to patients with performance status 0 or 1. The benefit of chemotherapy in performance status 2 patients is marginal.[4] For this later group there is no consistent standard and oncologists choose among several treatment options including best supportive care without chemotherapy; single-agent chemotherapy; non-platinum-based combination chemotherapy; and platinum-based combination chemotherapy. An European Experts Panel took place in April 2003 with the aims of reviewing the evidence supporting each of these therapeutic options, possibly reaching a consensus for treatment of PS 2 patients affected by advanced NSCLC in clinical practice, and suggesting the priorities for clinical research in this field. The paper reviews their findings.

COMMENT BY STUART M. LICHTMAN, MD

Evidence available for each of the following six topics in the treatment of PS 2 patients was reviewed: performance status as a prognostic factor; chemotherapy versus best supportive care; single-agent versus combination chemotherapy ; non-platinum based versus platinum-based polychemotherapy; possible role of new biological agents; ongoing trials. Relevant published papers reporting the results of randomized phase III clinical trials were obtained by Medline search in addition to abstracts from important oncology meetings and some authors were contacted directly to obtain data from papers not yet published. The greatest part of the evidence analyzed in the meeting comes from small sub-groups of patients with PS 2, enrolled in clinical trials usually including patients with a PS ranging from 0 to 2. The proportion of patients with PS 2 in these trials is often < 20% of the whole study population, suggesting the existence of a selection bias determining the exclusion of PS 2 patients with worse general conditions and co-morbidities. Median age of patients enrolled in randomized clinical trials is often significantly lower than that observed in clinical practice, and eligibility criteria request good renal, hepatic and cardiac function, as well as absence of other significant co-morbidities. Consequently, it is not surprising that the proportion of PS 2 patients in population-based studies not biased by inclusion criteria and not restricted by the characteristics of experimental treatment is consistently higher than that reported in the majority of clinical trials. Another significant limitation of the published data is the lack of information regarding symptom relief and/or health-related quality-of-life benefits in PS 2 patients.

Performance status has a clear prognostic role in advanced NSCLC. The survival analysis of 1960 patients with advanced disease treated with cisplatin based chemotherapy in 5 ECOG phase II or III trials conducted fro 1981 to 1994 showed an independent prognostic role of performance status: median survival was 9.4, 6.4 and 3.3 months in PS 0, 1 and 2 patients respectively. PS 2 patients have median overall survival that rarely exceeds 5 months with 1-year survival rates < 20%. The poor performance status is characterized by lower response rates to chemotherapy, shorter time to treatment failure and shorter progression free survival. A number of trials have shown the benefit of chemotherapy to best supportive care. There is a suggestion that patients with PS 2 have a small benefit to chemotherapy, particularly single agent therapy. A formal analysis of benefit has been limited by the small number of these patients on clinical trials. These patients often have a greater potential for palliation due to worse baseline conditions.

At present, platinum based combination chemotherapy is considered the standard treatment for advanced NSCLC. However, its benefit is usually restricted to PS 0-1 patients. In a randomized European phase II trial comparing vinorelbine, vinorelbine-cisplatin and vindesine-cisplatin, the

vinorelbine-cisplatin arm was superior.[5,6] The advantage was predominantly limited to fit patients: in PS 0-1 the median survival was 43% and 1-year survival was 38%. For PS 2 patients, grade 3-4 hematological toxicity occurred earlier and more frequently. Lower doses of cisplatin could probably be better tolerated, but there are no current data supporting this hypothesis. In a study evaluating the comparison of paclitaxel alone vs. carboplatin and paclitaxel the median survival in the group treated with combination chemotherapy was significantly longer than paclitaxel alone (4.7 vs 2.4 months).[7] Cisplatin free regimens are currently being evaluated and may represent a reasonable, less toxic option for PS 2 patients. There is no consistent evidence that combination chemotherapy without platinum is better than third generation drugs given as a single agent.[8] There is the emerging role of target agents which have less toxicity. ZD1839, a small molecular tyrosine-kinase inhibitor targeted again the epidermal growth factor receptor is one such drug. It has clinical benefit in pretreated patients.[10]

The consensus of the panel was that chemotherapy appears justified in patients with advanced NSCLC and PS 2. Several trials show that many cytotoxic agents are superior to supportive care alone. Single agent therapy with these drugs (eg, gemcitabine, vinorelbine, taxanes) could be the preferred option for palliative treatment. The drug of choice should be based on toxicity and the type of comorbidity present. Cisplatin combinations should use the drug at lower doses (< 100 mg/mg^2). Research priorities should include investigational agents (eg, pemetrexed), alternative dose and/or scheduling of single agents, carboplatin or low dose cisplatin combinations, biological target-based agents without chemotherapy and supportive treatment added to chemotherapy. ■

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Statins and Cancer Protection

ABSTRACT & COMMENTARY

Synopsis: *In an observational study enabled by a powerful drug-dispensing record linkage system, statin use among a large number of patients treated with cardiovascular drugs, was associated with a 20% reduction in incipient cancer diagnosis over a seven year period. Although not a definitive answer, drugs in this class may have cancer protective properties, and certainly further investigation is warranted.*

Source: Graaf MR, et al. *J Clin Oncol*. 2004;22: 2388-2394.

Because of their efficacy in reducing cardiovascular events, and decreasing morbidity and mortality, 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are often used in the treatment of lipid disorders, particularly hypercholesterolemia,. Statins inhibit HMG-CoA reductase, an enzyme that is involved in the cholesterol biosynthesis pathway, which in turn, directly leads to a decrease in the production of mevalonate, a precursor of cholesterol. Mevalonate is also the precursor of farnesyl and geranylgeranyl moieties, both of which are necessary for the activation of an array of intracellular proteins through farnesylation or prenylation. One protein that is dependent on this farnesylation is the Ras protein, which is important for the regulation of cell differentiation and proliferation. Approximately 30% of all human tumors have a mutation in k-Ras oncogene, and its expression is thought to be related to abnormal cellular growth. Thus, it has been hypothesized that statins, through inhibition of HMG-CoA, and consequently inhibition of the Ras protein, would reduce the expression of the malignant phenotype of a tumor cell and restore normal cellular growth. Several previous studies have implied that statins do have antitumor potential.

Graaf and colleagues from the Academic Medical Center, Departments of Clinical Pharmacy and Oncology, in Amsterdam, in conjunction with the Department of Pharmaco-epidemiology and Pharmaco-therapy at the Utrecht Institute for Pharmaceutical Sciences (UIPS) in the Netherlands, conducted a population-based, nested, case-control study to investigate the relationship between statin therapy and the risk of cancer.

For this, data were collected from the PHARMO record linkage system, which is a database that contains

drug-dispensing records for a population of approximately 300,000 individuals residing in eight medium-sized Dutch cities. The current study included all patients with prescriptions for cardiovascular drugs between January 1, 1985 and December 31, 1998. Cases were identified by a diagnosis of incident cancer. Overall, 3129 subjects developed a diagnosis of cancer during this period, and these were matched with 16,976 controls that were free of a cancer diagnosis. Statin use (at least 6 months) was associated with a risk reduction of incident cancer of 20% (adjusted OR, 0,80; 95% CI, 0.66-0.96). Additionally, when the patients using the statins were compared to those using other lipid-lowering therapies, an adjusted risk estimate of 0.89 (95% CI, 0.56-1.41) was found.

COMMENT BY WILLIAM B. ERSHLER, MD

Statins as a group are remarkable. Their lipid lowering capacity is irrefutable, and their widespread use has been associated with reduced morbidity and mortality in a wide range of cardiovascular domains.[1] Furthermore, perhaps because of anti-inflammatory properties,[2] amelioration of seemingly diverse clinical disorders such as Alzheimer's disease[3] and osteoporosis[4] has been proposed. The current observational study extends even further, the potential value for these compounds. Although a risk reduction of 20% would be considered modest and possibly even questionable, in light of the number of potential methodological confounders in a study such as this, it is consistent with a similar study in which the risk of incident cancer was reduced by 28% when statin users were compared with users of other lipid-lowering agents (bile acid-binding resins).[5] Furthermore, the investigators when through great effort to appropriately match cases and controls and in other ways minimize these inherent confounders. One example is the use of the PHARMO record linkage system, which captures prescription distribution and diagnoses into a powerful database. The database, however does not include lifestyle factors, such as cigarette smoking, diet or chronic stress, or associated socioeconomic factors, all of which may be relevant in choice of drug, and possibly compliance. Subjects included in this analysis (cases and controls) were all 'cardiovascular' patients, inasmuch as they were prescribed cardiovascular medications. For one reason or another, physicians chose to prescribe statins in some patients and not in others, and those factors that influence prescription pattern may also, through mechanisms unrelated to the drug, relate to cancer development or growth.

Nonetheless, the findings from this observational study are intriguing and warrant further investigation. Although the mechanism of protection as proposed in this paper (inhibition of farnesylation and thereby Ras activation) is quite plausible, others are as well. These would include free radical inhibition and modulation of proinflammatory cytokines, which are among the pleiotropic pharmacological effects observed with this class of compounds. By whatever mechanism, it would seem that a well-designed prospective clinical trial might resolve the issue of whether or not a cancer-protective effect exists. The difficulty is going to be finding enough volunteers who are not already taking a drug in this class!

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HIT (Heparin-Induced Thrombocytopenia) Complications in Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *In a retrospective review from the Royal Victoria Hospital in Montreal, among patients with heparin-induced thrombocytopenia, those who had underlying malignancy were found to have a greater risk for thrombotic events when compared to those without malignant disease.*

Source: Opatrny L, et al. *Am J Hematol*. 2004;76: 240-244.

Heparin induced thrombocytopenia (HIT) is an immune-mediated reaction occurring in up to 5% of patients receiving unfractionated heparin.[1] Some patients with HIT, even with severe thrombocytopenia, survive without significant complication, whereas others have thrombosis, gangrene resulting in digit or limb loss, and death. Previous studies have indicated that risks for the more dramatic outcomes include recent surgery and known vascular pathology[2,3] while other factors, such as heterozygosity for Factor V Leiden and deficiencies of protein C, antithrombin, and heparin cofactor II have proven negative as risk indicators for

thrombosis development in association with HIT.[2] Opartny and Warner performed a retrospective review of all the patients from a single tertiary care hospital who met clinical criteria for HIT (including a > 50% drop in platelet count or an absolute platelet level of < 150 x 10^9/L 5 to 10 days after beginning heparin therapy, or sooner if patients had previously been treated with heparin in the absence of other causes of thrombocytopenia) and who were confirmed to have antibody to platelet factor 4 [PF4]) by ELISA to determine if the presence of malignancy is a predictor of thrombosis and other complications for HIT positive patients.

During a 22-month period, 64 patients met the above criteria for HIT and 55 were suitable for this analysis (complete records, etc). Active malignancy was present in11 and no evidence for malignancy was present in the other 44. The patients with malignancy all were with carcinoma from various organs, except one patient with melanoma. Thrombotic complications occurred more frequently in the patients with malignancy when compared to those without. This included both venous (odds ratio [OR], 13.6; 95% confidence interval [CI], 1.5-27.8) and arterial embolism (OR, 2.2; 95% CI, 0.5-9.3). Although the confidence interval for arterial embolism spanned unity, the odds ratio for combined venous/arterial event (6.4) had a 95% confidence interval that did not (1.5-27.8). Furthermore, amputation requirement was higher for those with malignancy (OR, 16.1; 95% CI, 1.5-175.2) indicating the greater risk or arterial complications. Mortality was also greater for those with malignancy, but when subject to statistical analysis, the confidence interval spanned unity (OR, 2.0; 95% CI 0.5-7.7).

COMMENT BY WILLIAM B. ERSHLER, MD

The data presented in this retrospective review support the contention that cancer patients who develop HIT have a greater risk of thrombotic complications. The high incidence of some form of adverse thrombotic event in 73% (8 of 11) of the cancer patients with HIT is remarkable. The finding is an important one and needs to be confirmed, both by examining the experience at other institutions and by prospective analysis. The latter would likely require a systematic protocol for recognition of HIT in heparin-treated patients and a uniform method of surveillance for complications (ie, ultrasound, CT scans, etc).

Another consideration raised by the current report is the implication that those HIT patients who develop thrombotic complications, should, once medically stable, be evaluated for the presence of malignant disease.

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Prediction of Optimal vs Suboptimal Cytoreduction of Advanced-Stage Serous Ovarian Cancer with the Use of Microarrays

ABSTRACT & COMMENTARY

Synopsis: *These data support the hypothesis that favorable survival that is associated with optimal debulking of advanced ovarian cancers is due to, at least in part, the underlying biologic characteristics of these cancers.*

Source: Berchuck A, et al. *Am J Obstet Gynecol*. 2004; 190(4):910-925.

The ability to characterize the expression of thousands of genes simultaneously has provided new insight into the underlying biology of disease for many cancers. Berchuck and colleagues adapt the technology to evaluate its ability to predict primary surgical outcome in patients with newly diagnosed ovarian cancer. RNA from 44 preselected advanced (21 with survival less than 3 years and 23 with survival more than 7 years) and 5 early stage ovarian cancers were evaluated with the Affymetric Gene Chip containing 22,283 genes for their relative expression among patients achieving optimal vs suboptimal cytoreduction. The top 120 differentially expressed genes were then used to generate a prediction model, which was validated in an out-of-sample process. Specific probability models were generated for gene set in order to optimize the ability to distinguish cytoreductive outcome (19 optimal vs 25 suboptimal and 5 early stage). Berchuck and colleagues identified 32 differentially expressed genes in the optimized prediction model. Patients' cytoreductive outcome was correctly classified by the model in 72.7% of cases. Five of 25 (20%) suboptimal cases, 7 of 19 (37%) optimal cases as well as 2 of 5 (40%) stage I cases were misclassified. There was no relationship between misclassified cases and clinical or pathologic features. Evaluation of gene clusters in this set did not

improve the predictive power. Berchuck et al conclude that these data do support the hypothesis that optimal cytoreduction is associated with prolonged survival and that at least in part, optimal status is due to underlying biological characteristics.

COMMENT BY ROBERT L. COLEMAN, MD

There are many factors which, by retrospective and prospective evaluation, have shown to be important in estimating survival in newly diagnosed or suspected ovarian cancer patients. The most recognizable, perhaps, is cytoreductive status following primary surgery; that is, the amount of residual disease following a maximal effort at removing it. In the last 30 years since the relationship was first well documented, many authors have correlated preoperative findings such as bulky radiographic disease, CA-125 levels and distribution of disease with the ability to render a patient "optimal."[1-5] While some of these factors have proven to be useful in certain circumstances (eg, patients with poor performance status) relying on them exclusively to triage patients for surgery would exclude a significant fraction (up to 30%) of debulkable patients, potentially lowering their survival by withholding an important part of their treatment package.

Most gynecologic oncologists appreciate that some tumors are just not "debulkable" and some patients rendered "optimal" have shorter than expected survivorship. Conversely, some "suboptimal" patients survive for extended periods of time—a measure of their chemosensitivity. The most frequently cited reason for these clinical observations is tumor biology—some underlying, tumor-specific feature or features that define the clinical behavior of a tumor. In the current article, Berchuck et al tackle this conundrum with state-of-the-art molecular profiling using a gene chip array. Since all human cancer appears to result from accumulating genetic mutation, studying patterns of thousands of genes simultaneously allows one to gain an insight, at the moment of tissue harvest, of the RNA being either over or under produced relative to "maintenance" standards. The technology has already proven beneficial in producing risk classifications for patients with prostate and breast cancer. There are currently a handful of similar array studies being conducted in ovarian cancer specimens evaluating risk analysis, survival and chemosensitivity.

Berchuck et al address the biology question (via the surrogate of debulking status) by evaluating a small cohort of patients (n = 44) dichotomized by their survival (less than 3 years vs greater than 7 years) collected from a previous study by which the gene chip technology was used to investigate patterns predicting survival. The primary end point of the current trial was to evaluate the expression profile of those rendered surgically optimal against those left with greater than 1 cm of residual disease. One hundred twenty genes were differentially expressed in these 2 cohorts and made up the sample from which a prediction model was constructed. Using novel statistical and probability methodology, 32 genes were subsequently teased out, optimizing the model predicting surgical outcome. In all, the accuracy in distinguishing optimal from suboptimal was 72.7%. Although the data support proof-of-concept—that is, a genetic expression profile underlies the clinical outcome found at surgery and suggest a biological component may render tumors less debulkable, the predictive power of the model is similar to that achieved with fairly unsophisticated tools such as serum CA-125 and radiographic assessment. Unfortunately, it did not completely segregate the early stage (and therefore, optimal by nature) cases nor control for optimal as a result of stage (eg, Stage IIIA and IIIB) or surgical effort. In addition, fresh tissue cores are needed making the technique less palatable as a preoperative tool. It is also unknown whether the current model or expression profile is generalizable to the population at large given the polarized profile of the sampled cases. Nonetheless, review of individually under- or over-expressed genes reveals important clues as to what biological processes are ongoing in dysregulated growth and metastases.

It is clear we have just scratched the surface of understanding the genomic-wide events that lead up to and characterize phenotypic behavior of individual tumors. And this is just the genomic level! Since their products, (ie, proteins) drive the real cellular machinery, similar profiling will ultimately provide the level of detail needed to ferret out individual characterizations of clinical behavior. This type of proteomic analysis is now being validated in ovarian cancer screening trials. It is hoped new technologies will make detailed analysis available to patients diagnosed with ovarian cancer enabling a tailored therapeutic program, truly maximizing tumor cytotoxicity while minimizing the effects of treatment. ■

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CME Questions

4. **In the report of thrombotic events in patients with heparin-induced thrombocytopenia, the presence of coexistant malignant disease was shown to significantly increase:**
   a. bleeding complications
   b. venous thrombotic events
   c. arterial thrombotic events
   d. overall, all cause mortality
   e. all of the above

5. **In the recent report of cancer development in statin-treated patients, the observed reduction in cancer incidence among statin users was approximately:**
   a. 5%
   b. 20%
   c. 50%
   d. 95%

6. **When compared to breast cancer in women, all BUT which of the following statements is true regarding breast cancer in men?**
   a. The age at presentation is generally older in men.
   b. The stage at presentation is generally more advanced in ment.
   c. Men are less likely to be ER/PR positive
   d. All of the above

Answers: 4 (b); 5 (b); 6 (c)

In Future Issues:

Predicting Irinotecan Therapy

PHARMACOLOGY WATCH

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The Importance of Publishing Negative Clinical Studies

Sources of funding for pharmaceutical research has come under scrutiny in the last decade as academic and government sources of funding have become increasingly scarce and the pharmaceutical industry has become the main source of research dollars. But the issue of objectivity has been raised, and some have even suggested that negative studies, that is studies that show a drug in an unfavorable light, may never be published. The American Medical Association has recently tackled this issue and has asked the department of Health and Human Services to establish a public registry of all clinical trials in United States. The registry would include information regarding the design of the study and the questions to be addressed. The registry would also contain data about the study results, both positive and negative. Some members of Congress have indicated interest in pursuing legislation to create such a registry, and even large pharmaceutical companies such as Merck and GlaxoSmithKline support the concept. But despite the AMA's valid concerns, several negative studies have been newsworthy in the last 2 months. This issue of *PharmWatch* highlights a few of those.

Cognitive Effects of Estrogen Therapy

Two studies in the *Journal of the American Medical Association* suggest that estrogen alone therapy may be associated with a decline in cognitive function in post-menopausal women and may increase the risk of dementia. Both studies are follow-ups from the Women's Health Initiative Memory Study (WHIMS) which had previously shown that estrogen plus progesterone therapy increases the risk of dementia in postmenopausal women. The first study was a follow-up of nearly 3000 women randomized in a double-blind fashion to conjugated estrogen, conjugated estrogen plus progesterone, or placebo. In the estrogen alone wing, 28 women taking estrogen developed probable dementia vs 19 assigned to placebo (HR, 1.49; 95% CI, 0.83-2.66). Similar rates were noted in the estrogen plus progesterone wing. When data were pooled for both estrogen and estrogen plus progesterone, the overall hazard ratio for dementia was 1.76 (95% CI, 1.19-2.60; P = .005). Increased risk of mild cognitive impairment was also noted in the estrogen alone group and the estrogen plus progesterone group. When the data were pooled, the hazard ratio for mild cognitive impairment was 1.25 (95% CI, 0.97-1.60). This study showed that there is no difference between estrogen alone vs estrogen plus progesterone therapy in the risk of dementia or mild cognitive impairment, and in fact, both therapies increase the risk of both these end points (*JAMA*. 2004;291:2947-2958). The second study asked whether estrogen alone alters global cognitive function in postmenopausal

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women. During a mean 5.4 years of follow-up, nearly 3000 women were randomized to 0.625 mg of conjugated estrogen or matching placebo per day. The women were assessed annually with the Modified Mini-Mental State Examination. The data showed that testing scores were 0.26 units lower among women assigned to conjugated estrogen compared to placebo (P = .04). When the data for estrogen alone was pooled with estrogen plus progesterone, the decrease was 0.21 (P = .006). The adverse effect of hormone therapy was more pronounced in women with low baseline cognitive function. The authors conclude that for women age 65 and older, hormone therapy, including estrogen alone therapy, had an adverse effect on cognition (*JAMA*. 2004;291:2959-2968). As pointed out in the accompanying editorial (*JAMA.* 2004;291:3005-3007), this study did not look at women who took estrogen in the years immediately following menopause. Previous observational data have suggested that there is a critical period just after menopause during which estrogen may be neuro-protective (*JAMA*. 2002;288:2123-2129). However, these current studies seem to conclusively show that neither estrogen nor estrogen plus progesterone are neuroprotective for older women.

Vitamin Therapy and Restenosis

Vitamin therapy to lower homocysteine levels has been touted as an effective way to prevent restenosis after coronary angioplasty. A new study, however, suggests that vitamin combination may actually increase the risk of restenosis in these patients. In a double-blind, placebo-controlled study from Germany and the Netherlands, 636 patients who had undergone successful coronary stenting were randomized to a combination of 1 mg of folic acid, 5 mg of vitamin B, and 1 mg of vitamin B12 intravenously, followed by daily oral doses of the 3 vitamins for 6 months; or to placebo. In a follow-up, the mean luminal diameter was significantly smaller in the vitamin group and placebo group (P = .008), and the extent of luminal loss was greater (P = .004). The restenosis rate was also higher in the vitamin group than the placebo group (34.5% vs 26.5%, P = .05). A higher percentage of patients in the vitamin group also required target vessel revascularization (P = .05). The authors conclude that contrary to previous findings, the administration of folate, vitamin B-6, and vitamin B12 after coronary stenting, may increase the risk of in-stent stenosis (*NEJM*. 2004;350:2673-2681).

Echinacea and the Common Cold

Echinacea purpurea, the commonly prescribed herbal remedy, may have no effect on the common cold, according to a new study. In this randomized, double-blind, placebo-controlled trial, 128 patients with early symptoms of the common cold were randomized to 1 mg of Echinacea or lactose placebo 3 times per day for 14 days or until cold symptoms were resolved, whichever came first. No statistically significant difference was observed between treatment groups for either a total symptom score (P range for symptoms = .29-.90) or mean individual symptom scores (P range = .09-.93). The time toward resolution of symptoms is not statistically significant between the 2 groups (*Arch Intern Med.* 2004;164:1237-1241). The authors admit, however, that testing different preparations and dosing ranges of Echinacea may be needed to confirm these findings.

Effects of Paxil in Children Under 18

GlaxoSmithKline has been accused of suppressing negative data about its antidepressant paroxetine (Paxil), showing that it is broadly ineffective in children and adolescents, and could increase the risk of suicidal behavior. The accusation comes in the form of a lawsuit from New York Attorney General Eliot Spitzer, who filed the suit in early June accusing the company of fraudulently suppressing the data. In response, Glaxo has published several studies on its web site, and states that these studies had previously been published in journals or presented at scientific meetings. The company also reiterates that paroxetine is not approved for treatment of patients 18 years or younger, and states that they do not promote off-label use of their products. The British firm has released data from 9 pediatric trials, as well as the bibliography of public communications derived from the studies, and letters to United States physicians summarizing the data. As mentioned earlier, GlaxoSmithKline, has stated publicly, it's support of the American Medical Association's proposal to create a national registry of all proposed pharmaceutical studies. More information is available at www.gsk.com/media.

FDA Actions

Schering has received approval from the FDA to market a new low dose estrogen patch for the treatment of osteoporosis. The patch, which is dime sized, is applied once a week, and delivers 14 micrograms per day of estradiol. It will be marketed this summer under the trade name Menostar. ■