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INSIDE

Circulating Tumor Cells, Disease Progression, and Survival in Metastatic Breast Cancer

ABSTRACT & COMMENTARY

In a prospective, multicenter study, Cristofanilli and colleagues tested 177 patients with clinically detectable metastatic breast cancer for levels of circulating tumor cells both before and after the initiation of various forms of therapy. The response to therapy was followed using standard clinical detection, but blood samples were also collected to determine the burden of tumor cells in the circulation. Cristofanilli and colleagues found that the levels of circulating tumor cells at baseline, and at the first follow-up visit, were the most significant predictors of progression-free and overall survival. Cristofanilli et al note that this study was made possible by technological advances affording detection of circulating tumor cells. In this study, Cristofanilli et al utilized a newly developed approach called CellSearch System by Veridex. The system is based on enumeration of epithelial cells, which are separated from the blood by antibody-coated magnetic beads, and identified using fluorescent-labeled antibodies against cytokeratin.

All but 10 of the 177 patients had a minimal follow-up time of 38.7 weeks. Circulating epithelial cells were rare in healthy women and in patients with benign breast disease. The levels of circulating tumor cells at baseline, and at the first visit after the initiation of therapy, predicted outcome better than estrogen-receptor status, progesterone-receptor status, HER2/neu status, or type of therapy. Tumor burden at the first follow-up visit was somewhat more predictive of outcome than tumor burden before treatment. Indeed, for those receiving adjuvant hormonal intervention, circulating tumor cell count was only predictive for outcome after treatment and not before (Cristofanilli M, et al. *N Engl J Med.* 2004;351:781-791).

COMMENT BY SARAH L. BERGA, MD

The main hypothesis guiding this study is both simple in concept and exciting in potential. Cristofanilli et al asked whether the number of cancer cells detected in the blood before and after therapy correlated with tumor behavior and survival in patients with known metastatic

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breast cancer. A key barrier to testing this hypothesis was surmounted by the development of a robust technique to both identify and quantify tumor cells in the circulation. Since the study results rest so directly on technique, the study is in part a validation of this technique for detecting breast cancer cells in the circulation. Since there is no readily available gold standard for detecting breast cancer cells in the circulation, the manufacturers of the new approach had to depend in part on clinical outcomes for validation. Thus, Cristofanilli et al, out of necessity, had to simultaneously test both a biological hypothesis and a new technological development.

Assuming that Cristofanilli et al's study results are valid and replicable, where do the results made possible by this new technique put us? If the technique is highly sensitive and specific, then we potentially have a new method for refining the stage of the patient's breast cancer prior to initial therapy. Having this information might lead to important prognostic information. Such a technique might even allow us to predict tumor aggressiveness, or its return after an apparent remission. We also might be able to say with greater accuracy which patients do and do not need adjuvant therapy, what type of adjuvant therapy would be best for a given breast cancer, or when to switch to another type of adjuvant therapy because the initial one chosen is not working. In short, this new technique might allow us to act on the notion that all breast cancers (and their hosts) are not the same. Given the many side effects of adjuvant therapy, having some way to individualize is truly exciting. The most far-reaching possibility, however, would be that such a technique could be used for advance detection of cancers, breast or otherwise, by a simple screening blood test. The widespread availability of a reliable and cost-effective screening technique would clearly be a welcome addition to our diagnostic armamentarium for those at high risk for breast or ovarian cancer, including those who carry BRCA1 and BRCA2 mutations. Realizing these clinical dreams hinges, in part, on whether tumor cells in the circulation adequately reflect the primary tumor across time and following intervention. Either way, though, this technique may help us to learn more about the multiple determinants of tumor behavior in vivo. ■

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Virtual Colonoscopy: How to Counsel Your Patients

ABSTRACT & COMMENTARY

Synopsis: *Although safer than traditional colonoscopy, virtual colonoscopy's lower sensitivity and efficacy coupled with the increased cost would rule against recommending this procedure at the current time.*

Source: Cotton PB, et al. *JAMA*. 2004;291:1713-1719.

NINE MAJOR HOSPITAL CENTERS PARTICIPATED IN THIS non-randomized, evaluator-blinded study of 615 patients, all of whom were 50 years of age or older, and who were referred for routine colonoscopy. Three hundred and eight patients underwent virtual colonoscopy just prior to the standard colonoscopy. Among the 827 lesions identified, sensitivities for the 2 procedures were as follows: for lesions 6 mm or less, virtual colonoscopy 39% (95% confidence interval [CI], 29.6-48.4%) vs conventional colonoscopy 99% (95% CI, 97.1-99.9% or greater); for lesions 10 mm or more, virtual colonoscopy 55% (95% CI, 39.9-70%) vs 100% for conventional colonoscopy.

The specificity for virtual colonoscopy to detect subjects without any lesions at least 6 mm was 90.5% (95% CI, 87.9-91.3%), and for 10 mm lesions 96% (95% CI, 94.3-97.6%). The specificity for conventional colonoscopy was 100% for both. Of the 8 cancers detected, virtual colonoscopy missed 2.

COMMENT BY FRANK W. LING, MD

Here's another chapter in the evolving book of primary that so many of us obstetrician/gynecologists help our patients thumb through. Clearly this new and sexy approach to screening for colon cancer has caught on in the lay public and lay press. It is fairly routine now that when I recommend that a patient undergoes colon cancer screening that she asks about virtual colonoscopy. These data help us to counsel patients in that tried and true mold: if it sounds too good to be true, it probably is, ie, don't believe everything you hear. The results of this study would certainly suggest that this technique is not quite ready for our routine recommendation.

Since any lesion on virtual colonoscopy must be biopsied or removed via the conventional route, the patient would not avoid the more invasive procedure in those cases. In addition, many patients would say that it's not conventional procedure that is so bad, but the bowel prep that precedes it. That is still required for virtual colonoscopy. What about the price? More importantly, will the patient's insurance company pay for it? Yes, it's non-invasive and, therefore, safer, but it's a lot pricier (particularly if the patient has to pay for it herself), and would appear to not be as good a test as conventional colonoscopy.

I was on an airplane a few months ago and a passenger next to me noted that I was working on some medical paperwork. That led us to discussing why he had been to New York for the past 3 days. You guessed it—this resident of Memphis, Tennessee, had been to the Big Apple for his annual physical and a virtual colonoscopy. As I queried further, I found it fascinating that he was in his early 40s, had no cancer risk in his family, and did not have a physician who had recommended the procedure. He had scheduled himself and paid for it because he felt that it was the right thing to do. I guess if you've got the time and money, you can decide how to use both.

As always, then, what is our bottom line? Recommend colonoscopy for your patients based on their individual risk factors when it is appropriate and, at least for now, recommend the technique which is best supported by the data—conventional colonoscopy. ■

Determining the Position of the Fetal Head in the Second Stage of Labor

ABSTRACT & COMMENTARY

Synopsis: *The vaginal exam was correct in 71.6% of cases, and the ultrasound was correct in 92% of cases.*

Source: Chou MR, et al. Vaginal vs Ultrasound Examination of Fetal Occiput Position During the Second Stage of Labor. *Am J Obstet Gynecol.* 2004;191:521-524.

A VERY SIMPLE STUDY APPEARED IN THE AUGUST edition of the *American Journal of Obstetrics and Gynecology*. It dealt with the ability of clinicians to precisely determine the position of the fetal head in the maternal pelvis during the second stage of labor.

Chou and colleagues studied 88 patients after full dilatation. One clinician was asked to determine the position of the fetal head digitally, and another blinded examiner, using transabdominal and transperineal ultrasound, assessed the fetal position in the same patient shortly before or after the digital examination. The ultrasound clues to determining the position of the fetus were the position of the fetal spine and the alignment in the pelvis of the fetal orbits and occiput. The end point used by Chou et al was the position of the cranium at delivery after restitution.

The vaginal exam was correct in 71.6% of cases, and the ultrasound was correct in 92% of cases. The 3 cases where the ultrasound information was discordant with the delivery results probably involved spontaneous rotation, only 1 of which was directly observed before birth.

COMMENT BY JOHN C. HOBBINS, MD

To suggest that super-trained physicians and certified nurse midwives can misdiagnose fetal position at the end of labor represents fighting words. Well unfortunately, there are at least 4 studies showing that vaginal examination is incorrect between 27% and 76% of the time. Once we set aside our defensive responses to this, we should realize that it is not easy to separate a Y from a diamond, or even to accurately determine the direction of the sagittal suture when being confronted with 3-4 cm of caput.

A few studies have pitted clinical exams against ultrasound evaluations in determining fetal posi-

tion, and have found a major difference. However, in these studies, the gold standard was assumed to be the ultrasound. In this study, Chou et al used a third, and supposedly objective, variable, the position of the fetal head at delivery after restitution.

I suppose we could quibble over the nuances in study design, but it is very clear that ultrasound could become an important, yet simple, adjunct to clinical decision making. For example, Rayburn et al addressed the concept that in patients with dystocia, one might give a little extra time in the second stage if an occiput posterior position was noted on ultrasound. On the other hand, those with occiput anterior or oblique positions would benefit little from further expulsive efforts. Also, the correct application of forceps could be aided by this technique. Very few clinicians can honestly say that they have not delivered a fetus sunny-side up when they thought the fetus was in an occiput anterior position when they applied their forceps.

Every Labor and Delivery floor should have an ultrasound on-site or conveniently available. For transperineal scanning, one can simply use a standard transabdominal curved array transducer housed in a glove, but in most cases, the information can be gained transabdominally.

Also, soon to be published information will be available to help the clinician precisely determine fetal station using transperineal ultrasound. This, in turn, will allow practitioners to truly assess progress in descent. ■

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Physical Activity, Including Walking, and Cognitive Function in Women

ABSTRACT & COMMENTARY

Synopsis: *Regular physical activity, such as walking, is associated with significantly better cognitive function and less cognitive decline.*

Source: Weuve J, et al. *JAMA.* 2004;292:1454-1461.

The present study involves yet another analysis of the Nurses' Health Study, which began in 1976 when 121,700 female registered nurses 30-55 years of age returned a questionnaire about their medical history and health-related behaviors. To test the present hypothesis that exercise protected against cognitive decline, participants ages 70 and older were queried about lifestyle factors, particularly exercise, and underwent a standardized telephone interview to assess cognition between 1995-2001. A total of 18,766 women enrolled, and 16,466 of them underwent a second assessment a mean of 1.8 years later.

Women who exercised the most were also less likely to smoke and more likely to consume moderate amounts of alcohol. Also, cardiovascular disease, pulmonary disease, and diabetes were all less prevalent among women who exercised the most. On the global score of cognition, women in the highest quintile of exercise had 20% lower odds of cognitive impairment at baseline, when compared to women in the lowest quintile, OR = 0.8, confidence interval 0.67-0.95. The association was not restricted to women engaging in strenuous activities. Walking the equivalent of at least 1.5 hours per week at a 21-30 min./mile pace was also associated with better cognitive performance.

Weuve and colleagues suggest that exercise helps because it improves the brain's vascular health by lowering blood pressure, improving lipoprotein profiles, and promoting endothelial function. Exercise may also help by lowering insulin, and by directly promoting neuronal survival. Weuve et al do not provide the body mass index or use of menopausal hormone therapy past or present for women by quintile of exercise.

■ COMMENT BY SARAH L. BERGA, MD

In the aftermath of the Women's Health Initiative, physician and patients alike have been searching for alternative strategies to health maintenance. Of course, most of the approaches that might be viewed as alternatives would

also complement each other, and may even complement menopausal hormone therapy (MHT). Now that it appears that no one strategy, including MHT, can undo the negative effects of a lifetime of bad habits, it is time to get even more serious about quantifying the extent to which lifestyle variables promote health. Fortunately, most lifestyle factors that promote health also make great fashion sense. Gone are the days when the gaunt figure ruled, and smoking was a fashion aid. Best of all, for most lifestyle factors, moderation appears to be the best course. Thus, it is a relief to read yet another study showing that moderate physical activity is highly beneficial, in this case for the brain.

So much for common sense. Now we need advice as to how we as a society, or as physicians, can get ourselves and our patients to actually adopt a healthy lifestyle. If the answer is clear that lifestyle matters, then how do we promote adherence? First, it has to be recognized that physicians alone cannot be the only advocacy force. But, we do have influence, and we need to know how to exercise our influence, as well as our bodies. We can start by following our own advice, and in so doing, set an example. We can urge that our workplaces provide healthy foods. We can walk whenever possible, and urge the construction of workspaces and urban spaces that enhance the pedestrian's safety and aesthetic experience. Studies show that simply reminding patients has an effect!

Perhaps the most important message trickling out of the science of health promotion is that combinations count. What do I mean? It appears that there is synergism between healthy lifestyle variables, such that you get greater impact than predicted when you add good diet, exercise, and intellectual stimulation. There are many examples of this type of synergism in the field of prophylaxis. Take bone health, for example. Even though about 60-70% of bone mass relates to genetics, there are many behaviors that modulate the other 30%, including sufficient vitamin D exposure, sufficient calcium and mineral intake, overall nutritional status, physical fitness, absence of major illness, lack of glucocorticoid excess, sleep hygiene, social integration, and lack of reproductive compromise. By engaging in all of the recommended behaviors, one minimizes the risk of fracture much more than would be predicted. Unfortunately in the past, at least, there was a tendency to think that taking hormones after menopause meant that one did not need to worry so much about vitamin D intake or getting enough exercise or vice versa. It has been commonplace also to assume that sufficient calcium alone would do the trick. Studies now show that calcium alone is relatively ineffective, but that sufficient calcium intake is a necessary to achieve full protection against osteoporosis and fracture, when other health-promoting behaviors are undertaken.

The same principle is likely to hold true for brain, as well as for bone. Thus, to maximally protect against dementia and cognitive decline, one has to do more than crossword puzzles. However, we have yet to perfect the recipe that maximally safeguards our brains as we age. In all likelihood, our recommendation will involve encouraging patients to exercise, get enough rest, eat sensibly, treat hypertension, and stay intellectually engaged. Whether menopausal hormone therapy will also be part of the armamentarium remains to be seen. I suspect that certain forms of menopausal hormone therapy may well augment the neuroprotective effects of a healthy lifestyle, but no study has yet to be designed or undertaken that adequately addresses this hypothesis. Until we have better data about MHT and neuroprotection, we must continue to make sure that patients know that lifestyle, including exercise, helps. Indeed, taking the time to conduct a thorough review of lifestyle factors probably makes as much sense as anything that we do in the office to protect the health of women as they age. ■

Special Feature

Chemotherapy Sensitivity/Resistance Assays in Gynecologic Cancer: Are We There Yet?

By Robert L. Coleman, MD

STATE OF AFFAIRS

OVER THE LAST FEW DECADES, TECHNOLOGY HAS existed to evaluate the cytotoxic effects of single-agent and combination chemotherapy on cancer cell lines derived from an individual patient's tumor specimens.[1-4] However, investigators and clinicians have been frustrated as the fruit of this technology—a reliable and reproducible assay to help them treat their patients with the agent or agents most likely to benefit them—has yet to be proven. Currently, the determination of chemotherapy to be used individually is a decision made empirically; supported for the most part by clinical data generated ideally from randomized and non-randomized clinical trials on like cohorts of patients. However, since in all such trials, only a proportion of patients respond, the science is obviously imperfect and the decision subject patients to potentially toxic therapy that, on a individual basis, may have little chance for

success. Tailored chemotherapy remains an important and extensively sought after endpoint in cancer treatment, and as such, drives many clinicians to utilize some of the many currently available technologies that claim to provide some improved guidance over our best guess.

DEFINITIONS

A chemotherapy sensitivity and resistance assay is a laboratory algorithm wherein a sample of human tumor is subjected, under experimental conditions, to various chemotherapeutic agents and concentrations in order to assess response (tumor survival). Two broad categories of assay-intent separate the available technologies: those that evaluate the inhibition of cell growth and those that address chemotherapy-associated cell death. While these intents appear similar, they are very different in their laboratory aim and may produce vastly disparate results.[5] In most cases, several drugs and combinations are evaluated. Theoretically, the most active agent or combination could be picked (sensitivity assay) or eliminated (resistance assay) from an empiric program, offering a more precise decision tool. The hypothesis is that this maneuvering will benefit patients in the ultimate outcome, survival. While the concept is simplistic and rational, the effects of chemotherapy response and patient survival are complex and sometime counterintuitive. For instance, it is probably over-reaching to assume a limited sample of tissue obtained from either the primary or a metastatic site, at primary diagnosis or in recurrence and following prior chemotherapy or radiation exposure will be representative of active disease at any one time. Similarly, the relationship between response and overall survival is at best tenuous and reflects issues not measured in the lab such as toxicity, quality of life, and performance status.

THE ASSAYS

Comprehensive discussion of the individual available assays is beyond the scope of this commentary but they will be categorically introduced for orientation. Most available assays evaluate isolated tumor cells from a tissue biopsy or fluid specimen after which the cells are incubated in the presence of a chemotherapeutic agent. Inhibited growth and/or cell death are endpoints allowing a sensitivity characterization. Other assays reach this determination by evaluating the ability of a chemotherapeutic or combination to kill a certain proportion of cells relative to baseline. Those agents reaching a specified cut-off are allocated as sensitive. Individual assays and their description are shown in Table 1.

OFFICIAL EVALUATION

In the September 1, 2004 issue of the *Journal of Clinical Oncology*, the American Society of Clinical Oncology (ASCO) commissioned a Working Group[6,7] "to develop a technology assessment of chemotherapy sensitivity and resistance assays in order to define the role of these tests in routine oncology practice." Collaborating with the Blue Cross and Blue Shield Association Technology Evaluation Center, the 2 groups independently evaluated the world's written literature, seeking to identify clinical trials which assessed the ability of an assay to positively affect clinical outcome when it was incorporated in a decision process. Despite the plethora of abstracts dealing with the topic (over 1100), a surprisingly limited number of clinical trials (12) met a priori requirements of: prospective design, comparative outcome between assay-directed and empirically treated groups, sufficient sample size, and contemporaneously treated cohorts. While some of the trials did show various end point advantages, such as response or progression-free survival, superior overall survival was only inconsistently documented. The conclusion reached by both organizations was that the technology was not ready for prime time. However, conceding the importance of the concept in general, they called for prioritized investigation with inclusion of the technology in future prospective clinical trials.

ASSAY-DIRECTED THERAPY AND MALIGNANCIES

While the conclusions reached from the ASCO Working Group appear sound, it is important to consider these conclusions in the context from which they were derived. The strict criteria for study inclusion limits available data to published series, some incorporating older and/or impractical technology. In addition, several studies, evaluated by the Group, demonstrated response and survival outcomes that were favorable or significantly improved for the assay-directed treatment cohorts. Many of these were among ovarian cancer patients. The applicability of assay-directed therapy may be better suited for gynecological malignancies, particularly ovarian cancer, given not only the large emporium of active agents, but also the significant duration of time one may have to treat a patient. However, without a well-designed, randomized clinical trial, generalized utilization of (and reimbursement for) assay-directed treatment, even among these patients, will not be realized.

For assay-directed therapy to make a real impact in the treatment of a disease, several obstacles, conditions, and challenges need to be met and overcome. First, the assay must return reliable results in a timely manner. A corollary is that in the majority of cases, an interpretable result is returned. In the case of ovarian cancer, many patients are ready for chemotherapy shortly after cytoreductive surgery or tissue biopsy. Although the relationship of early treatment after surgery to survival has been challenged,[8] delay of therapy in a symptomatic, anxious patient may be difficult. Assay results that take weeks to

return are likely to be of limited benefit if a delay in treatment initiation is required; even more so if the probability of a meaningful assay is low (less than 75%). In addition, the allocation of resistance and sensitivity needs to be meaningful, reproducible, and reflective of in vivo observations. Second, a 1-time biopsy is likely not to be accurately reflective of all disease conditions in which the assay may be intended. In reference again to the ovarian cancer model, tissue is usually available from primary debulking surgery, and an assay may be run on tissue from the primary, and a metastatic site to determine a rational drug choice at primary therapy. However, when the tumor recurs, does it retain the same phenotype? In addition, does acquired resistance from previous therapy alter subsequent assay allocations with other agents? For instance, would a recurrent ovarian cancer patient, not previously resistant to doxorubicin, but failing second-line paclitaxel, now become so in the acquiring of this drug-resistant phenotype? Likely, additional information such as molecular profiling will be needed to make better predictive inferences. Third, clinical trials evaluating the technology will need to take into account the likelihood that the assay-directed therapy will pick the empiric choice, or a regimen with fractionally lower response probability. In disease sites where the proportion of difference is less than 25%, a significant increase in patient numbers will need to be enrolled, unless the assay-directed survival difference is large (not likely). Likewise, if drug A is the most sensitive, and produces a response rate of 50%, but drug B (empiric) produces a response rate of 45%, large accrual cohort will be needed, and a decision as to whether this difference is clinically meaningful will need to be addressed. Since in many gynecologic cancers the number of active agents may be considerable, the number of combinatorial options produces a highly complex and factorial set of possibilities; some up front prioritization will need to be determined for trial design. Lastly, in the event that no agent is active in a particular patient, clear validation of the assay's predictive nature needs to be explored. Potential for harm may be present in the event a patient is denied standard therapy based on an invalidated negative assay result.

Table 1

Description of Available Chemotherapy Sensitivity/Resistance Assays

Assay Name	Description
Subrenal capsular assay	Human tumor specimens are cultured in the subrenal capsule of mice. Tumor growth in mice is measured following treatment with various drugs or saline to determine drug sensitivity.
Human tumor cloning assay; Capillary cloning system	Single cell suspensions prepared from patients' tumors are cultured in vitro for several weeks. The colony-forming effi ciency of these cells in the presence and absence of various drugs is evaluated to determine drug sensitivity.
Differential staining toxicity	Tumor cells are cultured in vitro in the presence or absence of 3 concentrations of drugs. After a 6-day incubation, differential dye staining is used to identify viable cells and determine drug sensitivity.
Methylthiazolyl-diphenyltetrazolium bromide (MTT)	Tumor cell suspensions are cultured with various chemotherapy agents for 4 days. MTT is added because it reduces intracellularly to a blue dye, the intensity of uptake yields an estimate of the number of viable cells to determine drug sensitivity
Adenosine triphosphate bioluminescence	Tumor cells are cultured in the presence or absence of test drugs, and then the cells are analyzed. The amount of ATP, a reflection of the number of viable cells, is measured by adding luciferin. Low ATP concentration manifests as low luminescence to identify efficacious test drugs.
Extreme Drug Resistance	After successful culture, tumor cells obtained from fresh biopsy specimens are labeled with tritiated thymidine. The level of uptake is tracked after exposure to chemotherapy concentrations that approximate the peak level achieved clinically. Extreme resistance is identified when thymidine incorporation is inhibited in the presence of the drug by less than one standard deviation of the median cell inhibition measured for several hundred reference tumor samples.
Precision therapeutics	Tumor cells are isolated, cultured and plated in wells exposed to 6 different clinically achievable drug concentra tions. After washing non-adherent cells from the wells, the remaining cells are fixed and stained. Percentage of cell death in reference to drug concentration is used to allocate sensitivity.
Rational therapeutics	Tumor cells are isolated from fresh tissue and cultured ex vivo. Median drug concentrations needed to achieve 50% cell kill in culture [IC50] are evaluated to assign sensitivity.

FINAL THOUGHTS

The appeal of developing a tailored therapeutic program that offers a patient the best chance to live the longest or cure their disease is great, and will always drive the search for inventing a better cog in the decision process over empirical therapy. It is time to incorporate these assays into a well-designed clinical trial, preferably randomized with attention paid the challenges outlined above. Simplification, sophistication, and availability

at a reasonable cost will be necessary, as well for the assay-directed approach to enter mainstream cancer care. Development in genomics and proteomics, as well as microarray technologies will likely also help solve this clinical puzzle.[9] ■

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CME Question

9. In patients with metastatic breast cancer, which of the following best predicts disease-free progression and overall survival?

a. HER2/neu status of the primary tumor
b. Estrogen-receptor status of the primary tumor
c. Type of adjuvant therapy
d. Circulating tumor burden before treatment
e. Circulating tumor burden after treatment

Answer: 9. (e)

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OB/GYN Clinical Alert — October 2003

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Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			97	97

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2003 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Brenda L. Mooney, Publisher — Date: 9/30/03

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PHARMACOLOGY WATCH

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

The FDA and Merck Fielding Concerns About Vioxx

Merck announced on September 30th that it is voluntarily withdrawing rofecoxib (Vioxx) from the worldwide market. The decision was based on data from the APPROVe (Addenomatous Polyp Prevention on Vioxx) trial, a company sponsored perspective randomized, placebo-controlled trial designed to assess whether the drug reduces the risk of colorectal polyps in patients with a history of colorectal adenomas. However, after 18 months of the study, patients on 25 mg of rofecoxib were noted to have an increased risk of cardiovascular events such as myocardial infarction and stroke, compared to those patients taking placebo. The FDA supported Merck's action and acknowledged that, while the risk to any individual on rofecoxib is small, the risk increases with continued use. The APPROVe trial showed that the risk of cardiovascular events with rofecoxib was twice that of placebo, according to information published on the FDA News website (fda.gov/bbs/topics/news/2004/NEW01122.html). Previous studies, including a recently reported Kaiser Permanente/FDA retrospective trial, showed the risk to be 3 times that of placebo. The FDA is investigating whether cardiovascular risk may be a class effect of COX-2 inhibitors (coxibs), and is reviewing data from similar trials with celecoxib (Celebrex) and valdecoxib (Bextra). Meanwhile, Merck is initiating a buy-back program for unused Vioxx prescriptions, reimbursing patients for their unused prescriptions. The withdrawal has enormous implications for the company and its shareholders, not only from the loss of nearly $2 billion in revenues from drug, but lost share value for the company stock and the risk of future legal action. It is estimated that 2 million patients in the United States were taking Vioxx at the time of the withdrawal, and over 84 million people worldwide have taken drug at some point since its approval in May 1999. The October issue of the *New England Journal of Medicine* has 2 scathing reviews of Merck and the FDA with regard to the approval and marketing of rofecoxib. Dr. Eric Topol of The Cleveland Clinic, who was one of the first to raise concerned about rofecoxib, calls for a full Congressional review of this case. The senior executives at Merck, and the leadership of the FDA, share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health (*N Engl J Med.* 2004;351:1707-1709). Dr. Garrett FitzGerald of the University of Pennsylvania suggests evidence has been there all along that coxibs, including celecoxib and valdecoxib, may promote cardiovascular disease by blocking prostaglandin I2, which inhibits platelet aggregation, promotes vasodilation, and prevents the proliferation of vascular smooth muscle cells in vitro. At the same time, coxibs have little effect on thromboxane A2, which is responsible for platelet aggregation.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com.

Traditional NSAIDs and aspirin block thromboxane production, accounting for their cardioprotective effects. Dr. FitzGerald states, "It is essential to determine whether cardiovascular risk is or is not a class effect." The burden of proof now rests with those who claim that this is a problem for rofecoxib alone, and does not extend to other coxibs." (*N Engl J Med*. 2004;351:1709-1711).

Erythromycin and the Risk of Sudden Death

Erythromycin may be associated with an increased risk of sudden death, according to new study in the *New England Journal of Medicine*. Oral erythromycin, which is extensively metabolized by cytochrome P-450 3A (CYP3A), prolongs cardiac repolarization, and has been associated with reports of torsades de pointes. Commonly used medications that inhibit CYP3A may increase plasma erythromycin levels, increasing the risk of ventricular arrhythmias and sudden death. Researchers from Vanderbilt reviewed data from a Tennessee Medicaid cohort that included more than 1.2 million person-years of follow-up and 1476 confirmed cases of sudden death from cardiac causes. The patients in the study were relatively young, with a mean age of 45. Seventy percent were female, and 58% were white. The multivariate adjusted rate of sudden death from cardiac causes among patients using erythromycin was twice as high as that among those who had not used any of the study antibiotic medications (incident-rate ratio 2.01; 95% CI, 1.08-3.75; $P = 0.03$). There was no increase in sudden death among patients using amoxicillin, or former users of erythromycin. For patients who were taking erythromycin with concurrent use of a CYP3A inhibitor (nitroimadazole antifungal agent, diltiazem, verapamil, or troleandomycin), the adjusted rate of sudden death was 5 times as high (incident rate ratio 5.35; 95% CI, 1.72-16.64; $P = 0.004$). The authors conclude that erythromycin should be avoided in patients who are taking CYP3A inhibitors (*N Engl J Med.* 2004;351:1089-1096).

Vaccine Shortage Putting Americans At Risk

Just as healthcare providers are about to start their annual flu vaccination program, British regulators have shut down Chiron Corporation's Liverpool flu vaccine manufacturing plant due to sterility problems. Chiron was expected to supply nearly 50 million doses of vaccine this year, half of the hundred million doses health officials expected to be administered to Americans this fall. Aventis, the other major supplier of vaccine, has told health officials that he could produce an additional million doses this year, but no more. Compounding the shortage, is the addition of 2 groups of patients recommended to receive the vaccine this year—children between the ages of 6 and 23 months (who require 2 doses 1 month apart) and pregnant women (or women who anticipate being pregnant during the flu season). Other high-risk patients include people over age 65, people in nursing homes, people with chronic illnesses, and those caring for people in these groups. Healthcare workers are also considered the highest priority for vaccination. The nasal flu vaccine, FluMist, does little to alleviate the shortage since it is only indicated for healthy children and adults between the ages of 5 and 49 years.

FDA Actions

The FDA will move ahead with warnings for many antidepressants stating that the drugs sometimes raise the risk of suicidal behavior in youth. The recommendation comes after an agency advisory panel, on a split vote, recommended a Black box warning. The agency may not go that far, however, since some advisors were concerned that warnings may discourage treatment of depressed children and teens who can benefit from antidepressants medications. The drugs subject to the warning are those with the brand names Prozac, Paxil, Wellbutrin, Zoloft, Celexa, Effexor, Luvox, and Remeron.

The recently approved antidepressant duloxetine (Cymbalta) has received FDA approval for treatment of pain associated with diabetic neuropathy. This is the first drug approved for this indication in this country. In 2 studies submitted to the FDA, the drug reduced 24-hour average pain levels, compared with placebo, in patients who had diabetes for an average of 11 years, and had neuropathic pain for average of 4 years.

The FDA has approved a new extended release formulation of hydromorphone for the management of persistent moderate-to-severe pain in patients requiring continuous, round-the-clock opioid pain relief for extended periods of time. The product is an extended release formulation that can be dosed once a day, and will be available in 12, 16, 24, and 32 mg capsules. The drug is only recommended for patients already receiving opioid therapy who have demonstrated opioid tolerance, and who require a minimum total daily opioid dose equivalent to 12 mg of oral hydromorphone. It will be marketed by Purdue pharmaceuticals with the trade name Palladone.