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INSIDE

Capecitabine and Vinorelbine in Elderly Patients (Older than 65 years) with Metastatic Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *This regimen of capecitabine and vinorelbine is well tolerated and effective in elderly patients with metastatic breast cancer. Toxicity was mainly hematological and was observed at a lower dose in patients with bone involvement. A phase II study with the 2 different dose levels for elderly patients with and without bone involvement is currently being conducted.*

Source: Hess D, et al. *Ann Oncol*. 2004;15:1760-1765.

Elderly women are more likely than younger patients to have breast cancer that will metastasize. They are, however, less likely to be offered chemotherapy and radiation therapy treatment and are significantly underrepresented in prospective clinical trials.[1] One study from 3000 postmenopausal women treated for invasive breast cancer in the adjuvant setting showed that only 6.4% of patients older than 75 years had been offered chemotherapy and only 34.7% received standard radiotherapy after lumpectomy.[2] Only a few chemotherapy combinations have been designed for the specific needs of older patients, especially with regard to toxicity profile. In the adjuvant setting, chemotherapy regimens including cyclophsophamide, methotrexate, and 5-fluorouracil or doxorubicin appear to have similar or inferior efficacy in elderly patients, even though the cost in terms of toxicity is considerably higher.[3]

One of many possible solutions is developing low toxicity combinations from tolerable drugs without overlapping toxicity. Vinorelbine has been tested in several phase II trials in older patients (older than 65 years) with metastatic breast cancer and advanced non-small cell lung cancer. Capecitabine has also been extensively evaluated. In pretreated patients with advanced breast cancer, grade 3/4 diarrhea occurred in 10% treated with 2500 mg/m^2 per day for two weeks, followed by one week of rest. In combinations with taxanes, the safe dose of capecitabine seems to

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be 825 mg/m^2 per day for 14 days. This paper presents data from a phase I trial of the combination of capecitabine and vinorelbine. There have been few phase I studies in older patients.

COMMENT BY STUART M. LICHTMAN, MD

The eligibility for this trial was patients older than 65 years with metastatic breast cancer without prior chemotherapy for metastatic disease. The study was stratified for patients with and for patients without bone involvement. Standard phase I eligibility criteria were required. During the course of the trial, an amendment was added requiring that patients with a calculated creatinien clearance between 30 and 50 mL/min should receive 75% of the capecitabine dose. There were 36 patients on study with an age range of 65-85 years. Fifteen patients had bone involvement and 21 patients had no bone involvement. Visceral disease was present in 61% of all patients. The starting dose level was capecitabine 800 mg/m^2 two time daily and vinorelbine 20 mg/m^2 on days 1 and 8. In total, 69 cycles were administered to the 15 patient with bone involvement (mean, 4.6 per patients) and 96 cycles to the 21 patients without bone involvement (mean, 4.5 per patient). Hematologic side-effects were the most common toxicity with this regimen and were responsible for all but one dose limiting toxicity. Patients with bone involvement and patients older than 70 years, irrespective of bone involvement, were more prone to hematologic toxicity. Patients without bone involvement had a greater tolerance, and dose limiting toxicities were seen at a higher dose level. Non-hematologic toxicity was mostly moderate. Hand-foot syndrome was not observed, possibly due to the lower doses of capecitabine and that the number of cycles were limited. One grade 3 diarrhea and stomatitis was seen in the group with creatinine clearance between 50 and 80 mL/min. The hematologic toxicities were seen with a trend towards the patients with impaired renal function. Responses were seen at all dose levels. The response rate for patients with bone involvement was 53% and for patients without bone involvement was 48%.

The combination of 5-FU and vinorelbine has been studied in advanced breast cancer and has shown activity.[5] The combination of capecitabine and vinorelbine has been studied in metastatic breast cancer in younger patients. One studied treated 30 patients with capecitabine 825 mg/m^2 twice daily for days 1-14 and vinorelbine 25 mg/m^2 days 1 and 8 as first-line chemotherapy. The median age was 54 years. Another trial reported 32 patients with a median age of 52 years who had been pretreated with anthracyclines and/or taxanes. They found dose limiting toxicity on the dose level with capecitabine 2000 mg/m^2/day for days 1-14 and days 22-35 and vinorelbine 25 mg/m^2 days 1 and 5 and days 22 and 29 out of 42 days. Neutropenia was the main toxicity.[6,7] In the present trial for patients with bone metastases the recommended dose was defined with capecitabine 1000 mg/m^2 and vinorelbine 20 mg/m^2. For patients without bone metastases the doses were capecitabine 1250 mg/m^2 and vinorelbine 20 mg/m^2. These results show that elderly patients have a reduced bone marrow tolerance towards these agents. It emphasizes that study results on the tolerability of chemotherapy obtained in an average study population cannot always be transferred to an older breast cancer population often seen in daily practice.

This study also emphasizes that phase I studies specifically for older patients may increase the safety of their treatment by determining the appropriate, and often lower, dose. Under-representation in clini-

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cal trials is common. One study found that while 63% of people in the general population age 65 or older had cancer, only 25% of patients in that age group were represented in clinical trials.[8] One of the reasons for this may be physicians not offering clinical trials. It has been determined that while physicians asked 51% of patients younger than 65 years, only 35% of patients older than 65 were offered to participate in clinical trials.[9] In most cases, physician bias stemmed from the assumption that older people cannot tolerate chemotherapy or that the risks of therapy are not worth the benefits. This leads to poor representation of elderly patients in clinical trials, which unfortunately does not adequately represent the population developing cancer. When the number of patients who entered clinical trials was compared with the estimated number of patients with cancer in each decade of age, the under-representation was striking. More than half of children aged 5 to 9 years are accrued to NCI-sponsored clinical trials compared with less than 1% of adults aged 75 to 79 years of age. Among adults, those 80 years of age or older are least likely to be enrolled. For example, the publication of the recent adjuvant colon cancer trial of oxaliplatin, leucovorin and 5-fluorouracil had patients with a median age of 61 years, which is more than a decade younger than the median age of the disease in the general population. This highlights the information gap facing the practicing clinician.[10] There is a need for clinical trials specifically for elderly patients. In particular more phase I trials in the elderly are needed to enhance the safety and efficacy of care for this vulnerable population. ■

References

1. Talarico L, et al. *J Clin Oncol*. 2004;22:4626-4631.
2. Curigliano G, et al. *Proc Am Soc Clin Oncol*. 2003; 22:3065a.
3. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1992;339:1-15.
4. Hess D, et al. *Ann Oncol*. 2004;15:1760-1765.
5. Berruti A, et al. *J Clin Oncol*. 2000;18:3370-3377.
6. Welt A, et al. *Ann Oncol*. 2002;13(suppl 5):202p.
7. Kattan J, et al. *Ann Oncol*. 2002;13(suppl 5):201p.
8. Hutchins LF, et al. *N Engl J Med*. 1999;341: 2061-2067.
9. Kemeny MM, et al. *J Clin Oncol*. 2003;21:2268-2275.
10. Andre T, et al. *N Engl J Med*. 2004;350:2343-2351.

Efficacy of a Bivalent L1 Virus-Like Particle Vaccine in Prevention of Infection with Human Papillomavirus Types 16 and 18 in Young Women

ABSTRACT & COMMENTARY

Synopsis: *The bivalent HPV vaccine was efficacious in prevention of incident and persistent cervical infections with HPV-16 and HPV-18, and associated cytological abnormalities and lesions. Vaccination against such infections could substantially reduce incidence of cervical cancer.*

Source: Harper D, et al. *Lancet*. 2004;364:1757-1765.

The most important clinical manifestation of persistent human papillomavirus (HPV) infection is development of uterine cervix cancer. Worldwide this preventable cancer continues to be a dominant killer and a significant contributor to years of life lost in women. Two years ago efficacy of a monovalent vaccination program was demonstrated against the most common oncogenic HPV type, HPV-16. In the current report, Harper and colleagues report efficacy, safety, and immunogenicity of a bivalent HPV-16/18 L1 virus-like particle (VLP) vaccine. Outcome measures were the prevention of incident and persistent infection with these 2 virus types, associated cervical cytological abnormalities, and development of precancerous lesions. In this study, 1113 women between 15 and 25 years of age participated in this randomized, double-blind, placebo-controlled trial. All were required to be negative for HPV infection at enrollment.

The primary outcome measure was HPV-16/18 infection between 6 and 18 months after enrollment. Participants received 3 doses of either the vaccine formulated with AS04 adjuvant or placebo on a 0 month, 1 month, and 6 month schedule in North America and Brazil. Women were assessed for HPV infection by cervical cytology and self-obtained cervicovaginal samples for up to 27 months. Vaccine safety and immunogenicity were also evaluated. Among women who received all 3 doses, vaccine was 92% effective against incident infection and 100% effective against persistent infection with HPV-16/18. In the intention-to-treat analyses, vaccine efficacy was 95% against

persistent cervical infection with HPV-16/18 and 93% against cytological abnormalities associated with HPV-16/18 infection. The vaccine was safe, generally well tolerated, and highly immunogenic. Harper et al concluded that the bivalent HPV vaccine can prevent incident and persistent cervical infections with HPV-16 and HPV-18, and their associated cytological abnormalities and lesions. Widespread vaccination programs against these infections could substantially reduce incidence of cervical cancer.

COMMENT BY ROBERT L. COLEMAN, MD

The causal link between HPV infection and development of uterine cervix cancer is now well established and represents an important association underlying developmental therapeutics directed at reducing incident disease. In countries with well-established screening programs for HPV and its associated cervical precancerous pathologies, impressive reductions in disease-specific mortality are the fruit of these initiatives. However, most of the world's incident cancers are located in countries with little capacity for national screening efforts and affected women experience greater reductions in life expectancy from cervix cancer than complications associated with HIV, pregnancy, and tuberculosis. Even in countries where limited screening does exist, follow-up care, whether it be for treatment or repeat cytology, is even more limited and efforts to gain greater compliance are unlikely to make a measurable difference in incident disease. Clearly the cliché, "An ounce of prevention is worth a pound of cure. . ." is relevant and such an effort would be particularly life saving.

In a 2002 landmark article in the *New England Journal of Medicine*, Koutsky and colleagues demonstrated the merits of a vaccination program against HPV-16 with a monovalent L1 virus-like particle vaccine.[1] Given the association of this viral subtype in more than 60% of cervical cancers, this target was valid. The highly anticipated results demonstrated a clear benefit for 768 vaccinated women against persistent infection and associated cervical dysplasia. In the current well-conducted trial, a bivalent vaccine was used in a similar manner, targeting both HPV-16 and HPV-18. While the addition of HPV-18 represents only about an additional 10-15% of cancers, it is an important addition, as this viral subtype is associated with adenocarcinoma and its precursor lesions. Typically, these are more difficult to screen by Pap smear and represent and important increasingly recognized cohort.

The efficacy of the vaccine in preventing incident disease, reducing persistence of HPV infection (a recognized necessary component in the pathogenesis of cancer) and preventing cytological abnormalities is proof-of-principle and a critically important advance in this regard. Indeed, the one cytological abnormality identified in the vaccinated cohort was judged a result of a viral subtype (HPV-51) not vaccinated against. The measured acute immunogenicity brought about by the vaccine was hundreds of fold higher than that produced by a native infection and persisted as several folds higher for the duration of the trial.[2,3]

These latter 2 points represent some of the important questions that must be addressed as these products undergo further development. For instance, how many different HPV subtypes should be included? What effect will HPV infections with subtypes not immunized against have on clinical outcomes? How long will the immunity last? When should a booster be given? Will vaccination be efficacious in the treatment of known disease? When should first immunization be undertaken? Should both men and women be vaccinated? How do you roll out a national vaccination program? Answers to these questions will likely be answered in the years to come. Our distinct hope is that a global effort will be extended in eradicating this "preventable" cancer. ■

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

References

1. Koutsky LA, et al. *N Engl J Med*. 2002;347:1645-1651.
2. Pinto L, et al. *J Infect Dis*. 2003;188:327-338
3. Munoz N, et al. *Int J Cancer*. 2004;111:278-285.

Raloxifene and Breast Cancer: The CORE Study

ABSTRACT & COMMENTARY

Synopsis: *Raloxifene treatment of postmenopausal women with osteoporosis is associated with a lower incidence of estrogen receptor-positive invasive breast cancer.*

Source: Martino S, et al. *J Natl Cancer Inst*. 2004;96: 1751-1761.

MARTINO AND COLLEAGUES REPORT THE RESULTS OF the Continuing Outcomes Relevant to Evista

(CORE) trial, on the incidence of breast cancer. The MORE trial, the Multiple Outcomes of Raloxifene Evaluation trial, was a randomized, double-blind, multicenter clinical study of postmenopausal women with osteoporosis that reported a 72% reduction in estrogen receptor-positive invasive breast cancer in the treatment group after 4 years compared to placebo. The CORE study was designed to measure the impact of 4 additional years of raloxifene (60 mg/d), to begin during the fourth year of the MORE trial. Of the 7705 participants initially randomized in the MORE trial, 3510 women elected to continue raloxifene treatment (2336 completed the CORE trial) and 1703 continued on placebo (1106 completed the trial). During the 4-year CORE study, raloxifene treatment was associated with a 66% (HR = 0.34; CI = 0.18-0.66) reduction of estrogen receptor-positive invasive breast cancer in the treated group. There was no difference in estrogen receptor-negative tumors. Over the entire 8-year period, the reduction in estrogen receptor-positive cancers reached 76%. In the 8-year period, there was no difference in the number of deaths in the 2 groups.

COMMENT BY LEON SPEROFF, MD

Overall, these results support a preventive effect of raloxifene treatment on the incidence of estrogen receptor-positive invasive breast cancer. The strength of this observation, however, can be questioned because of some problems within the study. One concern is the fact that the beginning of the CORE trial did not exactly coincide with the end of the MORE trial. From the end of the first 4-year study to the beginning of the next 4-year study, participants were not involved in study regulation for a time period that ranged from 2.6 to 62 months. During this interval, some participants experienced a long period without exposure to raloxifene, others used a standard regimen of hormone therapy, and those who experienced an adverse event, including breast cancer during this interval were excluded from the study. The characteristics of this interval and the impact on the results are issues essentially not addressed in this report.

The reduction in breast cancer observed in the 4 years of the MORE trial continued during the 4 years of the CORE study, and it is possible that the results in the second 4-year period reflect the effect of the initial 4 years. At the same time, the results are compatible with an ongoing impact beyond 4 years. Although the percentage of reduction is impressive, keep in mind that the actual numbers are not large: 21 cases of estrogen receptor-positive cancers in the placebo group and 15 in the treated group. In the entire 8-year period, the numbers added up to 58 in the placebo group and 40 in the treated group.

It is impossible to determine if there is a special high-risk group for whom this treatment is recommended. At the beginning of the CORE study, the women were assessed with the Gail breast cancer risk model. There was no difference between the treatment and placebo groups Gail predicted risk (about half were considered to be at high risk).

If medical treatment is truly preventive, one would expect to see a reduction in noninvasive breast cancer in the treated individuals. In the CORE trial there were only 9 cases (2 in the placebo group and 7 in the treated group) and in the 8-year period only 7 cases in the placebo group and 16 in the treated group, a number too small to allow confident analysis. On the other hand, an effect only on invasive disease without an effect on noninvasive disease keeps the possibility alive that raloxifene is affecting preexisting tumors. In contrast, a reduction in noninvasive disease has been reported with the preventive use of tamoxifen.[1] One might conclude that the different results with tamoxifen and raloxifene reflect the risk level of disease in the 2 populations studied, high risk for breast cancer in the tamoxifen studies and low risk in the raloxifene osteoporosis study. However, as noted, assessment of breast cancer risk with the Gail model in the raloxifene study indicated that at least half of this population was also at high risk of breast cancer.

The evidence supports tamoxifen reduction of the risk for estrogen receptor-positive breast cancer, but at the same time, tamoxifen should not be recommended as a preventive agent, except for women at very high risk. This conclusion is based upon the degree of reduction in risk compared with the incidence of side effects. The evaluation by the National Cancer Institute is very helpful.[2,3] Because the risks associated with tamoxifen (endometrial cancer, stroke, pulmonary embolism, and deep vein thromboembolism) increase with age, balancing the risks and benefit indicates that tamoxifen is best for younger women with an elevated risk of breast cancer (an increased relative risk of approximately 1.7). A similar conclusion was reached by a working group of the American Society of Clinical Oncology.[4] This means that only a relatively small number of women qualify, about 5% of American white women and 0.6% of black women.[3]

The data are too limited to support the use of raloxifene as prophylactic treatment, and a stronger position awaits the outcome of the STAR trial comparing tamoxifen with raloxifene and the RUTH trial assessing the effect of raloxifene on both cardiovascular disease and breast cancer. The Medical Research Council of the United Kingdom and the National Cancer Institute of the United States have reached similar conclusions.

It is well-recognized that raloxifene shares with tamoxifen and estrogen about a two-fold increase in venous thrombosis. However, the increase observed in the 8 years of the combined MORE and CORE population did not achieve statistical significance, a problem of relatively small numbers because of the infrequency of this event. It is noteworthy that the 9 cases of pulmonary embolism all occurred in the raloxifene group. ■

Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health Sciences University; Portland, Ore.

References

1. IBIS INVESTIGATORS. *Lancet*. 2002;360:817-824.
2. Gail M, et al. J Natl Cancer Inst. 1999;91:1829-1846.
3. Freedman A, et al. *J Natl Cancer Inst*. 2003;95: 526-532.
4. Chlebowski R, et al. *J Clin Oncol*. 2002;20:3328-3343.

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 end points 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.

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.

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] ■

References

1. Loizzi V, et al. *Am J Obstet Gynecol.* 2003;189: 1301-1307.
2. Gazdar AF, et al. *J Natl Cancer Inst.* 1990;82:117-124.
3. Stratton JA, et al. *Gynecol Oncol.* 1984;19:336-347.
4. Greenberg PL, et al. *Cancer Res.* 1977;37:1794-1799.
5. Heppner GH, et al. *Cancer Res.* 1978;38:3758-3763.
6. Schrag D, et al. *J Clin Oncol.* 2004;22:3631-3638.
7. Samson DJ, et al. *J Clin Oncol.* 2004;22:3618-3630.
8. Sorbe B. *Int J Gynecol Cancer*. 2004;14:788-793.
9. Tanaka T, et al. *Int J Cancer*. 2004;111:617-626.

CME Question

1. **The following statements are true regarding raloxifene treatment and the risk of breast cancer *except*:**
   a. Raloxifene decreases the incidence of postmenopausal breast cancer in-situ.
   b. It is premature to recommend raloxifene for the prevention of breast cancer.
   c. The effect of raloxifene appears to be limited to postmenopausal estrogen receptor-positive, invasive breast cancer.
   d. There is no reason to believe that raloxifene, tamoxifen, and estrogen differ in their effect on the risk of venous thrombosis.

Answer: 1. a

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PHARMACOLOGY WATCH

Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

GEMINI Trial

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

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.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.