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INSIDE

European Trial Demonstrates Reduced Survival in Erythropoietin-Treated Head and Neck Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: *In a multicenter trial of anemic head and neck cancer patients, recombinant human erythropoietin (epoetin b) or placebo were administered as adjuncts to radiation therapy. As expected, hemoglobin levels rose in the epoetin-treated patients, but locoregional control and survival were diminished. This surprising result warrants prompt confirmatory study and expanded investigation to determine mechanism.*

Source: Henke M, et al. *Lancet*. 2003;362:1255-1260.

THE TREATMENT OF ANEMIA HAS BECOME COMMON PRACTICE IN the overall treatment of cancer patients, due in a large part to the prior demonstration of increased quality of life of treated patients demonstrated in large clinical trials. Because the presence of anemia is associated with poorer outcomes of therapy, there was a question of whether those patients in whom anemia was corrected by recombinant human erythropoietin (rHuEPO) would have more favorable responses to specific anti cancer treatments. In a recent multicenter trial, the opposite was observed.

Henke and colleagues performed an industry-sponsored multicenter, double-blind, placebo-controlled trial in which 351 anemic patients with carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were randomized to receive rHuEPO (epoetin β) or placebo. To qualify as anemic, hemoglobin level for women patients was < 12 g/dL and for men was < 13 g/dL. Epoetin β was administered at a dose of 300 IU/kg 3 times weekly. The primary end point was locoregional progression-free survival, and the analysis was by intention to treat.

Of the 148 patients treated with epoetin b, 82% achieved hemoglobin concentrations 14g/dL (women) or 15 g/dL (men). For comparison, only 15% of those receiving placebo were observed to have hemoglobin concentrations at that level. However, locoregional progression-free survival was poorer with epoetin b than with placebo

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(adjusted relative risk, 1.62 [95% confidence interval, 1.22-2.14]; P = .0008). For locoregional progression, the relative risk was 1.69 (1.16-2.47, P = .007) and for survival was 1.39 (1.05-1.84, P = .02). The univariate Kaplan-Meier estimate showed a median locoregional progression-free survival of 754 days for placebo compared with 406 days for epoetin b (P = .04).

Prior to randomization, patients had been stratified by extent of disease, and the planned radiation dose was greater for those with more extensive disease. Overall, the baseline characteristics and demographic data, as well as tumor and treatment features, were well balanced between placebo and treatment groups. Analysis by extent of disease revealed the negative effect of epoetin b treatment in terms of locoregional control and survival for all but those with limited disease.

Overall, 52% of patients in the placebo group and 61% in the epoetin b group died. Of these, 5 placebo and 10 epoetin β patients died from cardiac disorders and 1 placebo and 9 epoetin b patients from general (not cancer) disorders. Toxicity was slightly higher in the epoetin b treatment arm, with 4% vs 7% judged as having drug-related adverse events.

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COMMENT BY WILLIAM B. ERSHLER, MD

Thus, although epoetin β administration was successful in raising hemoglobin concentrations in the great majority of treated patients, this was not associated with favorable outcomes in terms of tumor control or survival. In fact, the opposite appears to be true. The trial methodology was sound, the experimental groups were well balanced, and, accordingly, it is unlikely that a flaw in study design or conduct can explain the findings. This result clearly runs contrary to what was expected and raises a cautionary flag to the low threshold use of rHuEPO in anemic cancer patients.

The basis for the widespread clinical use of rHuEPO was the demonstrated enhanced quality of life in treated patients.[1,2] The effect on tumor biology and clinical outcomes and survival had not, previously, been the focus of attention. Yet, for head and neck cancer, the pretreatment presence of anemia is known to be a negative prognostic factor in terms of locoregional control and survival,[3] and it was a logical step to anticipate more favorable outcomes in treated patients. Erythropoietin, may, however, have tumor-enhancing properties, by directly stimulating tumor cells known to have erythropoietin receptors,[4] inhibiting tumor cell apoptosis,[5,6] or enhancing angiogenesis.[7]

As with many important clinical trials, the findings raise important questions. Is this a phenomenon specific for squamous cell carcinoma, tumors in the head and neck region, or those treated by relatively high doses of radiation? Or is this a more general occurrence? Additional research to address these questions is of high priority. The concern, however, is who will fund such research? Which cooperative group will take the lead, and how quickly will we get some answers? Until that time when more answers are available, clinicians will need to balance the quality-of-life issue with the potential for enhanced tumor growth when treating anemic cancer patients. ■

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Bone Marrow Transplant Registry Data on Treatment of Follicular Lymphoma

ABSTRACT & COMMENTARY

Synopsis: *Follicular lymphoma is considered incurable by standard chemotherapeutic approaches, but speculation has arisen that more intensive therapy followed by allogeneic or autologous transplants may produce more durable remissions and possibly cures. In this analysis of bone marrow transplant registries, an attempt was made to determine which of the transplant strategies (allogeneic, purged autologous, or unpurged autologous) results in the most favorable outcomes. From this large data set of patients transplanted in the 1990s, it was apparent that transplant-related mortality was higher for those receiving allogeneic transplant, but relapses were fewer. Overall, the 5-year survival was comparable, approximating 50% in each group. Thus, bone marrow transplant remains an excellent option for patients with follicular lymphoma. However, when and which type of transplant are variables that need to be determined by future clinical trial.*

Source: van Besien K, et al. *Blood*. 2003;102: 3521-3529.

Follicular lymphoma is oftentimes clinically indolent but considered incurable by standard chemotherapy regimens. However, autologous stem cell transplantation has been shown in several phase II studies to induce remissions in patients with recurrent or newly diagnosed disease, and the speculation is that some of these may have been cured.[1] Furthermore, after allogeneic transplant, disease recurrence rates have been low, but treatment-related mortality has been high.[2-4] In the current report from the Lymphoma Working Committee of the International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry, the data from 904 patients undergoing transplantation for follicular lymphoma were presented. A total of 176 (19%) received allogeneic, 131 (14%) received purged autologous, and 597 (67%) received unpurged autologous transplants. Five-year treatment-related mortality rates were 30%, 14%, and 8%, and 5-year recurrence rates were 21%, 43%, and 58% after allotransplantation, purged autotransplantation, and unpurged autotransplantation, respectively.

In multivariate analyses, allotransplantaion had higher treatment-related mortality and lower disease recurrence. Purged autotransplantation had a 26% lower recurrence risk than unpurged autotransplantation. Five-year probabilities of survival were 51%, 62%, and 55% after allogeneic, purged autotransplantation, and unpurged autotransplantation, respectively. Advanced age, prolonged interval from diagnosis to transplantation, high lactic dehydrogenase (LDH), refractory disease, bone marrow involvement, and low performance scores were associated with adverse outcomes.

There was no association of acute or chronic graft-vs-host disease and recurrence after allotransplantation. van Besien and colleagues concluded that both allogeneic and autologous transplantation can induce durable remissions and suggest that there may be a benefit to graft purging in autologous transplantation. The decreased recurrence after allotransplantation is offset by increased treatment-related mortality.

COMMENT BY WILLIAM B. ERSHLER, MD

There has not been consensus on how best to achieve long remissions for patients with recurrent, follicular lymphoma; transplantation currently remains a commonly chosen approach, particularly for those with recurrent or refractory disease. There remains, however, a question about which transplantation strategy is likely to provide superior outcomes. Short of a randomized, prospective study, the analysis of the transplantation registry data may be the best approach to this question.

The International Bone Marrow Transplantation Registry is a voluntary working group of more than 350 transplantation centers worldwide, whereas the Autologous Blood and Bone Marrow Registry, maintained at the same data-coordinating center in Milwaukee, captures data from more than 250 transplantation centers in North and South America. It is estimated that approximately 35% of allogeneic transplantations worldwide and 50% of autotransplantations in North and South America are therein registered. From this data set, it is reasonable to make comparisons about treatment success. These comparisons, of course, need to be considered as retrospective assessments between groups that may not be comparable, due to selection bias. For example, patients may be referred for allogeneic transplantation because of characteristics that would suggest more aggressive disease. Similarly, patients may be referred for autotransplant at an earlier stage because of perceived lower transplant-associated mortality. The biostatistical expertise at the transplant registries is well aware of these potential confounders, and the data are presented in a fair manner, and the conclusions are not overstated.

The findings are as what might be expected: 1) Allogeneneic transplantation is associated with lower recurrence rates but higher transplant-related mortality; 2) Unpurged autotransplants are associated with higher recurrence rates and lower transplant-related mortality; and, 3) Purged autotransplants are intermediate in both categories. Overall, the 5-year probabilities of survival were not significantly different for the 3 approaches (a little better than 50%).

To this reviewer, the unexpected finding from this review was the improved (lower) recurrence rate for those who received purged compared to those who received unpurged autografts. With all the technical problems associated with such procedures, the findings would imply that continued research in the fine-tuning of marrow purging regimens is a worthwhile focus for continued intensive research. ■

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EORTC Cancer in the Elderly: Task Force Guidelines for the Use of Colony-Stimulating Factors in Elderly Patients with Cancer

ABSTRACT & COMMENTARY

Synopsis: *This study outlines recent EORTC cancer guidelines in chemotherapy in the elderly.*

Source: Repetto L, et al. *Eur J Cancer*. 2003;39: 2264-2272.

Advancing age is not, in itself, a contraindication to cancer chemotherapy, but many clinicians are reluctant to use chemotherapy in elderly patients. While myelosuppression is a common adverse consequence of the administration of many standard-dose chemotherapy regimens in both young and elderly patients with cancer, increasing age is associated with increasing hematological toxicity and is a significant independent predictor of the development of febrile neutropenia.[1] This increased risk of myelosuppression may contribute to a reluctance to administer chemotherapy in the elderly patient population. Chemotherapy dose reduction or delay is often used to manage chemotherapy-induced neutropenia. This may have a negative effect on outcome. An alternative strategy is to use hematopoietic growth factors. It has been documented that elderly patients respond well to administered granulocyte-colony stimulating factor (G-CSF).[2] G-CSF has been recommended to provide cost-effective support of the first and subsequent cycles of chemotherapy in patients who have an expected incidence of febrile neutropenia—40% of whom are at high risk of infection complications or for the avoidance of further episodes of febrile neutropenia following an initial occurrence.

The National Cancer Center Network (NCCN) has recommended that routine primary prophylactic growth factors should be used in patients aged 70 years who are receiving moderately myelotoxic chemotherapy of a comparable dose intensity to 21-day cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).

The American Society of Clinical Oncology (ASCO) Committee on Guidelines for the use of Hematopoietic Growth Factors has concurred with the NCCN recommendation.[3,4] The European Organization for Research and Treatment of Cancer (EORTC) has reviewed the existing published data and has derived evidence-based conclusions on the value of CSF administration in elderly patients.

COMMENT BY STUART M. LICHTMAN, MD, FACP

The task force did electronic searches using the MEDLINE database from 1992 to March 2002 using search terms relating to different tumor types, G-CSF or GM-CSF, with a median age of 60 years. Evidence levels used by ASCO were applied to the results of the literature search to classify the data. Seven tumor types were investigated: breast cancer, colorectal cancer, non-Hodgkin's lymphoma, non-small-cell lung cancer, ovarian cancer, small-cell lung cancer, and urothelial cancer. A total of 330 references were identified, but greater than 90% were excluded during review. The major reasons for exclusions were median age younger than 60 years and a lack of direct comparison of growth factor vs non growth factor. In total, 30 papers provided evidence considered relevant by the EORTC panel. There were very few data for patients older than 70 years of age.

A metaanalysis of 8 randomized, controlled trials, not restricted to an elderly population, has confirmed the value of G-CSF in reducing the risk of febrile neutropenia, documented infection, and the need for dose-

intensity reduction.[5] The EORTC literature review highlighted a lack of well-designed clinical trials to assess the use of hematopoietic growth factors in elderly patients with cancer. The data retrieved allowed consideration of the use of prophylactic G-CSF in elderly patients with urothelial cancer, non-Hodgkin's lymphoma and small-cell lung cancer. The available evidence endorses the use of prophylactic G-CSF 5 g/kg/d to support the administration of planned doses of chemotherapy on schedule in standard chemotherapy settings and reduce the incidence of chemotherapy induced neutropenia and its sequelae. Lack of available trial data does not allow similar conclusions to be drawn for the other malignancies, but it is likely that similar benefits would accrue from the use of prophylactic G-CSF. There is no evidence that the delivery of standard-dose chemotherapy on schedule improves outcome measures. There is evidence that dose-intensification can improve outcome in elderly patients with urothelial cancer, small-cell lung cancer, and non-Hodgkin's lymphoma. Their research provided no data to support the use of prophylactic G-CSF to reduce the incidence of toxic death. There is no evidence that prophylactic G-CSF improves efficacy outcome measures, including response rates, progression-free survival, or overall survival in standard dose regimens.

The task force recommended the use of prophylactic G-CSF to support the administration of planned doses of chemotherapy on schedule and reduce the incidence of chemotherapy-induced neutropenia, febrile neutropenia, and infections in elderly patients receiving myelotoxic chemotherapy. Since febrile neutropenic events are more likely to occur during the first and second cycles of chemotherapy, prophylactic measures should be considered early in the course of treatment. They also propose primary prophylactic use of G-CSF for all elderly patients receiving curative myelotoxic chemotherapy (CHOP or CHOP-like) and a risk-adapted strategy with primary prophylactic G-CSF administration in high-risk patients, as suggested by the ASCO guidelines for all patients. Further prospective trials are urgently needed. ■

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Long Durations and Different Regimens of Hormone Therapy and Risk of Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *The data in this case-control study of combined estrogen plus progestin therapy revealed an increased risk of breast cancer, particularly invasive lobular tumor, regardless of whether the progestin component was taken sequentially or continuously. There was no increased risk of breast cancer in those exposed postmenopausally to estrogen only.*

Source: Li CI, et al. *JAMA*. 2003;289:3254-3263.

The aim of this study was to investigate the role of progestin use in the risk of postmenopausal breast cancer. Li and colleagues conducted a thorough case-control study in which hormone use was carefully ascertained. The subject population was women living in 3 counties in the Seattle-Puget Sound metropolitan area. There were 1007 control women and 975 cases of breast cancer. More than 95% of all incident cancer cases were entered into a registry. Control women were culled from the same population using HFCA records. The designation of ERT use was restricted to women who were exclusive users of ERT. The 2 groups were comparable in almost all regards except that those with breast cancer were more likely to have a family history of breast cancer and higher levels of alcohol consumption. Those diagnosed with invasive ductal breast carcinoma were more likely to have never used oral contraceptives, while those diagnosed with invasive lobular breast cancer were more likely to have used oral contraceptive for greater than 5 years.

Compared to ERT-only users, exclusive users of combined HRT (CHRT) had a 1.8-fold (CI, 1.3-2.2) increased risk of breast cancer of all types. When examined by histologic type, ever users of CHRT had an increased risk of both invasive ductal (OR, 1.5; CI, 1.1-2.0) and invasive lobular carcinoma (OR, 2.7; CI, 1.7-4.3). The increases were greatest for those using CHRT the longest. The increased risk associated with ever and current use of CHRT differed little by progestin regimen (continuous vs sequential). In contrast, the OR for current use of only ERT was 1.0 (CI, 0.7-1.3) and in those using ERT ≥ 25 years (101 cases), the OR was 1.0 (CI, 0.7-1.5).

COMMENT BY SARAH L. BERGA, MD

This study complements other WHI data[1] and buttresses the notion that the progestin component of menopausal hormone therapy may explain the excess risk of breast cancer seen in the CEE+MPA arm of the WHI. If the data from these 2 studies are true, then they suggest that we ought to be doing all that we can to minimize progestin exposure in women who take hormone therapy after menopause. If there is an increased risk of dementia as was purportedly observed in the WHI in the CEE+MPA arm, it may also be attributed to the progestin component abrogating the neuroprotective effects of estrogen or via direct effects of progestins on neurons or glia. As far as I know, there are no known benefits associated with progestin use other than protection of the endometrium from hyperplasia and cancer. Progestins cause many symptoms, including dysphoria in some and bleeding in others.

What can we do to minimize progestin exposure in postmenopausal women who want to take estrogen? For years, there were some practitioners who advocated estrogen-only use even when the uterus was intact. However, the PEPI trial demonstrated high rates of hyperplasia in women given the standard dose of CEE of 0.625 mg. This led some to suggest the use of much lower estrogen doses, in the hope that this approach would confer benefits but avoid the risk of overstimulating the endometrium. In select individuals who consent to monitoring, this plan may have merit. The use of a progestin-containing intrauterine device also has merit, although some have raised concerns that even the small amount of progestin in the circulation that results from this approach may increase the risk of breast cancer. It is also possible that not all progestin preparations carry the same risk. The study by Li et al did not specify the type of progestin used by the cases, although medroxyprogesterone acetate is by far the most commonly used progestin. With regard to the vascular bed, it appears that synthetic progestins induce vasospasm while progesterone does not. Can we expect differential tissue responses to progestins in the breast and brain as well? Only ongoing research on this topic will tell us. In summary, taken together, these 2 studies strongly link the progestin component of CHRT to the increased risk of invasive breast cancer. One could also counter that, taken together, these 2 studies exonerate estrogens, but this latter statement is more controversial. In the meantime, it is abundantly clear that we need to explore the notion that not all progestins are the same while we simultaneously explore methods to give unopposed estrogen. The concept of "chemoamelioration" of aging has merit, but we must continue to refine the approaches with an eye toward safety and enhanced efficacy. ■

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Prevention of Breast Cancer with Tamoxifen

ABSTRACT & COMMENTARY

Synopsis: *Only 5% of white women and 0.6% of black women are potential candidates for tamoxifen chemoprevention.*

Source: Freedman AN, et al. *J Natl Cancer Inst*. 2003; 95:526-532.

Freedman and colleagues from the National Cancer Institute estimated the total number of US women in the year 2000 eligible for tamoxifen treatment to prevent or defer breast cancer. Of this number, applying a benefit/risk ratio substantially reduced the number of women who could expect a benefit from treatment.

COMMENT BY LEON SPEROFF, MD

The important numbers include the following: Tamoxifen 20 mg daily for 5 years produced a 48% reduction in estrogen receptor-positive cancers, no effect on estrogen receptor-negative cancers, an increase in the relative risk of endometrial cancer to 2.4, and an increase in the relative risk of venous thrombosis to 1.9. There is still insufficient follow-up to answer 2 important questions: 1) will tamoxifen treatment yield a difference in breast cancer mortality and; 2) does tamoxifen treatment prevent or defer the diagnosis of breast cancers. It is estimated that treatment of 1000 high-risk women would produce an 18% reduction in breast cancer mortality over the ensuing 10 years.

This recent report from the National Cancer Institute serves to emphasize that because of the side effects, only a small percentage of eligible US women stand to benefit from this treatment. However, this still adds up to about 2 million women per year.

The decision to take 5 years of tamoxifen chemoprevention, therefore, is not easy. The individual patient that can anticipate an expected benefit must be carefully chosen. The patient has to balance potential benefit

against the side effects and cost. Ultimately, this difficulty means that we need a better method for prophylactic treatment, and we must continue to emphasize early detection by exam and mammography. Whether raloxifene will provide a better benefit/risk ratio than tamoxifen awaits the outcome of the STAR (Study of Tamoxifen and Roloxifene) clinical trial. The problem with aromatase inhibitors is an increase in fractures and possibly coronary heart disease. The best chemoprevention method awaits future development. ■

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Trends in Surgery and Chemotherapy for Women Diagnosed with Ovarian Cancer in the United States

ABSTRACT & COMMENTARY

Synopsis: *Despite guidelines presented by several organizations, significant numbers of women with ovarian cancer are not being provided with appropriate care.*

Source: Harlan LC, et al. *J Clin Oncol*. 2003;21: 3488-3494.

Harlan and colleagues sampled patient cases from within the Surveillance, Epidemiology, and End Results (SEER) program to examine trends in care of women with ovarian cancer. They abstracted medical records of 601 patients with ovarian cancer diagnosed in 1991 and 566 women with ovarian cancer diagnosed in 1996 to compare findings. In addition, they verified treatment data with the attending physicians. Across these 2 time periods, the percentage of women with presumptive stage I, II, and IV disease who received lymph node dissection increased. However, a significant number still were not precisely staged. More than 65% of women with ovarian cancer were given cyclophosphamide in 1991 compared with about 14% in 1996. Paclitaxel use increased from 1% to 62% during that time. After adjusting for age, race or ethnicity, registry, income, insurance status, Charlson score, residency training program, and marital status, women with early stage disease were significantly more often given National Institutes of Health Consensus Development Conference guideline therapy in 1996 than in 1991. However, for women with stage III and IV disease, the use of guideline therapy did not significantly increase. Older women and minorities consistently received less guideline therapy, and lack of private insurance was an impediment for both Hispanic and non-Hispanic black women.

Harlan et al concluded that, despite guidelines presented by several organizations, significant numbers of women with ovarian cancer are not being provided with appropriate care. This was particularly true for older and minority women, especially those without private insurance. They recommended that educational strategies be devised to increase the number of women receiving guideline therapy and decrease disparities across population groups.

■ COMMENT BY DAVID M. GERSHENSON, MD

Ovarian cancer remains the most challenging of the gynecologic malignancies, with the highest death rate. Patients treated in a hospital with a residency program were more likely to having appropriate treatment compared with patients treated in a hospital without a residency program. For stage I and II patients, this was principally related to have lymph node sampling as part of surgical staging. Furthermore, non-Hispanic white women were more likely to receive appropriate therapy than non-Hispanic black women. In a multivariate analysis, women treated for apparent stage I and II disease received appropriate therapy significantly more often in 1996 than in 1991. For women with stage III and IV disease, approximately 40% did not receive appropriate therapy. This latter observation was essentially unchanged from 1991 to 1996. Age did, however, influence treatment. For women with advanced-stage disease, only 53% of women 65 years and older received guideline therapy compared with 73% of women younger than 65 years of age. The lack of private insurance also negatively influenced a woman's ability to receive guideline therapy. These findings are encouraging, in that some progress occurred in the period between 1991 and 1996. But it is not enough. American women in general are not receiving the level of excellence in ovarian cancer care that they deserve, and the elderly, minorities, and those without private insurance are being shortchanged the most. Oncologists and advocacy groups cannot relax their resolve to continue the fight for state-of-the-art care for all women with ovarian cancer. ■

Dr. Gershenson is Professor and Chairman, Department of Gynecology, M.D. Anderson Cancer Center, Houston, Tex.

CME Questions

22. Which of the following statements about bone marrow transplantation for follicular, non-Hodgkin's lymphoma is true?

a. Allogeneic transplantation offers a theoretical advantage because relapse rates are lower than with autologous transplantation.
b. Unpurged autologous marrow offers a theoretical advantage because transplant related mortality is less than with allogeneic transplantation.
c. Purged autologous marrow offers a theoretical advantage because transplant-related mortality is less than with allogeneic transplantation, and relapse rates are less than with unpurged autologous marrow.
d. All of the above
e. None of the above

23. In the multicenter trial of erythropoietin use in anemic head and neck cancer patients, which of the following findings was *not* observed?

a. Increased hemoglobin in the epoetin-β-treated patients
b. Increased quality of life in the epoetin-β patients
c. Decreased locoregional control in the epoetin-β-treated patients
d. Decreased survival in the epoetin-β treated patients

24. Based on the findings of Harlan et al in their study of trends in surgery and chemotherapy for women with ovarian cancer in the United States, the main factor responsible for an improvement in the frequency of appropriate treatment for women with early stage disease has been:

a. higher rate of cytologic washings
b. higher rate of peritoneal biopsies
c. higher rate of omentectomy
d. higher rate of lymph node sampling.
e. None of the above

25. Which of following statement is false of breast cancer chemoprevention with tamoxifen?

a. Tamoxifen treatment is associated with a reduction in all breast cancers.
b. The major side effects of tamoxifen treatment are endometrial cancer and venous thrombosis.
c. No chemoprevention drug is available that affects estrogen receptor-negative cancers.
d. Bone loss is a major side effect of aromatase inhibitors.

Answers: 22 (d); 23 (b); 24 (d); 25 (a)

In Future Issues:

ATAC Update on Early Stage Postmenopausal Adjuvant Breast Cancer Treatment

PHARMACOLOGY WATCH

Eplerenone Cleared for CHF Patients with Sustained MI

The FDA has approved Pfizer's eplerenone (Inspra) for the treatment of congestive heart failure (CHF) in patients who have sustained a myocardial infarction. The drug is a selective aldosterone blocker, a new class of drug for the treatment of CHF. It differs from spironolactone in that it selectively blocks the mineralocorticoid receptor, but not the glucocorticoid, progesterone, or androgen receptors. The approval of eplerenone for the treatment of CHF was based primarily on the findings of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which was published in the April 2003 issue of the *New England Journal of Medicine*. In EPHESUS, nearly 7000 patients with acute myocardial infarction and left ventricular dysfunction and heart failure were randomized to eplerenone 25 mg per day titrated up to 50 mg per day or placebo. Both groups also received optimal medical therapy. Following 16 months of follow-up, there was a significant reduction in death rate (RR, 0.85; 95% CI, 0.75-0.96; P = 0.008) in the eplerenone group. The drug also resulted in significant reductions in cardiovascular deaths and sudden cardiac death (*N Engl J Med*. 2003;348:1309-1321). The drug appears to be well tolerated with the primary adverse events being hyperkalemia and increased creatinine levels. Because of the selectivity of the drug for the mineralocorticoid receptor, there is no reported increase in menstrual disorders, gynecomastia, or impotence with eplerenone, adverse reactions that are frequently associated with spironolactone usage. Pfizer will make the drug available through an early access program by December 2003. Eplerenone was previously approved for treatment of hypertension alone or in combination with other antihypertensive agents.

No Adverse Effect with Concomitant Aspirin and ACE Inhibitor Use in CHF Patients

Aspirin does not adversely affect survival in patients with stable CHF who were being treated with an ACE inhibitor, according to a French study published in October. This study contradicts earlier studies, which raised concern about the concomitant use of aspirin and ACE inhibitors in CHF patients. In a retrospective analysis, 755 stable patients with left ventricular systolic dysfunction were followed for nearly 5.5 years. Most patients were on an ACE inhibitor and 317 were on aspirin, the majority on low-dose aspirin (< 200 mg/d). End points included cardiac-related deaths, version transplants, nonurgent transplants, and noncardiac deaths. The analysis revealed no relationship between the use of aspirin and survival among patients taking ACE inhibitors. Brunner-La Rocca and colleagues conclude that aspirin is not harmful for heart failure patients who are taking ACE inhibitors (*Chest*. 2003; 124:1192-1194, editorial 1250-1258).

HIV Treatment Shows High Failure Rate

A once-daily, triple nucleoside reverse transcriptase inhibitor (NRTI) HIV treatment regimen has seen a high number of treatment failures and HIV

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resistance. The rate of virologic failure reached 91% along with a high rate of HIV resistance to NRTIs in treatment-naive patients. Gilead Sciences has taken the step of notifying health-care professionals to discontinue the regimen in a "Dear Doctor" letter. The treatment failures were seen with a regimen containing didanosine enteric-coated beadlets (Videx EC, Bristol-Myers Squibb), lamivudine (Epivir, GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread, Gilead) in HIV-infected treatment-naive patients. Tenovir DF is no longer recommended for use in combination with didanosine and lamivudine in treatment-naive or experienced patients with HIV infections. The FDA is also recommending that patients currently on this regimen should be considered for treatment modification (http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#viread [Accessed Nov. 5, 2003]).

New Psoriasis Treatment Approved

The FDA has approved the second biologic for the treatment of psoriasis. Genentech's efalizumab (Raptiva) was approved for the treatment of moderate-to-severe psoriasis in October. It joins Biogen's alefacept (Amevive), which was approved in January 2003 and will probably soon be joined by Amgen's rheumatoid arthritis drug etanercept (Enbrel), which is also seeking approval for the treatment of psoriasis. Efalizumab is a humanized therapeutic antibody that blocks the activation, reactivation, and trafficking of T-cells that lead to the development of psoriasis symptoms. The drug requires a once-a-week self-injection and will cost $14,000 a year.

THG Controversy Gains Steam

The FDA has issued a warning regarding tetrahydrogestrinone (THG), a synthetic "designer" steroid, which is derived by simple chemical modifications from another anabolic steroid. Little is known about the safety of the drug or its structure, but its relationship to better-known products suggests that it may represent a considerable health risk. THG has been marketed as a dietary supplement; however, the FDA has determined that it is an unapproved drug and as such cannot be legally marketed. Urine assays have recently been developed for THG, and testing of athletes has revealed some disturbing findings. Four US Olympic athletes, as well as Britain's leading sprinter, have tested positive in the initial assay—further tests are to follow. A San Francisco grand jury is looking into a California nutritional supplement manufacturer that may be the source of the drug. The FDA statement is available at www.fda.gov/bbs/topics/NEWS/2003/NEW00967.html (accessed Nov. 5, 2003).

New Study Examines Sulfonamide Nonantibiotics

Is it safe to use a sulfonamide-based nonantibiotic in patients who have an allergy to sulfonamide antibiotics? A large retrospective cohort study from the United Kingdom looked at this issue and suggests that penicillin allergy is as likely or more likely to be associated with nonantibiotic sulfonamide reactions as a history of sulfonamide antibiotics allergy. Nearly 10% of patients with a history of allergy to a sulfonamide antibiotic had an allergic reaction after receiving a sulfonamide nonantibiotic compared to only 1.6% of patients who have no history of allergy to sulfonamide antibiotics. Patients who had a history of hypersensitivity to penicillin were most likely to have an allergic reaction to a sulfonamide nonantibiotic (adjusted odds ratio, 0.6; 95% CI, 0.5-0.8). Strom and associates conclude that there is a relationship between hypersensitivity to sulfonamide antibiotics and subsequent allergic reaction with sulfonamide nonantibiotics such as thiazide diuretics; however, this risk seems to be due to a predisposition to allergic reactions rather than a cross reactivity between sulfonamide-based drugs (*N Engl J Med*. 2003;349:1628-1635).

FDA Actions

Novavax Inc has received FDA approval to market a new topical estrogen therapy for the treatment of hot flashes in menopausal women. The white lotion is an emulsion of estradiol topical that women apply only to their legs, thighs or calves on a daily basis. The topical preparation is absorbed through the skin allowing estradiol to bypass enterohepatic circulation. Estradiol topical emulsion will be marketed under the trade name Estrasorb.

The FDA has issued an approvable letter to Cephalon, Inc. regarding expanded indications for modafinil (Provigil). The drug is currently approved for excessive daytime sleepiness associated with narcolepsy. The letter states that modafinil is approvable for improving wakefulness in patients with excessive sleepiness associated with shiftwork and in patients with obstructive sleep apnea/hypopnea syndrome. Cephalon had also sought approval for other causes of excessive sleepiness including jet lag; however, the FDA panel could not come to agreement on that recommendation. ■