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INSIDE

Second Malignancies Following Adjuvant Chemotherapy

ABSTRACT & COMMENTARY

Synopsis: *HEC, as delivered in this trial, cannot be recommended in clinical practice because of the lack of superiority over classic CMF and because of the increased risk of AML observed in this arm. Prolongation of conventional anthracycline-based treatment beyond the current standard of 4-6 cycles is not recommended in clinical practice.*

Source: Bernard-Marty C, et al. *Ann Oncol*. 2003;14(5):693-698.

THE BENEFITS RELATED TO THE ADMINISTRATION OF ADJUVANT chemotherapy in breast cancer are well established. Significant reductions in the risk of relapse and death are observed in both node-positive and node-negative patients. However, long-term survivors appear to be at increased risk for developing treatment-related complications. This issue could raise doubts about the risk/benefit ratio in patients with very favorable prognosis, in whom the absolute survival gain from chemotherapy may be < 5%. The increased risk of leukemia in patients with early breast cancer treated with alkylating agents, particularly melphalan, is well documented.[1] More recently, topoisomerase-II inhibitors, including anthracyclines and anthracenediones, have also been associated with the occurrence of acute myelogenic leukemia and myelodysplastic syndrome.[2-4] A prospective multicenter phase III trial was conducted comparing 2 epirubicin-cyclophosphamide regimens with classical cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).[5] As part of the analysis of the study, the incidence of secondary malignancy was evaluated.

The long-term toxicity of treatment of cancer patients with a good tumor-related prognosis is extremely important. Chronic morbidity and increased mortality from treatment can negate the benefit of the treatment. This has been exemplified in the analysis of outcomes with Hodgkin's disease.[6] There have also been a number of trials that show patients being treated in the adjuvant setting for breast cancer have an increased risk of leukemia and possibly solid tumors. The current Belgian trial consisted of 770 patients younger than age 70 with histologically confirmed, node-positive breast can-

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cer were considered eligible for the study. After primary surgery, patients were randomized to: 1) CMF using oral cyclophosphamide 100 mg/m^2 orally days 1-14; and i.v. methotrexate and 5-fluorouracil i.v. days 1 and 8, cycles every 28 days for 6 cycles; 2) EC (epirubicin 60 mg/m^2 i.v. day 1 and cyclophosphamide 500 mg/m^2 i.v. day 1, cycles every 21 days); or 3) HEC (epirubicin 100 mg/m^2 i.v. day 1 and cyclophosphamide 830 mg/m^2 i.v. day 1, cycles every 21 days). Both anthracycline-based regimens were administered for 8 cycles. At a median follow-up of 73 months, the following 8-year actuarial rates of second solid primaries were observed: CMF 5.5% (95% confidence interval [CI], 1.5-9.5%), EC 4.1% (95% CI, 0.1-8.1%), and HEC 7.2% (95% CI, 3.2-11.2%) (P = .79 by log rank test). Three secondary acute myeloid leukemias (AML) were reported, all in the HEC arm (incidence = 1.2%, 95% CI, 0.0-2.5%), which by a 3-arm comparison allows us to conclude that HEC is statistically different (borderline significance) from CMF and EC (P = .05). The first AML case was an M5 AML, according to the French-American-British (FAB) classification, and occurred 21 months after randomization. Cytogenetic analysis showed a 11q23 translocation. The second case was an M6 AML showing multiple chromosomal abnormalities, diagnosed 57 months after randomization. The third case was an M5 AML with a translocation t(9;11), which occurred 32 months after randomization. There was no statistical difference in the development of solid tumors between the 3 arms.

COMMENT BY STUART M. LICHTMAN, MD, FACP

It is widely recognized that there are 2 different syndromes of chemotherapy-induced acute nonlymphocytic leukemia. The first is related to the use of alkylating agents and involves a first stage of myelodysplasia, with a maximal incidence between 5 and 10 years of follow-up. Its morphology is usually of the M1 or M2 type, with frequent deletion of chromosomes 5 and 7. The second syndrome is related to the use of topoisomerase II inhibitors, such as anthracyclines. Patients do not develop a previous period of myelodysplasia, and the morphology includes a monocytic M4 or M5 component. The induction period is shorter, 2 or 3 years, and there are translocations in 11q23, 21q22, and 3q23.

This paper suggests that the effect of epidoxorubicin-based chemotherapy is dose- or cumulative dose-related. Their results are consistent with those published by the National Cancer Institute of Canada (NCI-C).[7]

The risk of acute myeloid leukemia was observed in these trials with an epidoxorubicin dose of 100 and 120 mg/m^2 per cycle and a cumulative dose of 800 and 720 mg/m^2, respectively. In a Belgian trial, in patients treated with an epidoxorubicin dose of 60 mg/m^2 per cycle and a cumulative dose of 480 mg/m^2, no acute leukemia was reported. These results are consistent with a recently published French trial, conducted in 835 high-risk postmenopausal patients treated with adjuvant tamoxifen and randomized to FEC/FAC at an anthracycline dose of 50 mg/m^2 per cycle and a cumulative dose of 300 mg/m^2, in which no differences were found in the incidence of acute leukemia. Other issues to be considered in the report of new primary malignancies are related to the duration of follow-up, the registration of adverse events and the methodology used in the calculation of event rates. Late complications of adjuvant treatments, generally ignored in early reports, need randomized trials with a long-term follow-up.[8,9]

The long-term toxicity of cancer treatment is of critical concern, particularly in patients with a good prognosis. This paper demonstrates the potential leukemogenic effect of anthracyclines that seems to be dose-related. It emphasizes that prospective randomized trials are necessary to demonstrate the efficacy of regimens and their

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potential toxicity that can mitigate the benefit of the therapeutic regimen. ■

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BRCA Mutations Associated with Improved Survival in Patients with Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Approximately 10% of invasive ovarian carcinomas are due to genetic predisposition and are associated with inherited mutations in either the BRCA1 or BRCA2 gene. In certain ethnic groups, such as Ashkenazi Jewish women, the frequency of these gene mutations are approximately 2%, and these women have a 16-44% lifetime risk of developing ovarian cancer. In the current report, histological and biological features of ovarian cancer occurring in Jewish women were compared in the context of the presence or absence of BRCA mutations. Women heterozygous for BRCA1 but not BRCA2 presented with ovarian cancer at a younger age. Histological features were comparable, but when matched for stage, those with BRCA mutations were more responsive to chemotherapy, and survival was significantly better.*

Source: Cass I, et al. *Cancer*. 2003;97:2187-2195.

BRCA MUTATIONS OCCUR WITH INCREASED FREQUENCY in certain ethnic groups. The purpose of the study by Cass and colleagues from Cedars-Sinai Medical Center, UCLA, was to determine the clinical characteristics, treatment response, and frequency of p53 overexpression in Ashkenazi Jewish women with BRCA-associated hereditary ovarian cancer compared to non-BRCA-associated (sporadic) ovarian cancer.

There were 71 Jewish patients with epithelial ovarian cancer, and each was tested for the 3 BRCA founder mutations. Clinical and histopathological data were reviewed retrospectively. In vitro chemoresistance was analyzed in 32 patients, and mutations of the p53 were determined by examining for increased expression of p53 using immunohistochemistry.

Thirty-four of 71 Jewish patients with epithelial ovarian cancer (48%) had germline BRCA mutations, including 22 BRCA1 and 12 BRCA2 mutations. BRCA heterozygotes were younger, compared to Jewish ovarian cancer patients without BRCA mutations (50 years vs 59 years; $P = .01$). BRCA1 heterozygotes were younger than BRCA2 (48 years vs 57 years; $P = .01$). Histopathological tumor features were similar in those that occurred sporadically compared with those associated with BRCA mutations. BRCA heterozygotes had higher response rates to primary cytoreductive chemotherapy regimens. BRCA heterozygotes with advanced-stage disease had improved survival compared with patients with similarly staged sporadic ovarian cancer (91 months vs 54 months; $P = .046$) and a longer disease-free interval (49 months vs 19 months; $P = .16$).

Thus, BRCA1 heterozygotes developed ovarian cancer at a younger age compared with BRCA2 heterozygotes or those without BRCA mutation. BRCA heterozygotes had a better response to platinum-based chemotherapy regimens and better overall survival.

■ COMMENT BY WILLIAM B. ERSHLER, MD

That ovarian cancer patients with BRCA mutations had improved survival when compared to those without mutation has been previously observed,[1,2] but some have speculated that this was related to earlier stage at diagnosis or less malignant histological variants. However, in the current series, there were no significant histological differences among those with BRCA-associated or sporadic ovarian carcinomas, and there were sufficient number of patients included that survival by stage could be determined. The data indicate that tumors that developed in BRCA heterozygotes were more chemosensitive in vitro, more chemoresponsive in vivo, and were associated with a longer survival time when compared to sporadic variants.

The mechanism that would account for this seemingly counter-intuitive observation has yet to be determined, but the hypothesis proposed by Cass et al seems reasonable. BRCA1 and 2 are considered tumor suppressor genes that regulate cellular proliferation and

DNA repair by maintaining chromosomal integrity.[3,4] Cass et al speculate that the absence of BRCA renders tumor cells more sensitive to the chemotherapy-induced cytotoxicity due to the impaired DNA repair capacity.

The findings reported confirm earlier observations that Jewish BRCA mutation carriers develop ovarian carcinoma at a younger age. It is apparent from the current series that this observation (earlier age of disease onset) is true for BRCA1 and not BRCA2 carriers. This finding has significant implications for counseling mutation carriers with regard to the timing of preventative measures, such as prophylactic oophorectomy, as those with BRCA1 mutations will develop ovarian cancer 5-10 years younger than those with BRCA2 mutations or than those who develop ovarian cancer sporadically. The added information with regard to enhanced chemosensitivity in those with BRCA mutations will need additional research for both confirmation and to elucidate mechanisms. ■

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10-Milligram Coumadin Loading for Outpatient Management of Deep-Vein Thrombosis

ABSTRACT & COMMENTARY

Synopsis: *In this randomized outpatient clinical trial of anticoagulation nomograms for patients with acute deep-vein thrombosis, a 10-mg initial dose of warfarin (coumadin) proved superior to an initial 5-mg dose with regard to time reaching therapeutic INR. The scheme presented, including initial treatment with low-molecular-weight heparin, is immediately applicable to the outpatient management of DVT.*

Source: Kovacs MI, et al. *Ann Intern Med*. 2003;138: 714-719.

THE OPTIMAL METHOD TO ACHIEVE THERAPEUTIC anticoagulation in the outpatient setting has yet to be established. In the current report, outpatients with acute deep-vein thrombosis (DVT) were randomized to 1 of 2 nomograms that included loading with either 10 mg or 5 mg of coumadin. The study was undertaken at the clinics associated with 4 Canadian hospitals and was a randomized, double-blind (physician/patient) interventional trial. The clearly stated hypothesis was that patients receiving the 10-mg coumadin induction nomogram would achieve therapeutic international normalized ratios (INRs) more rapidly than those managed with a 5-mg coumadin nomogram. The question, of course, was whether this could be done without an increased risk of bleeding.

Consecutive patients (n = 201) with objectively confirmed acute DVT were treated with low-molecular weight heparin for a minimum of 5 days and until therapeutic INR (> 1.9) was achieved. Patients were randomly assigned to initially receive a 10-mg or 5-mg dose of coumadin.

Demographic characteristics were similar in both groups. Patients in the 10-mg group achieved therapeutic INR 1.4 days earlier than patients in the 5-mg group ($P < .001$). By day 5, 83% of those in the 10-mg group had reached the therapeutic INR compared with 46% in the 5-mg group ($P < .001$). There were no significant differences between the 2 groups in recurrent events, major bleeding, survival and number of INR measurements greater than 5.0. Kovacs and colleagues concluded that the 10-mg coumadin induction nomogram was superior to the 5-mg nomogram because it allows more rapid achievement of therapeutic INR.

COMMENT BY WILLIAM B. ERSHLER, MD

Outpatient management of DVT has become common practice in many communities because it decreases cost and is associated with improved quality of life.[1] However, there are burdens on the patient, family, and clinic associated with daily injections of low-molecular-weight heparin and the need for frequent monitoring of INR. The minimum duration for LMWH therapy is 5 days,[2,3] and although extension beyond this point is unlikely to be harmful, it adds expense and the additional inconvenience of needle injections. The current report provides convincing evidence that a 10-mg starting dose of coumadin is more effective than a 5-mg dose in achieving therapeutic INR in a timely way and without added toxicity.

The study was performed in an outpatient setting and is relevant most clearly for that setting. The nomogram employed involves INR determination at baseline, day 3, and day 5, with a prescribed dose adjustment on those days. For example, on day 3, those who had an INR of < 1.3 received 15 mg of coumadin on days 3 and 4, whereas others who had an INR of 1.7-1.9 would have coumadin doses reduced to 5 mg for days 3 and 4.

In the hospital setting, there has been a suggestion that patients are more sensitive to coumadin, presumably on the basis of nutritional factors or the likelihood of antibiotics or other potential drug interactions,[3] and at least 1 group has indicated that a 5-mg loading dose of coumadin is more effective[4,5] in that setting.

Although there was no significant difference observed for recurrent DVT or bleeding, the current report was not adequately powered to conclude that these differences do not exist. Thus, the data must be reviewed with caution and additional, larger trials will be needed. Furthermore, the selection of patients for outpatient treatment of acute DVT is likely to exclude the sickest patients and those that are at greater risk for bleeding. Thus, the current report provides a very useful strategy for effective anticoagulation of acute DVT patients who are otherwise well enough to be treated in the outpatient setting. A copy of the nomogram, included as Figure 1 in the manuscript, may well be a useful addition to the clinic bulletin board. ■

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Carboplatin and Gemcitabine: Developing a More Gentle Approach for the Treatment of Advanced Transitional Cell Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Transitional cell carcinoma frequently occurs in older patients and the current standard therapy, which includes cisplatin combinations, may be too toxic for some patients. In the current report, fairly impressive results with carboplatin-gemcitabine chemotherapy used in patients with advanced transitional cell carcinoma are described. This combination may be particularly effective therapy for older, more frail patients, or for those with significant comorbidities.*

Source: Nogue-Aliguer M, et al. *Cancer*. 2003;97: 2180-2186.

Cisplatin-based chemotherapy is currently considered a standard approach for advanced transitional cell carcinoma. Until recently, the most commonly used regimen was M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin), which had proven superior when compared to single-agent cisplatin,[1] but the associated toxicity (including nausea/vomiting, mucosal, bone marrow suppression and renal, cardiac and neurologic damage) has been substantial. More recently, a cisplatin gemcitabine doublet was compared to M-VAC and proved to be equally efficacious with regard to response rates and time to treatment failure and overall survival, but with less toxicity.[2]

The current report is of a phase II trial of carboplatin and gemcitabine in patients with advanced transitional cell carcinoma. Patients with lower performance status (ie, Karnofsky scores of 60 or greater) and with mild-to-moderate renal insufficiency (ie, creatinine clearances > 30 mL/min) were considered candidates. Gemcitabine (1000 mg/m^2) was given on days 1 and 8, and carboplatin (area under the concentration time curve [AUC] of 5) was given on day 1 of each 21-day cycle.

Forty-one patients were enrolled and received an average of 5.5 cycles of drug. Creatinine clearance was below 60 in 54% of patients, and Karnofsky score was 70 or below in 37%, and 37% were older than age 70. Although grade 3/4 neutropenia occurred in 63%, there were only 3 episodes of febrile neutropenia. However, one patient died with neutropenic sepsis. Nonhematologic toxicity was mild, with asthenia the most frequently reported event. Six patients experienced complete responses and 17 partial responses for an overall response rate of 56.1% (95% CI, 40.6-71.6). Progression-free survival was 7.2 months (95% CI, 5.7-8.5), and median survival was 10.1 months (95% CI, 8.8-12.2).

Nogue-Aliguer and associates conclude that the combination of carboplatin and gemcitabine is an effective alternative treatment to cisplatin-based regimens and may offer the potential advantage of being less toxic.

■ COMMENT BY WILLIAM B. ERSHLER, MD

Transitional cell carcinoma occurs most commonly in elderly patients, with the median age of close to 70 years in both men and women. Although combination therapy has been shown to be effective, a fairly large segment of patients are not eligible for standard treatment, primarily because of existing comorbidities and associated impairment of renal or cardiac functions that preclude the use of aggressive, cisplatin-based combinations. Thus, the current report is of importance. It appears that the combination of carboplatin and gemcitabine achieves a similar result to doublets using cisplatin. Furthermore, the more favorable toxicity profile

enables patients with impaired renal function and/or poor performance status to be treated. Short of a randomized trial comparing cisplatin-gemcitabine with carboplatin-gemcitabine, the latter combination offers a reasonable alternative for the typical patient with coexisting illnesses or organ impairment. ■

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Trends in Incidence Rates of Invasive Lobular and Ductal Breast Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Ductal carcinoma incidence rates remained essentially constant from 1987-1999 while lobular carcinoma rates increased steadily. This increase presents a clinical challenge given that lobular carcinoma is more difficult to detect than ductal carcinoma by both physical examination and mammography.*

Source: Li CI, et al. *JAMA*. 2003;289:1421-1424.

The rationale for the present investigation was that a growing number of studies have reported that the risk of breast cancer associated with use of combined hormone replacement therapy (CHRT) differs by histological type. Specifically, 5 separate studies have shown that ever use and current use of CHRT are associated with 2.0-fold to 3.9-fold increased risks of invasive lobular breast carcinoma, the second most common histological type of breast cancer. These same studies show little effect on risk of the most common histological type, invasive ductal breast cancer. Li and colleagues note that these 5 studies also found that use of unopposed estrogen replacemnet therapy (ERT) was not strongly associated with risk of either type. The 2 studies that had sufficient power to examine the relationship between duration of CHRT use and invasive lobular breast cancer found a positive correlation. Li et al also note that invasive ductal breast cancer is more likely to be hormone receptor-positive and to have a better prognosis than invasive ductal breast carcinoma. However, invasive lobular breast cancer is less likely to be detected by mammography and clinical breast examination.

Given the above considerations, Li et al examined 9 cancer registries that participate in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute to ask about incidence trends in types of breast cancers. These registries cover the regions of Atlanta, Detroit, San Francisco-Oakland, Seattle, Connecticut, Hawaii, New Mexico, and Utah. A total of 190,458 women were included who were 30 years or older and who had had breast cancer. There was no increase in breast cancer rate from 1987 to 1999 (about 210 cases per 100,000). Rates of lobular carcinoma increased 1.52-fold and those of ductal-lobular 1.96-fold, for a combined increase of 1.65-fold (19.8/100,000 to 33.4/100,000). Rates of invasive ductal breast cancer remained at 154/100,000. Thus, the percentage of invasive breast cancers that was lobular increased from 9.5% to 15.6% for the 12-year interval. The registry does not allow for ascertainment of hormone use, but Li et al note that the data are consistent with the hypothesis that CHRT is associated with an increased risk of invasive lobular breast cancer.

COMMENT BY SARAH L. BERGA, MD

I chose to review this study because it illustrates a number of important concepts and because the results suggest ways to refine our prescription of postmenopausal hormone therapy. A methodological strength of the study is that the analysis is based on a very large number of cases of known invasive breast cancer. There were more than 190,000 cases of breast cancer in which the histological type was known! In contrast, the conclusions of the Women's Health Initiative were based on only 290 cases of invasive breast cancer, and the histological type was not considered in that analysis. The conceptual strength is that the present study is based on the premises that not all breast cancers are the same and that not all hormone regimens are the same. While these caveats might seem intuitively obvious, most studies ask if "hormone use causes breast cancer," and the underlying assumptions are that hormone use is homogeneous and that all breast cancers are the same with regard to causality (and that all women have the same host characteristics). These assumptions have always struck me as unjustified simplifications, but it is nice to have data that reveal the error of this reductionistic question and analytic approach.

The current study design would have been immeasurably strengthened if actual hormone use could have been ascertained, but there are other data in

which hormone use has been determined, and these studies also suggest that it is the progestin rather than estrogen component that increases the risk of breast cancer. As Li et al point out in the introduction, in the Women's Health Initiative, a strength of which is that hormone use is known, combined hormone use was associated with "a statistically nonsignificant 26% increase in risk of breast cancer after 5.2 years." If one assumes that the interpretation suggested by the present study results is valid, namely, that it is combined estrogen-progestin use that increases the risk of lobular breast cancer, then this might well change prescribing practices. One prescribing response would be to give very low doses of unopposed estrogen to women with intact uteri while monitoring the endometrium. Another strategy would be to minimize circulating progestin levels by prescribing the most minimal dose of progestin possible or by confining the progestin exposure to the uterus by inserting a progestin-containing intrauterine device (which gives trivial circulating levels of progestin). Based on extant data, it is reasonable to hope that strategies that minimize or eliminate progestin exposure also might confer better brain (mood and cognition) and cardiovascular outcomes as well.

Questions that are raised by the study include whether the type of progestin matters (Does medroxyprogesterone acetate confer greater risk than norethindrone or progesterone?) and whether there is a difference in risk between cyclic and continuous progestin regimens. The study by Marchbanks et al (*New Engl J Med.* 2002;346:2025-2032 and reviewed in the August 2002 issue of *OB/GYN Clinical Alert*) regarding risk of breast cancer among oral contraceptive users found no increase in risk from combined estrogen-progestin exposure, but both the estrogen and the progestin component in oral contraceptives differs from the most commonly used estrogen and progestin preparations used for postmenopausal hormone use during the study period. The present study provides the rationale for additional studies that address these points. Given the paucity of data that address these questions, however, it is too soon to draw conclusions or become dogmatic.

The current study illustrates another key point, which is that the best conclusions are those that reconcile competing data and conclusions by refining both the questions and the answers. In this case, the question "Does hormone use cause breast cancer?" now becomes "Does a particular regimen of postmenopausal hormone use increase the risk of any given type of breast cancer?" This would not be the end of the refinements, however, because one still wants to know about the "host characteristics" that also modify risk. It is a statement of the obvious that not all women are the same, but most epidemiological studies have done little to help us delineate which women might be at higher risk of getting lobular breast cancer from extended combined hormone use.

My final parting shot is to ask where was the news coverage about this article? It was in *JAMA*, and most of the time articles in *JAMA* about breast cancer are widely reported. There might be a number of explanations, but I wonder if the conclusions are not simple enough for the newspaper audience. In other words, the findings are too "gray" and we all know that the best news is "black and white." ■

Dr. Berga is Professor and Director, Division of Reproductive Endocrinology and Infertility, University of Pittsburgh, Pittsburgh, Penn.

CME Questions

20. Which of the following statements about the gemcitabine-carboplatin combination for advanced transitional cell carcinoma is true?

a. It has been shown to have a greater response rate and less toxicity than a gemcitabine-cisplatin combination in a phase III trial.
b. It has been demonstrated to produce complete and partial responses in a phase II trial that are comparable to that reported earlier for cisplatin-gemcitabine combinations.
c. It is less effective (fewer responses) than when cisplatin is given as single agent.
d. It is more toxic than the standard M-VAC combination.

21. With regard to anticoagulation schemes for the treatment of acute deep-vein thrombosis in the outpatient setting, which of the following statements is true?

a. Coumadin alone, without heparin or low-molecular-weight heparin, has been shown to be safe and effective.
b. Coumadin administered initially at 10 mg daily has been shown to achieve therapeutic INRs earlier than coumadin at 5-mg initial dosing.
c. There was no difference in the time to reaching therapeutic INRs, when coumadin was initially administered at 5 mg or 10 mg.
d. Coumadin administered at 5 mg took approximately 2 days longer to reach therapeutic INR when compared to the 10-mg dose, but bleeding episodes were fewer.

22. Jewish women who carry the BRCA1 gene mutation:

a. are more likely than those Jewish women who carry BRCA2 mutation or those who are without mutation in BRCA genes, to develop ovarian cancer.
b. will present with ovarian cancer 5-10 years earlier than those who carry BRCA2 mutation or who are without mutation in BRCA genes.

c. are more likely, if they develop ovarian cancer, to have chemoresponsive tumors and greater survival when compared to Jewish women who develop ovarian cancer without BRCA mutations.
d. All of the above

Answers: 20 (b); 21 (b); 22 (d)

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Detection of Alzheimer's Disease and Dementia in the Preclinical Phase

Source: Palmer K, et al. *BMJ*. 2003; 326:245-247.

Alzheimer's disease (AD) is the most common form of dementia in America, but often escapes clinical attention until symptoms compromise quality of life, activities of daily living, or safety. Interventions might be enhanced by early detection of AD, but little investigation of early detection techniques has been done.

Palmer and colleagues evaluated 1435 persons aged 75-95 years who were without dementia at baseline. All persons underwent evaluation at baseline, 3 years, and 6 years with 3 different tools; subjects were asked, "Do you currently have any problems with your memory?" Additionally, each subject underwent mini-mental status examination, and neuropsychological testing assessed cognitive function.

At follow-up, almost 20% of survivors had dementia. All 3 screening tools, if positive, increased relative risk of AD. Having a memory complaint at baseline doubled the relative risk of subsequent dementia, and cognitive impairments increased relative risk of dementia by 2- to 5-fold.

Although using all 3 tools had a high predictive value if positive, the tools are too insensitive for routine employment, since only 18% of persons who ultimately developed dementia were identified using this 3-step process. That we can identify, with some reliability, a subgroup of persons likely to progress to dementia is promising. For broader applicability, more sensitive screening tools will be required. ■

Shoe Design and Plantar Pressures in Neuropathic Feet

Source: Praet S, et al. *Diabetes Care*. 2003;26:441-445.

Clinicians have tried a variety of maneuvers to reduce the incidence and effect of neuropathic foot ulcers in an attempt to reduce their subsequent morbidity. Since a substantial proportion of diabetics will ultimately develop distal sensory neuropathy and be at risk of foot ulcers, learning which type of footwear might help minimize the consequences of this neuropathy is of great importance. The most commonly used orthopedic shoe for diabetic neuropathy is the "rocker bar" variety (RB shoe), others suggest that a simple extra depth shoe, which is typically less expensive, more cosmetically pleasing, and more readily accessible, may be equally effective.

Praet and colleagues studied 10 diabetic women suffering from peripheral sensory neuropathy, but without evidence of foot deformity or ulceration. Women were tested in 3 categories of shoes: Category A were simple popularly styled traditional shoes, category B were extra depth shoes, and category C were specially crafted (based upon plaster casts of feet) shoes with rocker bottoms.

Overall, only the RB shoes effectively reduced forefoot pressure more than traditional "over the counter" footwear. Praet et al acknowledge that choosing footwear for any one individual diabetic remains a difficult choice and that shoe-specific pressure measurements in different types of footwear may be the best alternative for some patients, especially for those who balk at use of the less cosmetically acceptable RB shoes. ■

TSH in Assessment of Hypothyroidism

Source: Meier C, et al. *BMJ*. 2003; 326:311-312.

Although there is good agreement that thyroid stimulating hormone (TSH) is the most appropriate indicator of hypothyroidism, it is little understood whether absolute levels of TSH correlate either with degree of tissue effect of hypothyroidism, or levels of thyroid hormone. Meier and colleagues used a composite of clinical score, ankle reflex time, CK, and total cholesterol as markers of what they term "thyroid hormone action at the tissue level." They then correlated TSH with thyroid hormone levels and tissue parameters.

The correlation of tissue parameters and TSH was weak. This review suggests that there is a poor correlation between levels of TSH and clinical or metabolic severity of hypothyroidism. Meier et al have no quarrel with the sensitivity and diagnostic accuracy of TSH to discern the presence or absence of hypothyroidism. Rather, they hypothesize that once TSH is maximally stimulated, no further increase will occur, despite progressively greater degrees of hypothyroidism. Meier et al suggest that thyroxine treatment should be guided by clinical signs and thyroid hormone concentrations, rather than solely by TSH concentration. ■

Oral Vitamin D3 Supplementation on Fractures and Mortality

Source: Trivedi DP, et al. *BMJ*. 2003;326:469-472.

Despite recent enhanced clinician and public awareness, prevention and treatment goals for osteoporosis (OSPS) remain inadequately fulfilled. A variety of lifestyle and pharmacologic tools have been applied to OSPS management, including Vitamin D (VitD) supplementation, with some, albeit inconclusive, success.

This trial was a pilot study using VitD (cholecalciferol) supplementation in a British senior citizen population (age range, 65-85) solicited by mail (n = 2686) to participate in a placebo-controlled trial lasting 5 years. Unusual in this trial was the dosing methodology, which administered a single 100,000 IU VitD capsule once every 4 months for 5 years—not once daily, but once (total capsules administered in 5 years = 15). Participants were instructed to take the capsule they received in the mail immediately upon receipt, and respond by mail on a form indicating that they had indeed taken the medication.

Compared to placebo, the treatment group had a 22% lower rate for first fracture (any site) and a 33% lower hip, wrist, forearm, or vertebrae fracture rate. The parathyroid hormone concentrations did not differ significantly between active VitD and placebo, despite a 40% higher VitD level in the former.

Ultimately, the 100,000 IU dose of VitD is approximately equivalent to 800 IU per day, which has been used in other trials. However, the convenience, lack of toxicity, and monetary savings (in the United Kingdom, 3 capsules of 100,000 IU vitD costs less than 1 pound) provide intriguing stimuli for a larger trial. ■

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Oral Opioid Therapy for Chronic Peripheral and Central Neuropathic Pain

Source: Rowbotham M, et al. *N Engl J Med*. 2003;348:1223-1232.

Neuropathic pain (NPP) is often described as "opioid resistant," based upon some limited human and animal studies. On the other hand, parenteral opioid analgesia has produced success in NPP. Although data on postherpetic neuralgia indicate a degree of efficacy with opioid analgesia, other NPP syndromes are not well studied in prospective, blinded studies.

Because of the ethical boundary of administering placebo to patients suffering chronic pain, a study was performed comparing 2 different dosing levels of levorphanol, a potent mu-opioid agonist, for patients (n = 100) suffering chronic NPP, in a double-blind fashion. Patients were administered either 0.15 mg or 0.75 mg capsules, and allowed to titrate up to as many as 7 capsules 3 times daily (levorphanol has a 6-8 hour duration of analgesia). The primary outcome of the study was degree of pain reduction; secondary outcome was time to pain relief. The study period was 8 weeks duration.

As perhaps might be intuitive, high-strength levorphanol reduced pain to a significantly greater degree than in the lower-strength group, despite the option available to patients of up-titrating their medication dose. Encouragingly, both groups did report levorphanol efficacy (pain reductions, 21% and 36%). Contrary to popular wisdom, tolerance to opioid analgesia was not evidenced. Additionally, the magnitude of pain reduction in the high-strength group was similar to that achieved with other more traditionally used NPP tools like tricyclic antidepressants and gabapentin.

Clinicians who have excluded opioid analgesia as an effective tool in NPP may need to consider these data in their decision process. ■

Tacrolimus Ointment vs. Topical Corticosteroids in Atopic Dermatitis

Source: Ellis C, et al. *J Am Acad Dermatol*. 2003;48:553-563.

For several decades the mainstay of management of atopic dermatitis (AD) has been corticosteroids (CSD), usually administered topically. When AD is mild-moderate, low, and mid-potency, CSD often suffices, but more severe disease may require high-potency agents, or even systemic therapy. Since CSD can produce both local effects like skin atrophy and systemic effects such as hypothalamic-pituitary suppression, chronic administration requires a degree of caution. Recently, a class of topical immunomodulator agents (IMA), exemplified by tacrolimus (Protopic) and pimecrolimus (Elidel), has been offered for clinical use as an alternative to CSD and appears to be equally efficacious. There are no serious side effects of IMA, and they have been demonstrated to be both safe and effective in children as young as 2 years, with minimal side effects.

For patients with moderate-to-severe AD, the cost of treatment was similar for either high-potency CSD and IMA for a 4-week treatment regimen. For short-term treatment (2 weeks), IMA is more cost effective than CSD because there is less requirement for secondary interventions. If lower potency and less costly CSD are used efficaciously, the cost efficacy of IMA becomes less favorable. The combination of safety, efficacy, and cost has important therapeutic implications for the role of IMA in AD. ■