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INSIDE

The Long Look: 10-Year Follow-Up of Adjuvant Colon Trial NSABP C-01

ABSTRACT & COMMENTARY

Synopsis: *The 10-year disease-free and overall survival rate is presented from a trial of adjuvant therapy (chemo-, or immunotherapy) for Dukes' B and C colon cancer conducted by the National Surgical Adjuvant Breast and Bowel cooperative group. The disease-free and overall survival advantage for the chemotherapy arm, apparent at 5 years, was no longer evident by 10 years. Although new, likely more effective regimens are currently used in this setting, the report raises caution concerning the need for extended follow-up and the use of surrogate markers such as disease-free survival in predicting cures.*

Source: Smith RE, et al. *J Natl Cancer Inst*. 2004;96:1128-1132.

In 1988, Wolmark and colleagues reported the 5-year data from the National Adjuvant Breast and Bowel Project C-01.[1] In that early trial, conducted between November, 1977 through February 1983, 1166 patients with resected Dukes' stage B and C adenocarcinoma of the colon were randomly assigned to receive no further therapy (surgery alone; 394 patients), adjuvant chemotherapy (MOF [methyl CCNU, vincristine and 5-fluorouracil]; 379 patients), or adjuvant immunotherapy (bacillus Calmette-Guerin [BCG]; 393 patients). The adjuvant chemotherapy consisted of eight 10-week cycles of drug, whereas the immunotherapy (BCG) was administered weekly for a total of 12 injections. The results at 5 years[1] indicated that MOF adjuvant chemotherapy was associated with a statistically significant improvement in disease-free survival (58% vs 51%; $P = 0.02$) and overall survival (67% vs 59%; $P = 0.05$) when compared with surgery alone. Adjuvant BCG therapy was associated with a trend toward improvement in disease-free survival (56% vs 51%; $P = 0.09$) and a statistically significant overall survival advantage (67% vs 59%; $P = 0.03$). However, when deaths with no evidence of tumor recurrence were eliminated, BCG therapy had no statistically significant benefit in either disease-free survival or overall survival, whereas benefit from chemotherapy was retained.

In the current manuscript, complete survival data at 10 years is

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presented. At this point, MOF adjuvant chemotherapy showed no benefit compared with surgery alone in terms of disease-free survival, relapse-free survival, or overall survival. With regard to immunotherapy with BCG, tumor relapses were not prevented, but there remained a statistically significant improvement in overall survival (53% vs 47%).

Thus, the disease-free and overall survival benefit associated with adjuvant chemotherapy (with MOF) was found to be of limited duration—apparent at 5 years but gone at 10.

COMMENT BY WILLIAM B. ERSHLER, MD

Without doubt, the results are a bit discouraging. However, it must be recalled that neither of the experimental arms examined (MOF chemotherapy or BCG immunotherapy) are currently used in this setting; the field having advanced somewhat with the introduction of more active chemotherapies, particularly irinotecan and oxaliplatin.[2] However, certain points are worth noting. First, it is apparent that the drugs undertaken in this early trial delayed recurrences, but did not eradicate disease. This is made evident by the apparent advantages in overall survival at 5 years, but the disappearance of this difference by 10. Although adjuvant chemotherapy is generally prescribed with curative intention, a delay in tumor recurrence would also be considered a favorable outcome, particularly if the treatment is not associated with substantial toxicity. Another point is that clinical investigators are inclined to consider surrogates for overall survival, such as the recently proposed 3-year disease-free interval.[3,4] Indeed, the 3-year disease-free interval may well predict 5 year overall survival, but continued surveillance would seem warranted, based upon this cooperative trial experience presented herein.

The long-term follow-up of the BCG-treated patients is also worthy of note. Although tumor recurrences were not avoided, overall survival at 10 years was better than the control group. One factor is that the BCG group experienced one half the frequency of life-shortening second malignancies (9 vs 18). Although this is a relatively small number of cases, it is tempting to speculate that this brief course of non-specific immunostimulation, somehow resulted in more effective tumor surveillance.

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Doxorubicin + Cisplatin vs Doxorubicin + 24-h Paclitaxel + Filgrastim in Endometrial Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Doxorubicin and 24-h paclitaxel plus filgrastim was not superior to doxorubicin and cisplatin in terms of response, PFS or survival in advanced endometrial cancer.*

Source: Fleming G, et al. *Ann Oncol*. 2004;15: 1173-1178.

MOST PATIENTS WITH ENDOMETRIAL CANCER PRESENT with early stage disease and are cured with

local therapy. However, the prognosis for patients with inoperable stage III or IV, or recurrent, endometrial cancer remains poor. Prior to the availability of taxanes, anthracyclines and platinum compounds represented the most active cytotoxic agents, each producing single-agent responses in the range of 20-30%. In 1993, the Gynecologic Oncology Group (GOG) reported 45% of patients responding (including 22% complete responses) to the combination of 60 mg/m^2 doxorubicin plus 50 mg/m^2 cisplatin in advanced or recurrent endometrial carcinoma. This was significantly superior in a randomized trial to the 27% response obtained from doxorubicin alone.

Overall survival (OS), however, was not significantly better in the combination arm, with a median of 9 months. Similarly, a randomized phase II/III trial conducted by the European Organization for the Research and Treatment of Cancer/Gynecologic Cancer Cooperative Group reported 43% of patients responding using a doxorubicin/cisplatin doublet vs 17% responding using doxorubicin only. Survival was not significantly superior in the combination arm (9 vs 7 months). The GOG evaluated single-agent paclitaxel 250 mg/m^2 as a 24-h continuous infusion with granulocyte colony-stimulating factor (G-CSF) support in previously untreated patients.

Overall, 36% of patients responded, including 14% who experienced complete responses. The current study was performed to determine whether 24-h paclitaxel plus doxorubicin and filgrastim was superior to cisplatin plus doxorubicin in patients with endometrial cancer with respect to response, progression-free survival (PFS) and OS.

COMMENT BY STUART M. LICHTMAN, MD

Patients with measure stage III/IV endometrial cancer were randomized to one of two treatment arms. Arm 1, the standard treatment arm, consisted of doxorubicin 60 mg/m^2 intravenously followed immediately by cisplatin 50 mg/m^2 IV. Patients who had received prior pelvic radiotherapy or who were older than age 65 were to receive reduced starting doses of doxorubicin 45 mg/m^2 and cisplatin 40 mg/m^2. The treatment plan for arm 2, the experimental treatment arm, consisted of 50 mg/m^2 of doxorubicin on day 1 administered by IV bolus or brief infusion followed 4 hours later by paclitaxel at a dose of 150 mg/m^2 administered as a 24-h infusion.

Filgrastim was to be given subcutaneously at a dose of 5 mg/kg on a daily basis, starting on day 3 of each cycle and continuing until day 12 or until the white blood cell count (WBC) was at least 10,000/mm^3 (post nadir). Patients who had received prior pelvic radiotherapy or who were older than age 65 years were to receive reduced starting doses of doxorubicin 40 mg/m^2 and paclitaxel 120 mg/m^2. Treatment was continued for 7 cycles, or until disease progression or unacceptable toxicity necessitated therapy discontinuation. Doses were reduced for grade 3 or 4 WBC, granulocyte or platelet toxicity, and could be re-escalated if subsequent cycles produced toxicity of no more than grade 1. Filgrastim was to be added for patients on arm 1 who had persistent grade 4 hematological toxicity or treatment delays despite dose reduction. Response was measured according to standard GOG criteria. Three hundred and twenty-eight patients with primary stage III, stage IV or recurrent endometrial carcinoma were enrolled and 317 patients are included in the survival analysis (157 on arm 1, and 160 on arm 2). Three hundred and thirteen patients received at least one cycle of therapy and were evaluable for toxicity (156 on arm 1 and 157 on arm 2).

Patient characteristics, with the exception of age at entry, were well balanced between the arms. Arm 2 had more patients older than 61 years (69% vs 58%). Sixty-nine percent of patients on arm 1 and 64% of patients on arm 2 received an initial dose reduction because of prior pelvic radiation and/or age older than 65 years. Seventy patients on arm 1 (45%) and 78 patients on arm 2 (49%) received all 7 cycles of therapy. Median follow-up for those alive at last contact was 61 months. No improvement in response was observed for the experimental arm. The overall response rate was 40% in arm 1 and 43% in arm 2. The common odds of response ratio in arm 2 relative to arm 1 stratified by PS was 1.12. Patients with prior pelvic radiotherapy were overall less likely to respond (35%, both arms combined) than were patients with no prior pelvic radiotherapy (48%, both arms combined). Statistically significant factors related to poorer response included PS of 2, prior radiotherapy, liver metastases, and disease that was recurrent after presentation at an earlier stage. There were no significant differences in PFS or OS between the 2 treatment arms. Median PFS was 7.2 months on arm 1 and 6 months on arm 2. Adjusting for PS, the hazard ratio relative to arm 1 is 1.01. Median OS was 12.6 months on arm 1 and 13.6 months on arm 2. Adjusting for PS, the death hazard ratio relative to arm 1 is 1.00. Statistically significant factors predicting for longer OS include good PS, grade 1 histology, extrapelvic disease other than lung and abdomen but including the liver, and months to first recurrence.

Hormonal therapy can produce responses in a minority of patients with advanced endometrial cancer. However, most endometrial cancers will not respond to hormonal treatment, and those that do will eventually

become refractory. The GOG has been systematically evaluating new cytotoxic agents for activity in endometrial cancer, and phase II data suggest that paclitaxel is among the most active agents ever tested. It was hoped that inclusion of paclitaxel in a first-line chemotherapy regimen would both improve response rates (and, by association, symptoms) and prolong patient survival. However, substituting paclitaxel for cisplatin in a first-line chemotherapy regimen did not positively effect response rates, PFS or OS. The main predictors of poorer outcome were performance status and prior radiotherapy. Older age was not an adverse prognostic factor. The study design called for dose reduction based on age and prior radiotherapy. Dose reductions based on age alone and not based on other factors such as comorbidity, endorgan dysfunction, poor performance or functional status are rarely necessary. In fact, these arbitrary dose modifications, which in this study was the majority of patients may have contributed to reduced response rates. Trials using a 3-h paclitaxel infusion have been shown to have substantial activity in endometrial cancer and shorter, less myelotoxic infusions have replaced more prolonged infusions in treating most tumor types. Other investigators have combined 3-h paclitaxel with carboplatin, which is less neurotoxic than cisplatin and also has activity in endometrial cancer;[2] preliminary results of that combination are also encouraging.[3] Conclusions from this trial can include that the lack of improvement in the paclitaxel + doxorubicin arm may be due to the fact that cisplatin or carboplatin may be essential in the therapy of endometrial cancer. The latter hypothesis is supported by a very recent trial.[4]

The benefit seen in prior trials with paclitaxel may have been due to factors such as patient selection. In terms of other therapy, the role of adjuvant radiation therapy has been defined much more clearly in recent years, at least for patients with stage I and very early stage II disease. Pelvic radiation therapy dramatically reduced the risk of locoregional recurrence in three randomized controlled trials. None of these trials revealed a significantly beneficial effect of radiotherapy on survival. The adjuvant medical therapy of endometrial cancer remains poorly investigated.

A systematic review and meta-analysis of the Cochrane Collaboration revealed that the adjuvant use of progestational agents may indeed be dangerous. They do not significantly reduce the risk of recurrence and endometrial cancer-related death, but significantly increase the risk of non-cancer-related death. Numerous small trials have investigated the efficacy of adjuvant chemotherapy in endometrial cancer, but were not adequately powered to detect a difference in survival.[5] Adjuvant chemotherapy with doxorubicin and cisplatin has been compared with whole abdominal radiation therapy in stage III and IV disease, and chemotherapy turned out to be superior to radiotherapy with regards to progression-free (hazard ratio, 0.81) and overall survival (hazard ratio, 0.71; $P < 0.05$). The combination of doxorubicin and cisplatin is considered standard therapy based upon 2 trials that revealed a very moderate advantage of the combination over single drug doxorubicin, despite the greater toxicity experienced with the combination. ■

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Breast Feeding and the Risk of Breast Cancer in BRCA1 and BRCA2 Mutation Carriers

ABSTRACT & COMMENTARY

Synopsis: *The influence of breast feeding upon breast cancer development was examined in women who carry deleterious mutations of the BRCA gene. They found that one or more years of breast feeding in women with deleterious BRCA1 gene mutations was associated with a reduction in breast cancer risk of 45%, an effect that is much greater than that observed in the general population.*

Source: Jernstrom H, et al. *J Natl Cancer Inst*. 2004; 96:1094-1098.

Breast cancer risk, in general, decreases with increasing duration of breast feeding. In the current report, the influence of breast feeding duration upon cancer development in women with BRCA1 or BRCA2 mutations was examined. For this, a case-control method was used. From an international registry of women with such BRCA mutations, breast cancer patients were compared with appropriately matched

controls (women with BRCA mutations but without cancer). The study involved 965 cases and 965 paired controls. Among women with BRCA1 mutations, the mean total duration of breast feeding was significantly shorter for case subjects (breast cancer patients) than controls (6.0 vs 8.7 months, respectively; mean difference = 2.7 months; 95% confidence interval [CI] = 1.4-4.0; $P < 0.001$). The total duration of breast-feeding was associated with a reduced risk of breast cancer (for each month of breast feeding, odds ratio [OR] = 0.98; 95% CI = 0.97-0.99; $P < 0.001$). Women with BRCA1 mutations who breast-fed for more than 1 year were less likely to have breast cancer than those who never breast-fed (OR = 0.55; 95% CI = 0.38-0.80; $P = 0.001$). The number of cases/controls with BRCA2 mutations was less and no association between breast feeding duration and breast cancer development was demonstrable for this group.

COMMENT BY WILLIAM B. ERSHLER, MD

Jernstrom and colleagues observed that women carrying deleterious BRCA1 mutations had a reduced risk of breast cancer if they breast fed for 1 year or more. Unfortunately, in this study, the reasons for not starting, or for stopping breast feeding were not ascertained. Thus, as the authors speculate, it is possible that women who have trouble with breast feeding are particularly susceptible to breast cancer. Indeed, one study[1] of women with nonhereditary breast cancer found that the risk of breast cancer was increased among women who tried to breast feed, but could not.

The data from this report support the conjecture, that breast cancer occurring in women with deleterious BRCA1 mutations are under the same, or similar, hormonal and reproductive influences as the occurrence of breast cancer in the general population. In fact, it was found that 1 or more years of breast feeding was associated with a reduction in breast cancer risk of 45%, an effect that is much larger than seen in the general population.[2,3]

The influence of breast feeding on breast cancer development remains incompletely explained, but certainly it may relate to changes in mammary gland differentiation or to effects on breast estrogen levels. There are a number of changes within the breast that occur during pregnancy, including the development of more well-differentiated alveolar lobules.[4] It is known that BRCA1 is critical to both appropriate proliferation and differentiation within the mammary gland[5] and it is possible that women with low levels of normal BRCA1 have increased breast epithelial cell proliferation in response to the increased estrogen of pregnancy.

Of course, this is an epidemiological finding from which clinical recommendations should be drawn with caution. However, a prospective, randomized trial of breast feeding duration in BRCA1 carriers would be logistically and ethically problematic. Thus, common sense will have to suffice. The data from this report are consistent with current understanding of breast cancer in general, and it is conceivable that the high risk of breast cancer development in BRCA1 mutation carriers may be reduced by successful breast feeding of one year or more. Furthermore, BRCA1 carriers who find that they are unable to breast feed may be at a particularly higher risk of cancer development. This latter concern may well be addressed by additional epidemiological investigation. ■

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Rethinking Combination Chemotherapy: Concomitant vs Sequential Drug Treatment for Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *Epirubicin and paclitaxel were administered either in combination or sequentially to 202 patients with metastatic breast cancer to demonstrate noninferiority of the sequential approach. Response rates and survival were comparable in the 2 groups, but toxicity was greater (neutropenia and neuropathy) in those that received the drugs sequentially rather than in combination. Thus, sequential treatment with epirubicin and paclitaxel is an effective approach, but at the doses used in the current protocol, the approach is associated with greater, not less, toxicity.*

Source: Conte PF, et al. *Cancer*. 2004;101:704-712.

SYSTEMIC CHEMOTHERAPY REMAINS THE PRIMARY treatment for metastatic breast cancer, particularly for those with hormone-resistant tumors. Combinations, including those of anthracyclines with taxanes are commonly used in this setting. In the current report, a group of

Italian oncologists performed a randomized trial to evaluate whether the results of sequential, rather than concomitant administration of drug would result in equivalent (non-inferior) results. The drugs selected were epirubicin (90 mg/m^2) and paclitaxel (200 mg/m^2) given in combination for a for a total of 8 cycles (concomitant arm, n = 108) or epirubicin at a dose of 120 mg/m^2 for 4 cycles followed by paclitaxel at a dose of 250 mg/m^2 over 3 hours for 4 cycles every 21 days (sequential arm, n = 94).

The median progression free and overall survival were 11 months (95% confidence interval [95% CI], 9.7-12.3) and 20 months (95% CI, 17.2-22.6) respectively, in the concomitant arm, and 10.8 (95% CI, 7.9-13.6) and 26 months (95% CI, 18.1-33.8) respectively in the sequential arm (*P* = not significant). Patients who received the sequential regimen experienced a higher incidence of Grade 3/4 neutropenia (62/2% of courses vs 50.62%; *P* = 0.03), whereas 6 patients who received the concomitant regimen developed Grade II cardiotoxicity. Quality-of-life analyses revealed no significant differences between the 2 regimens. Conte et al were therefore confident in rejecting the null hypothesis that the sequential treatment is less active than the standard concomitant regimen in this clinical setting.

COMMENT BY WILLIAM B. ERSHLER, MD

Since the introduction of MOPP chemotherapy for Hodgkin's disease several decades ago, there has been a deeply seated dogma, based upon sound rationale, experimental data and clinical trial experience supporting the notion of combined, rather than single agent chemotherapy for malignant disease. The rationale is based upon the expectation that efficacy is likely to be greater if drugs with different mechanisms of activity are used, and that acquired drug resistance would be less. Indeed, in both the adjuvant and metastatic disease treatment setting, combined drug regimens usually prove superior to single drug treatments.[1-3] However, with the introduction of newer, and potentially more powerful agents, the issue of single-agent treatment has arisen again. In fact, in the treatment of lung cancer, single agents therapy is commonly selected based upon a number of phase II and III trials demonstrating comparable efficacy and improved tolerability when compared to the more intensive combinations.[4] Sequential therapy has been introduced to capitalize on certain of the benefits of combination therapy but with the hopeful expectation of reduced toxicity, and possibly expense.

In this regard, the current report is quite interesting. Metastatic breast cancer patients were randomized to a standard paclitaxel/epirubicin either in combination (standard) or in sequence (experimental arm). The doses of each agent were lower when used in combination. In fact, when used alone (sequential arm), the doses selected were at, or near the maximum tolerated dose (120/mg^2 for epirubicin and 250/m^2 for paclitaxel).

What was observed is that sequential single-agent treatment was no less effective than the combination, but, unfortunately, it was no less toxic either. In fact, Grade 3/4 neutropenia (during the epirubicin phase) and Grade 2 to 4 neurotoxicity (during the paclitaxel phase) were both more common during in the sequential treatment arm. Furthermore, quality-of-life measures did not reveal either arm to be superior. Thus, the trial succeeded in demonstrating that active drugs in sequence may be comparable to combined therapy, but there was no advantage in terms of tolerability or quality of life.

Physicians need to be cautious about adopting the concept of sequential therapy but using lower doses, such as what would be used in combined regimens. Although reduced toxicity would be likely, the data indicating that such an approach has the same level of success with regard to survival, or even response rates are yet to be established. Hopefully, this group or others will examine lower doses of single agents, used sequentially to provide this clinically important benchmark. ■

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Frequency of Symptoms of Ovarian Cancer in Women Presenting to Primary Care Clinics

ABSTRACT & COMMENTARY

Synopsis: *Symptoms that are more severe or frequent than expected and of recent onset warrant further diagnostic investigation because they are more likely to be associated with both benign and malignant ovarian masses.*

Source: Goff BA, et al. *JAMA*. 2004;291:2705-2712.

It has been recently recognized and increasingly reported that ovarian cancer patients fre-

quently manifest symptoms, predominately related to their gastrointestinal or urinary tracts, a significant period of time ahead of their diagnosis. Goff and colleagues advance this line of investigation further by conducting a prospective study ascertaining the frequency of self-reported ovarian cancer-associated symptoms between 2 cohorts of patients seeking medical care. The case patients were those about to undergo surgery for a known or suspected pelvic or ovarian mass; the controls were women presenting to one of 2 primary care clinics, in which approximately two thirds were being seen for a specific problem.

The voluntary questionnaire instrument administered to both cohorts asked the respondents to score the severity, frequency, and duration of 20 symptoms generally reported by ovarian cancer patients. In both groups, recurring symptoms were common and non-specific. Symptomatology in control patients was related to the purpose of the visit (general check up vs specific complaint), their underlying disease co-morbidities and their menopausal status.

Not surprisingly, women with the final diagnosis of ovarian cancer generally reported numerically more symptoms of greater severity but of shorter duration of onset compared to either the clinic controls or patients with benign ovarian tumors. Ovarian cancer patients were also statistically more likely to report increased abdominal size, bloating, urinary urgency, and pelvic pain. The combination of the former 3 symptoms was reported 5 times more often in cancer patients than controls. The frequency and severity of these associated symptoms prompted Goff et al to conclude that the symptom triad was important enough to warrant further clinical investigation when identified.

COMMENT BY ROBERT L. COLEMAN, MD

One of the more frustrating aspects in the scientific pursuit to identify early stage ovarian cancer is that there is, as yet, no reliable way to accurately allocate individual risk. The prize when such study or modality is discovered would not only be better screening and surveillance but also improved survivorship through earlier stage detection. Currently, clinicians use a variety of radiographic and biologic tests to survey their patients either deemed at increased risk for the disease by history or in response to some symptomatology or physical exam finding that may suggest neoplastic ovarian pathology. Nonetheless, the algorithms developed so far are largely inefficient and imprecise. With respect to symptoms, the imprecision stems from the lack of correlative representation of stage and symptoms experienced and the broad spectrum of these complaints not specifically focused to the ovary or pelvic structures. For instance, many patients will have undergone a series of gastrointestinal diagnostic procedures and interventions before the diagnosis is made or suspected—many times before a pelvic exam is performed.

The current study does affirm previous reports that women with ovarian cancer do have a set of recognizable symptoms. The prevalence is high among women with this disease.[1-3] More than 90% of ovarian cancer patients were symptomatic in the 12 months preceding the diagnosis and two thirds of these reported recurring symptoms. The implication from the identification of the symptom cluster among case patients is that their occurrence should alert the clinician to work-up the patient for ovarian cancer. Unfortunately, strictly using the cluster as a decision tool would miss more than half the cancers and subject many women without cancer to unnecessary and expensive testing and procedures. To bridge this gap, one is called once again to practice the art of medicine. Consideration of these findings obviously can't be done in a vacuum and attest to the importance of appropriate evaluation of key clinical parameters and clues. It also mandates that clinicians hear what their patients are telling them and asking them what they are not. Without more precise diagnostic tools, the detection of early ovarian cancer will rely on this age-old, but arguably diminishing art. ■

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CME Questions

7. For patients with metastatic breast cancer, the recently reported Italian study demonstrated that sequential as compared with concomitant epirubicin and paclitaxel was:

a. more effective and less toxic.
b. comparably effective but less toxic.
c. comparably effective and less toxic.
d. comparably effective but more toxic.

8. **For women with deleterious mutations of BRCA1, breast feeding for one or more years is associated with a risk reduction of breast cancer development by approximately:**
   a. 5%
   b. 20%
   c. 45%
   d. 90%

9. **Which of the following statements about MOF adjuvant chemotherapy, as administered in the NSABP C-01 trial is most correct:**
   a. MOF chemotherapy resulted in approximately 40% better overall survival at ten years of follow-up, when compared to surgery-only.
   b. MOF chemotherapy resulted in approximately 20% better disease-survival but no significant advantage in overall survival at ten years, when compared to surgery-only.
   c. MOF chemotherapy resulted in significant disease-free and overall survival apparent at 5 years, but only disease-free and not overall survival at ten years..
   d. MOF chemotherapy resulted in significant disease-free and overall survival apparent at 5 years, but no significant advantage in either disease-free or overall survival at 10 years.

Answers: 7 (d); 8 (c); 9 (d)

In Future Issues:

New Combinations for Ovarian Cancer

PHARMACOLOGY WATCH

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

New Clinical Guidelines on Cholesterol Management

The National Cholesterol Education Program (NCEP), a product of a collaboration of the National Heart, Lung, and Blood Institutes, the American College of Cardiology, and the American Heart Association, has updated its clinical practice guideline on cholesterol management. Based on several recent studies, that suggest that aggressive lowering of LDL cholesterol benefits high-risk patients, the new guidelines recommend aggressive treatment for patients who are at risk for coronary artery disease. Specifically, patients who are defined as "very high-risk" should be considered for aggressive treatment. Very high-risk patients are defined as those who have cardiovascular disease together with multiple risk factors (especially diabetes), severe and poorly controlled risk factors (such as continued smoking), or metabolic syndrome. The guideline had previously recommended drug therapy in these patients only if the LDL cholesterol was greater than 130 mg/dL, with a goal of 100 mg/dL. The new guideline recommends a treatment threshold of 100 mg/dL, with a goal of 70 mg/dL. "High-risk patients" are defined as those who have coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or 2 or more risk factors (such as smoking or hypertension) that give a greater than 20% chance of having heart attack within 10 years. The LDL goal for these patients remains 100 mg/dL or less, and the new guideline now recommends drug treatment for those high-risk patients with an LDL > 100 mg/dL. Moderately high-risk patients are defined as those with 2 or more risk factors for coronary heart disease and a 10-20% risk of heart attack within 10 years. For these patients, drug therapy is recommended to lower LDL cholesterol under 130 mg/dL, and the option is given to treat to levels under 100 kg/dL. For lower-risk patients, the guideline was not changed. Drug therapies recommended by the NCEP include statins, bile acid resins, nicotinic acid, and ezetimibe. As in previous NCEP guidelines, the role of lifestyle modification is stressed. The full guideline can be viewed in the July 13th issue of *Circulation*, and highlights can be reviewed on-line at www.nhlbi.nih.gov.

Hypothyroidism and Pregnancy

A new study clarifies thyroid replacement therapy during pregnancy. Researchers at Harvard followed 19 women with hypothyroidism through 20 pregnancies, of which 17 resulted in full-term births. Thyroid function, HCG levels, and estradiol were measured before conception, every 2 weeks for the first trimester, and monthly thereafter. Oral doses of levothyroxine were increased during pregnancy to maintain preconception levels. The mean levothyroxine requirements increased 47% during the first half of pregnancy, plateaued by week 16, and remained

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stable until delivery. The authors recommend that hypothyroid women, who become pregnant, should increase their levothyroxine dose by 30% as soon as pregnancy is confirmed, and should be monitored carefully throughout the duration of their pregnancy (*N Engl J Med*. 2004;351:241-249). Although simple in its design, this is an important study because it is estimated that 1 to 2% of all pregnant women are hypothyroid and need replacement therapy. Hypothyroidism during pregnancy is associated with poor fetal outcomes including impaired cognitive development and increased mortality. Clinicians now have a clear guide to levothyroxine dosing changes during pregnancy.

Anti-Depressants and the Risk of Suicide

The risk of suicidal behavior is relatively high after starting anti-depressants, however, there is no statistical difference between anti-depressants used, according to a new study. Researchers reviewed data from the UK General Practice Research Database from 1993 to 1999, and compared nearly 160,000 users of 4 anti-depressant drugs, 2 SSRIs and 2 tricyclics; fluoxetine, paroxetine, amitriptyline, and dothiepin (a trycyclic anti-depressant not marketed this country). The outcome was first-time non-fatal suicidal behavior, or suicide in treated patients vs comparable patients who did not exhibit suicidal behavior. The relative risks for non-fatal suicidal behavior were 0.83 for amitriptyline (95% CI, 0.61-1.13), 1.16 for fluoxetine (95% CI, 0.90-1.50), and 1.29 for paroxetine (95% CI, 0.97-1.70), compared to those using dothiepin. Perhaps the most startling finding in this study was the 4.07 relative risk for suicidal behavior within 9 days of starting any anti-depressant (95% CI, 2.89-5.74), compared to patients prescribed an anti-depressant 90 days or more before their suicidal behavior. Even more concerning, was a relative risk for fatal suicide among new users of anti-depressants of 38.0 (95% CI, 6.2-231). The authors found no significant associations between use of the various anti-depressants and the risk of suicide (*JAMA.* 2004;292:338-343, ed 379-380). The accompanying editorial points out the timeliness of the study, with regard to current congressional hearings in the use of anti-depressants in young adults. The authors point out that the data on patients aged 10 through 19 is limited however, and further study may be needed in this group.

FDA Actions

The FDA has approved acamprosate (Campral-Merck) for the maintenance of abstinence in patients in alcohol recovery programs. The drug, which has been available in Europe for several years, may not work if patients are still drinking or abusing other drugs when initiating therapy. Acamprosate's mechanism of action is unknown, but it appears to act in the central nervous system. Common side effects include diarrhea, nausea, vomiting, and abdominal pain.

The FDA has approved Merck and Schering-Plough's Vytorin for the treatment of hypercholesterolemia. The drug combines Merck's simvastatin (Zocor) with the jointly developed ezetimibe (Zetia), and is touted to be as potent as the so-called "super statins" atorvastatin (Lipitor) and rosuvastatin (Crestor). The new drug, which is expected to garner a hefty market share, will be priced at $2.30 a pill and should be available this fall.

Imiquimod (Aldera-3M) has received the expanded indication for treatment of superficial basal cell carcinoma. The drug, which is a topical immune modulator, was recently approved for treatment of actinic keratosis, and was initially approved for the treatment of venereal warts.

Brief Notes

The over-the-counter cough medications, dextromethorphan and diphenhydramine, are no better than placebo in suppressing cough in children (*Pediatrics.* 2004;114:e85-e90).

Many women are turning to phytoestrogens in lieu of hormone replacement therapy. The most commonly used of these, isoflavone soy protein, does not improve cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women (*JAMA.* 2004;292:65-74).

Ginseng reduces the effectiveness of warfarin in healthy volunteers. Patients on warfarin should be questioned as to their herbal supplement use (*Ann Intern Med.* 2004;141:23-27).