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A monthly update of developments in cancer treatment and research

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INSIDE

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Clinical Oncology Alert's Editor, William Ershler, MD, is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Peer reviewer V.R. Veerapalli, MD reports no financial relationship to this field of study.

Chloroquine as an Adjunctive Therapy for Glioblastoma

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Based upon preclinical in vitro and in vivo studies that exhibit a more prolonged susceptibility of glioma cells to chemotherapy with the adjunctive chloroquine, a small but randomized placebo-controlled trial was conducted. The addition of daily chloroquine for one year after surgery was associated with a trend for reduced deaths in patients who received chemotherapy and radiation when compared to similarly treated patients but without chloroquine. These intriguing findings warrant large-scale investigation.*

Source: Sotelo J, et al. Adding chloroquine to conventional treatment for glioblastoma multiforme. *Ann of Intern Med*. 2006; 144:337-343.

PATIENTS WITH GLIOBLASTOMA MULTIFORME CONTINUE to have a very poor prognosis despite the common use of aggressive combination therapy with surgery, chemotherapy, and radiation. Most recent studies, for example, report a median survival of approximately one year after therapy.[1,2] The infiltrative nature of this tumor combined with the presence of inherently resistant or readily acquired chemo- and/or radiotherapy resistant cells, make it a particularly challenging cancer to effectively treat. The development of resistant clones may be facilitated by the high rate of mutagenesis in glial cells exposed to ionizing radiation or chemotherapy.[3,4]

Sotelo and colleagues at the National Institute of Neurology and Neurosurgery in Mexico have previously shown that cultured glioblastoma cells exposed to chloroquine or quinacrine in vitro maintain sensitivity to carmustine for longer duration and, in a rat model of malignant glioma, both chloroquine and quinacrine potentiate the antineoplastic effect of carmustine.[5]

Based on these experimental findings, their group conduct-

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ed a preliminary, open-label, non-randomized trial on patients with glioblastoma multiforme who were being treated by conventional methods but with added chloroquine. For comparison, concurrently treated patients who were treated with conventional therapy alone (no added chloroquine) were followed. Survival was found to be significantly longer for the chloroquine-treated patients.[6]

Encouraged by these preliminary findings the current study was conducted. It was a double-blind, placebo-controlled trial to evaluate the effect of chloroquine as adjuvant therapy for people with glioblastoma multiforme who were otherwise treated by conventional surgery, radiation and chemotherapy. The study period extended for 40 months from October 2000 through January 2004. To be enrolled, patients younger than 60 years with good performance status (Karnofsky scores of 70 or greater) and with MRI evidence that the tumor was restricted to one hemisphere were invited to participate. Thirty patients who met these criteria were enrolled and were treated by a standardized regimen of ablative surgery, four courses of carmustine and radiation (60 Gy administered over 30-32 treatments. In addition, 15 patients were randomized to receive 150 mg of chloroquine daily starting on day five after surgery for 12 months. The other 15 patients received placebo.

The chloroquine was well tolerated. There were no differences with regard to hematological toxicity when compared to placebo-treated patients. Furthermore, though of theoretical concern, no patients developed any signs of chloroquine-induced retinopathy. No patient from either group discontinued treatment or was lost to follow-up.

Median survival was 24 months for the patients in the chloroquine-treated group and 11 months for controls. At the end of the observation period, six patients treated with chloroquine had survived 59, 45, 30, 27, and 20 months respectively, whereas 3 patients from the control group had survived 32, 25, and 22 months respectively. Although the findings did not reach statistical significance (most certainly because the number of subjects enrolled was small), the rate of death with time was approximately half as large in patients receiving chloroquine as in patients receiving placebo (hazard ratio, 0.52 [95% confidence interval, 0.21-1.26]; $P = 0.139$).

COMMENTARY

Every once in a while, significant advances occur from insightful extension and investigation of theoretically sound ideas. Certainly, for the treatment of glioblastoma multiforme, advances have been slow to come and are sorely needed. Thus, the group of investigators from Mexico, aware that antimalarial drugs such as chloroquine and quinacrine are strong DNA-intercalating agents with demonstrated antimuagenic activity, postulated that concurrent treatment would be associated with more sustained efficacy of adjuvant chemo- and radiation therapy by virtue of their inhibition of mutation-associated resistance. The results would seem to support this notion. Of course, the observed advantage of chloroquine treatment in this study could have been due to chance alone, as the study was too small to reach statistical confidence. Chloroquine, inexpensive and available generically, is an unlikely candidate for a large-scale pharma-supported clinical trial. Nonetheless, the potential for a meaningful clinical advance is high, and hopefully the cooperative groups will take note and proceed to a definitive, multi-site trial. ■

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VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MARKETING PRODUCT MANAGER: Gerard Gernazian.
MANAGING EDITOR: Robert Kimball.
Associate Managing Editor: Leslie Hamlin

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Editorial E-Mail: robert.kimball@thomson.com

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Monoclonal Gammopathy Common in the Elderly

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Section of Hematology/Oncology, University of Chicago

Dr. Artz reports no financial relationship to this field of study.

Synopsis: *In this observational study of Olmstead County Minnesota, the authors describe the prevalence of monoclonal gammopathy of undetermined significance (MGUS) in residents 50 years or older. The overall prevalence was 3.2%. Male sex and older age were risk factors for having MGUS. Among those 80 years and over, an MGUS was detected in 6.6%. MGUS is common among older adults.*

Source: Kyle RA, et al. Prevalence of Monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2006;354:1362-1369.

Monoclonal gammopathy of undetermined significance (MGUS) is a common incidental finding but requires differentiation from multiple myeloma (MM). Distinguishing MGUS from MM once a serum or urine monoclonal protein has been detected requires a serum monoclonal protein concentration < 3 g/dL, fewer than 10% plasma cells in the bone marrow, and absence of lytic bone lesions, anemia, hypercalcemia or renal insufficiency related to a plasma cell disorder. MGUS remains a concern because of a heightened risk of progression to a plasma cell dyscrasia such as MM or primary amyloidosis. In the case of IgM MGUS, a lymphoproliferative disorder may subsequently develop. Prior reports have estimated the incidence of MGUS to occur in approximately 1-3% of adults and the risk of progression after an MGUS at 1% annually.

This epidemiologic study evaluated the prevalence of MGUS among residents 50 years and older in Olmstead County, Minnesota. Serum samples were available for over 20,000 residents, entailing most of the eligible residents. Immunofixation was performed on samples with an abnormality on serum electrophoresis.

MGUS was identified in 3.7% of men, 2.9% of women, and 3.2% among the entire cohort of 21,463 residents 50 years and older. Prevalence rose in concert with advancing age, from 1.6% for those 50 to 59 years rose to 6.6% for those 80 years or older. Isotypes involved were IgG in 69%, IgM in 17%, IgA in 11% and biclonal in 3%. Kappa light chain occurred in 62% and lambda in 38%.

COMMENTARY

This observational study by Kyle and colleagues offers a reasonable estimate of the prevalence of MGUS in the Caucasian population 50 years and older. The increased prevalence of MGUS with advancing age and male sex are not novel, but confirm prior work. The IgG isotype accounted for the majority of cases.

Limitations from this observational study include lack of knowledge about what evaluation patients had for the monoclonal protein. Some may have had an incomplete evaluation and actually had MM or other plasma cell dyscrasia. Alternatively, MGUS may be under diagnosed as light chain only monoclonal proteins would be missed by this screening modality. The almost entirely Caucasian population prevents inferences into other ethnic or racial groups. This may be particularly problematic among African-Americans, a group where MGUS and MM occurs more commonly.

MGUS is a common laboratory abnormality, particularly in the elderly. A challenging task remains

in determining how extensive an evaluation is necessary to exclude MM after finding a monoclonal protein. Clearly, in the presence of symptoms or other laboratory abnormalities (unexplained anemia, renal insufficiency, hypercalcemia, and significant urinary light chains) a complete evaluation is needed. Even with a negative evaluation, most would suggest following the monoclonal for evidence of progression. Risk factors previously published for progression to MM or other disorder include a serum M protein > 1.5 g/dL, a non-IgG monoclonal isotype, or an abnormal serum free light chain concentration ratio. In light of the numerous and effective therapies available for MM, recognition of MM is essential. ■

XELOX: Safe and Effective for Elderly Patients with Colon Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *A phase II study of combined capecitabine and oxaliplatin for elderly patients with metastatic colorectal cancer demonstrates safety and efficacy. The regimen may well become the treatment of choice in this setting because of the added convenience of oral administration of capecitabine.*

Source: Feliu J, et al. XELOX (capecitabine plus oxaliplatin) as first-line treatment for elderly patients over 70 years of age with advanced colorectal cancer. *Br J Cancer*. 2006;94:969-975.

Colorectal cancer is primarily a disease of older people, with more than 50% of patients being older than age 70.[1] Although chemotherapy has demonstrated benefit for colorectal cancer patients, older patients are less likely to receive treatment, either in the adjuvant[2,3] or metastatic[4] setting. The purpose of the current study was to examine the efficacy and tolerability of combined capecitabine and oxaliplatin (XELOX) in elderly patients who present with metastatic disease. The premise for the study is that this combination might be equally efficacious, but better tolerated and more convenient than comparable regimens that include parenteral fluorouracil (FU), leucovorin (LV), and irinotecan.

Fifty elderly (> 70 years) patients with metastatic colorectal cancer (MCRC) were enrolled in this phase II patients. Each received oxaliplatin 130 mg/m^2 on day 1 followed by oral capecitabine 1000 mg/m^2 twice daily on days 1-14 every three weeks. Patients with creatinine clearance of 30-50 mL/min received a reduced dose of capecitabine (750 mg/m^2) twice daily on the same schedule. By intent-to-treat analysis, the overall response rate was 36% (95% CI, 28-49%), with 3 (6%) complete and 15 (30%) partial responses. In total, 18 patients (36%) had stable disease and 14 (28%) progressed. The median times to disease progression and overall survival were 5.8 months and 13.2 months, respectively.

In general, the regimen was well tolerated. Nonetheless, 32 patients (64%) had an adverse event, but usually grade 1 or 2. The main adverse events were gastrointestinal and hematological. A total of 14 patients (28%) had grade 3/4 adverse events: 11 (22%) diarrhea, 8 (16%) asthenia, 7 (14%) nausea/vomiting, and only 2 (4%) with hand/foot syndrome and 1 (2%) with neurotoxicity.

Thus, the authors conclude that XELOX is well tolerated and effective therapy for elderly patients with MCRC. Furthermore, they speculate that the added convenience of oral treatment may be particularly agreeable to elderly patients who might have less favorable venous access and possibly transportation issues to and from clinic.

■ COMMENTARY

Capecitabine, either alone or in combination has proven to be a safe and effective drug for elderly patients with either colorectectal or breast cancer.[5] Capecitabine monotherapy as a first-line therapy for metastatic colorectal cancer has been shown to be more active in elderly patients than standard 5-FU/LV therapy. In a randomized, controlled study comparing single-agent oral capecitabine with the Mayo Clinic regimen (bolus 5-FU/LV) in patients > 60 years of age,[6] the overall response rate (ORR) was significantly greater with capecitabine (26% vs 16%; $P = 0.018$). As well, the ORR among patients treated with single-agent capecitabine did not significantly differ between those > 60 years of age and those ≤ 60 years of age (26% vs 24%; $P = 0.688$). Similarly, there was no significant difference in response rates in patients ≥ 65 years of age and < 65 years of age treated with XELOX (52% vs 58%; $P = 0.54$).[7] These findings suggest that elderly patients with colorectal cancer who are treated

with capecitabine are as likely to respond favorably to therapy as younger patients. Thus, the current Phase II study, focused particularly on elderly patients, confirmed suspicions that the combination would be effective. In fact the response rate of 36% and median time to progression (5.8 months) are quite similar to other published reports of XELOX treatment[8-10] although the median survival was somewhat less (13.2 months compared with 17-20 months in the other studies.[8-10] However, the current study was performed exclusively on elderly patients and the survival was comparable to other regimens so designed.[11,12]

There was, however, one surprising finding in the current report with regard to toxicity. Overall, the combination appeared comparable to other treatment regimens in this regard. Noteworthy, however was the very low incidence of grade 3/4 neurotoxicity which was less than one might expect, given the dose of oxaliplatin and the age of the patients. Indeed, in the Cassidy report,[10] grade 3/4 neurotoxicity occurred in 17%. Although the explanation for this is not obvious, the authors speculate that in the current series the cumulative dose of oxaliplatin was less (median, 4.5 doses per patient compared with 8 doses in the Cassidy trial), suggesting that with continued treatment may be associated with increased rates of developing this adverse outcome.

Thus, the current report confirms the confirms the efficacy and safety in the elderly of the XELOX regimen, when compared to other commonly used combinations for metastatic colorectal cancer. The combination has definite advantages when it comes to convenience, particularly for elderly patients. ■

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Pretreatment CA125 and Risk of Relapse in Advanced Ovarian Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *The baseline CA125 level before initiation of maintenance chemotherapy strongly predicts the risk of subsequent relapse.*

Source: Markman M, et al. Pretreatment CA-125 and risk of relapse in advanced ovarian cancer. *J Clin Oncol*. 2006; 24:1454-1458

IT HAS BEEN RECENTLY IDENTIFIED THAT nadir values in serial CA125 values during

adjuvant primary post-operative chemotherapy are prognostic even within the normal range (less than 35). Markman and colleagues set out to determine if a similar finding might be observed in evaluating the outcomes of patients entered into clinical trials evaluating the efficacy of maintenance therapy. Two trials were included in the current report: GOG-178/SWOG-9701, a phase III randomized study which evaluated paclitaxel (3 vs 12 cycles) and SWOG-9386, a single-arm open-label phase II trial that evaluated altretamine in patients with complete clinical response.

Consistent with the adjuvant study, the authors of the current study defined 3 categories of CA125 (≤ 10 u/mL, 11-20 u/mL and 21 to 35 u/mL). In addition to CA125, residual disease and age were considered in the final analysis. Similar to the previous report, patients with pre-registration CA125 values of 10 or less were associated with the best survival. This was observed in each of the 3 cohorts and in both studies. Overall, median PFS was 24 months, 17 months, and 7 months in the three CA125 groups. Of interest, in the randomized trial (GOG-178/SWOG-9701), the effect amounted to an improvement (12 cycles vs 3 cycles) of 9 months, 4 months, and 0 months in the 3 CA125 groups. The authors concluded that pre-treatment CA125 strongly predicts relapse in patients with complete clinical response following primary adjuvant chemotherapy.

COMMENTARY

Most patients and clinicians are acutely aware of the prognostic significance a normal CA125 implies following therapy. It has also been recognized that patients will typically manifest a nadir value from which serial determinations are compared in estimating recurrence. Sequentially doubling of these values even within the normal range (35 u/mL or lower) has been used as a surrogate of disease recurrence even in the absence of measurable disease. In addition, a provocative recent finding is that the value of this nadir is prognostic of recurrence.

The current trial expands this line of investigation by documenting a similar prognostic effect in pre-treatment CA125 values for patients with a clinical complete response undergoing maintenance chemotherapy. No difference in effect was observed between agents or among the treatment arms. The magnitude of the observed differences by CA125 category was impressive and amounted to nearly a year and a half. Perhaps even more provocative, in the randomized trial, the observations in PFS demonstrated that no difference was observed between the 12-month and 3-month arms for patients with CA125 values of 21-35 u/mL.

While the data are retrospective and not properly powered to determine the effect, they provides some insight into a potentially important factor by which patients may be identified who could benefit most from the maintenance strategy. Prospective trials with defined CA125 stratification will help to shed light on this important prognostic variable. Since maintenance therapy is not without complication, improving the precision of therapy will be a welcomed clinical finding. ■

Pulmonary Embolism after Major Abdominal Surgery in Gynecologic Oncology

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *Patients with cancer undergoing major abdominal surgery and using pneumatic compression for thromboembolic prophylaxis had 14-fold greater odds of developing a pulmonary embolism compared with patients with benign disease. Randomized studies are needed to determine whether additional prophylactic measures may benefit this high-risk group of patients.*

Source: Martino M, et al. Pulmonary Embolism After Major Abdominal Surgery in Gynecologic Oncology. *Obstet Gynecol.* 2006;107:666-671.

VENOUS THROMBOEMBOLISM (VTE) IS A MAJOR complication following gynecologic abdominal surgery that may be fatal in up to 1 in 4 affected patients. While several risk factors for VTE have been identified, carcinoma remains among the most

significant. Incidence rates of VTE in gynecologic cancer patients are estimated to be among the highest of all primary carcinoma sites. Martino and colleagues conducted a retrospective cohort study to evaluate the incidence of VTE among gynecologic cancer patients who had undergone surgery at their center over a 3-year period. Both major (n = 839) and minor (n = 507) procedures were evaluated among patients with known or suspected malignancy. Surgical VTE prophylaxis was pneumatic compression boots alone. Cancer diagnosis, age, and type of surgery (major vs minor) were evaluated in the context of VTE which was confirmed by spiral CT, pulmonary angiography or ventilation/perfusion scans. Overall, 22 cases of VTE were diagnosed among the 839 patients undergoing major abdominal surgery. Twenty-one of 507 (4.1%) cancer patients were identified with VTE—a mean 11 days post-operatively. Only 1 of 332 (0.3%) patients with benign disease were diagnosed with VTE. The odds ratio for VTE in cancer patients relative to those with benign disease was 13.8 ($P < 0.001$). Other factors identified with increased risk were ovarian cancer and age. Survival was statistically unaffected by the occurrence of VTE. The authors concluded that patients undergoing major abdominal surgery and using pneumatic compression devices for prophylaxis had 14-fold greater odds of developing a pulmonary embolus than patients with benign disease. The incidence of VTE identified in this study provides important baseline information upon which to develop randomized clinical trials to improve prophylaxis.

COMMENTARY

The clinical evaluation of VTE prophylaxis among patients with gynecologic malignancy has spanned more than 20 years. In 1983, Clarke-Pearson and colleagues conducted 2 randomized, controlled clinical trials of heparin and pneumatic compression to controls and confirmed that the latter was effective in preventing VTE. Pneumatic compression in that study was administered before surgery and continued for 5 days post operatively. The 2 modalities were studied against each other in a follow-up trial 10 years later documenting equivalency in the prevention of VTE. However, patients receiving heparin experienced bleeding complications. With the development of low molecular weight heparin (LWMH), Maxwell and colleagues re-evaluated this therapy compared to pneumatic compression in gynecologic oncology patients. In this randomized trial, both were effective in preventing VTE and bleeding complications were similar, prompting the authors to recommend either as a reasonable option for VTE prophylaxis in this cohort. Nonetheless the current trial, consistent with others in the literature, document that nearly 1 in 20 cancer patients and nearly 1 in 15 ovarian cancer patients will suffer a VTE under one of these recommended prophylaxis strategies. Clearly, this represents an important area of clinical investigation. While a small trial combining LWMH and compression boots was unable to document an improvement over single modality prophylaxis, it remains to be seen if other combination strategies can "move the bar" in VTE prophylaxis. Given the low overall absolute risk of VTE as identified in the current study, such trials will be necessarily large and focused in the gynecologic oncology population. Fortunately, the Gynecologic Oncology Group is currently developing such a study. ■

Suggested Reading

1. Maxwell GL, et al. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. *Obstet Gynecol*. 2001;98: 989-995.
2. Geerts WH, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(Suppl):338S-400S.

CME Questions

11. Chloroquine treatment for patients with glioblastoma multiforme, when combined with surgery, chemotherapy and radiation was shown:

a. to be well tolerated, except for retinopathy which occurred in about 1/3 of treated patients.
b. To be associated with statistically significant enhancement of overall survival.
c. To be associated with a trend to improved overall survival but to a level that did not reach statistical significance.
d. To have no added benefit when compared to similarly treated patients but without chloroquine.

12. What features of Monoclonal Gammopathy of Undetermined Significance (MGUS) were described in this study of Olmstead County Minnesota residents?

a. MGUS occurs more often in with advancing age
b. MGUS occurs more in women
c. Monoclonal proteins are commonly in the elderly and thus no multiple myeloma evaluation is ever needed
d. IgM is the most common isotype of MGUS

13. In the treatment of metastatic colon cancer in elderly patients, XELOX (capecitabine and oxaliplatin) was shown by Feliu et al. in Phase II trial to be:

a. Comparable to other reported regimens with regard to response rate and time to progression.
b. Associated with an intolerable incidence of hand/foot syndrome.
c. Associated with an intolerable incidence of neurotoxicity.
d. Less effective than comparable 5-FU based regimens in this setting.

Answers: 11 (c), 12 (a) 13 (a)

CME Objectives

The objectives of *Clinical Oncology Alert* are:

- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

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Reversal of Atherosclerosis Via Intensive Statin Therapy

Aggressive LDL lowering with statins, so-called "very intensive statin therapy," leads to reversal of coronary atherosclerosis, according to a new study. The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, a perspective, open label, blinded end-points trial, utilized the potent statin rosuvastatin in evaluating whether very intensive statin therapy resulting in LDL cholesterols in the low 60s associated with increases in HDL cholesterol could reverse atherosclerosis. Five hundred and seven patients were initially evaluated with intravascular ultrasound (IVUS) to determine baseline atheroma burden. Patients were then treated with intensive statin therapy with rosuvastatin 40 mg daily for 24 months, which resulted in an average LDL cholesterol of 60.8 mg/dL (mean reduction, 53.2%) and increased HDL cholesterol by 14.7%. IVUS was performed again at 24 months. The mean change in atheroma volume in the most diseased 10 mm sub segment was -6.1 (10.1) mm^3, with a median of -5.6 mm^3 ($P < .001$ vs baseline). Change in total atheroma volume showed a 6.8% median reduction. Adverse events were infrequent. Specifically there were no cases of rhabdomyolysis.

The authors conclude that lowering LDL-C to levels below currently accepted guidelines, when accompanied by significant increases HDL-C, can regress atherosclerosis in coronary disease patients, and is indicated for high-risk patients with established coronary disease (*JAMA*. 2006;295:1556-1565). An accompanying editorial notes that the study had several limitations, including lack of a control group or a comparator drug. They also note that the modest plaque reduction noted in this study "may not be the best measure of the treatment's effect on hard cardiovascular end points", however, they do applaud the pioneering work using intravascular ultrasound to help understand the anatomy and pathophysiology of coronary atherosclerosis and the effect of medical therapy on atheroma (*JAMA*. 2006;295:1583-1584).

Alternative Therapy for Depression?

Patients who fail SSRI treatment for depression may respond to an alternative medication, or the addition of a second medication, according to 2 studies in the March 23 *New England Journal of Medicine*. In the first study, 727 adults with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram (Celexa) were randomized to receive sustained release bupropion

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

(Wellbutrin) in a maximal daily dose of 400 mg, sertraline (Zoloft) at a maximum daily dose of 200 mg, or extended release venlafaxine (Effexor-XR) at a maximal daily dose of 375 mg for up to 14 weeks. The primary outcome was remission of symptoms based on the Hamilton Rating Scale of Depression (HRSD-17). Secondary outcomes included scores on the Quick Inventory of Depressive Symptomatology (Self-Report) (QIDS-SR-16). Remission rates, as assessed by the 2 scales, respectively, were bupropion - 21.3% and 25.5%, sertraline - 17.6% and 26.6%, venlafaxine - 24.8% and 25.0%. Response rates based on the QIDS-SR-16 were bupropion 26.1%, sertraline 26.7%, and venlafaxine 28.2%. There was no significant difference with respect to outcomes, tolerability, or adverse effects among the 3 drugs.

The authors conclude that after unsuccessful treatment with an SSRI, 1 in 4 patients have a remission after switching to another antidepressant, and all 3 drugs in the trial were reasonable choices (*N Engl J Med*. 2006;354:1231-1242). Another option for treating patients who failed treatment with citalopram was explored in the second study in the same issue. In the study, 565 adults who had a nonpsychotic major depressive disorder without remission after 12 weeks of citalopram therapy were randomized to receive add-on therapy with sustained release bupropion up to 400 mg per day, and 286 were randomized to receive buspirone (Buspar) at a dose of up to 60 mg per day. The same depression rating scales were used in this study as in the previous study. For bupropion and buspiron, respectively, HRSD-17 remission rate was 29.7% vs 30.1%, QIDS-SR-16 remission rate was 30.9% vs 32.9%, and QIDS-SR-16 response rate was 31.8% vs 26.9%. Bupropion was associated with a greater change in QIDS-SR-16 score, as well as the overall lower QIDS-SR-16 score at the end of the study and a lower dropout rate to due to intolerance (12.5% vs 20.6%, $P < 0.009$).

The authors conclude that the addition of bupropion or buspirone to citalopram is useful; however, the addition of bupropion may have some advantages, including a greater reduction in the severity of symptoms in fewer side effects (*N Engl J Med*. 2006;354:1243-1252).

FDA Actions

The FDA has approved the first generic HIV/AIDS drug for use in the United States. Zidovudine, manufactured under the trade name Retrovir by GlaxoSmithKline, was initially approved in 1987, and the company has had exclusive manufacturing rights until the drug's patent expired in September 2005. The generic is made by Aurobindo Pharma LTD of India. This is the same company that recently received approval from the FDA to co-package 3 antiretroviral drugs for the treatment of HIV/AIDS outside the United States. The regimen consists of lamivudine/zidovudine combination tablet along with efavirenz tablets. The co-packaging of these products has met the clinical safety, efficacy, and manufacturing quality standards required by the FDA. The approval is part of the Presidents Emergency Plan for offering full HIV treatment regimens for targeted areas of the world that are at risk to prevent HIV transmission and to treat AIDS and associated conditions. Patents and exclusivity prevent marketing of this combination in United States.

The FDA has approved a transdermal patch for the treatment of children with attention-deficit hyperactivity disorder. The patch delivers methylphenidate, the same ingredient found in Ritalin, in a daily patch that is applied early in the morning and removed 9 hours later. Methylphenidate patch is manufactured by Shire Pharmaceuticals and Noven Pharmaceuticals under the trade name Daytrana.

Salix pharmaceuticals has received approval to market a new tablet bowel prep for colon cleansing prior to colonoscopy. The virtually tasteless sodium phosphate tablets are an alternative to traditional liquid PEG bowel preps. The recommended dose is 32 tablets taken orally with a total of 2 quarts of clear liquids, administered as 4 tablets with 8 ounces of liquid every 15 minutes. Twenty tablets are given on the night prior to the procedure, with the remaining 12 tablets administered 3 to 5 hours prior to colonoscopy. Sodium phosphate tablets will be manufactured under the trade name OsmoPrep. ■