

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

by Milo Gibaldi, Ph.D., School of Pharmacy

CONTENTS

CLINICAL PRACTICE

- Evidence Does Not Support OTC Cough Preparation Use
- Choosing a First-Line Antidepressant
- UK Experts Assess Lung Cancer Treatments
- Predicting Efficacy After Start of Antiretroviral Treatment

NEW DRUGS & INDICATIONS

- Drug Approved for Benign Prostatic Hyperplasia
- FDA Approves Long-Acting Pegylated Filgrastim

DRUGS IN DEVELOPMENT

- Promising New Agents for HIV Infection

DRUG SAFETY

- Decreased Mitochondrial DNA & Nucleoside Toxicity
- HRT and Breast Cancer Revisited

DRUG EVALUATION

- Vitamin B12 May Augment Folic Acid Benefit
- ACE Inhibitor Ramipril Prevents Strokes
- Hematologic & Cytogenetic Responses to *Gleevec* in CML
- Amiodarone or Lidocaine for Shock-Resistant V. Fib

ERRATA: Irinotecan

Drug Therapy Topics Supplement

a monthly insert to *Drug Therapy Topics*

A Drug Information Center /
School of Pharmacy publication.
Written by Milo Gibaldi, Ph.D.
Edited by Nelda A. Murri, Pharm. D.
Prepared by Sandra Walston, M.C.
(206) 598-6612/nelda@u.washington.edu

Copyright © 2002
by the University of Washington.
No material may be reproduced in whole
or in part without written permission
from the editor.

CLINICAL PRACTICE

Evidence Does Not Support Use of OTC Cough Preparations

There is little evidence that over-the-counter (OTC) cough medicines are effective. This is the conclusion of British investigators after a systematic review of 15 randomized controlled trials, with a total enrollment of 2166 subjects, that compared in ambulatory settings oral OTC preparations with placebo in adults with acute cough due to upper respiratory tract infection. Each study had cough symptoms as an outcome [*BMJ*;2002;324:329-31].

In nine of the trials, treatment was no better than placebo. In two trials, antihistamines were without benefit. There was conflicting evidence on the effectiveness of antitussives, expectorants, antihistamine-decongestant combinations, and other combinations compared with placebo. The investigators noted that even when trials had significant results, effect sizes were small and of doubtful clinical relevance.

British physicians are encouraged to recommend OTC medicines for acute coughs, and the UK's health advice service, NHS Direct, also recommends cough medicines for dry coughs. While calling for an end to such recommendations, the investigators also recognize that, ultimately, it is up to patients whether to take a cough medicine. "There is little evidence that they do any harm, but they may also not have any benefits" [*Ibid*].

Choosing a First-Line Antidepressant

Patients, physicians, health insurers, and pharmaceutical manufacturers all have a considerable stake in the initial selection of an antidepressant. Patients and physicians hope to minimize the trial and error needed to find the treatment with the greatest benefits and fewest adverse effects, health insurers hope to satisfy patients and insurer purchasers while minimizing drug acquisition costs, and drug makers hope to demonstrate a unique advantage for a specific drug product.

A report in *JAMA* [2001;286:2947-55] compared the effectiveness of three widely prescribed selective serotonin reuptake inhibitor antidepressants—fluoxetine, paroxetine, and sertraline—among primary care patients initiating antidepressant treatment. In this randomized trial, investigators tried to replicate the conditions of everyday practice. They found that more than two thirds of the 573 patients beginning treatment recovered during nine months of follow-up, and that about 20% switched medication one or more times. The initial medication had

(Continued on Supplement page 2)

CLINICAL PRACTICE (continued)

Choosing a First-Line Antidepressant (continued)

no significant effect on clinical outcome. They concluded that the three SSRI antidepressants were similar in effectiveness for depressive symptoms as well as multiple domains of health-related quality of life over nine months, and that none can be recommended over another.

A related editorial observed, “The fact that SSRI drugs are equally effective on average does not mean that they are equally effective for individual patients. Among patients who do not respond to one SSRI antidepressant, half or more will experience significant benefit from another drug in the same class” [*Ibid*, 3003-04].

UK Experts Assess Lung Cancer Treatments

The *UK Drug and Therapeutics Bulletin* is not convinced there is a role for chemotherapy in managing non-small-cell lung cancer (NSCLC), which represents more than 75% of patients with lung cancer. The bulletin concludes that in early NSCLC, postoperative chemotherapy appears to offer no benefit, and whether preoperative chemotherapy to enable resection helps in locally advanced disease is not clear. It says that such treatment should only be used in the setting of controlled clinical trials.

For advanced-stage disease, which is the most common presentation, with a five-year survival rate

of less than 10%, chemotherapy used with best supportive care can lengthen a patient’s survival. According to the bulletin, UK oncologists believe it will benefit up to 50% of NSCLC patients. Platinum-containing regimens are widely used in the UK. The National Institute for Clinical Excellence has recommended consideration of four newer products—docetaxel, gemcitabine, paclitaxel, and vinorelbine—as part of first-line chemotherapy options for patients with advanced disease (in combination with a platinum agent) [*Scrip*, 27 February 2002].

Predicting Long-Term Efficacy After Start of Antiretroviral Treatment

Concentrations of HIV RNA in plasma predict the risk of AIDS and death during the natural course of the disease and serve as a marker of the efficacy of antiretroviral therapy. Current guidelines for changing therapy are based on measurements of plasma HIV RNA concentrations four or eight weeks after the start of treatment. Now, investigators have considered the possibility of assessing drug efficacy from measurements of plasma HIV RNA made during the first week of therapy. They analyzed the kinetics of virus decay during the first 12 weeks of treatment in 124 HIV-

infected patients newly introduced to a protease inhibitor. Patients in whom HIV RNA was undetectable or declined by more than 1.5 log were defined as good responders. The rest were poor responders.

Individual virus decay rate constants at day six correlated significantly with changes in HIV concentrations at 4, 8, and 12 weeks, and correctly predicted 84% of the responses. Reductions in plasma HIV RNA of less than 0.72 log by day six after initiation of therapy predicted poor long-term responses in 99% of patients [*Lancet* 2001;358:1760-65].

NEW DRUGS AND INDICATIONS

GlaxoSmithKline Drug for Benign Prostatic Hyperplasia

The FDA has approved Glaxo’s dutasteride for the treatment of benign prostatic hyperplasia (BPH). Dutasteride is the first 5-alpha reductase enzyme inhibitor to inhibit both enzymes responsible for converting testosterone to dihydrotestosterone in the prostate—a key process in the development and progression of BPH. A critical issue for dutasteride’s market potential is whether it will prove superior to

finasteride (*Proscar*), which has a 10-year head start. Other marketed products to treat BPH are terazosin (*Hytrin*), doxazosin (*Cardura*), and alfuzosin (*Xatral*), all of which are alpha-1-adrenergic blockers. They relieve BPH symptoms but, unlike 5-alpha reductase inhibitors, do not reduce the size of the prostate gland [*Reuters Health*, 26 November 2001].

FDA Approves Long-Acting Pegylated Filgrastim

Amgen received FDA approval for *Neulasta* (pegfilgrastim), a long-action version of the febrile neutropenia drug *Neupogen* (filgrastim). *Neulasta* has polyethylene glycol molecules added to filgrastim to extend the drug's half-life. Consequently the new product requires less frequent dosing than does *Neupogen*.

FDA approval was based on two clinical trials, in which the longer-acting formulation was shown to re-

duce the number of injections needed from about 10 or 11 per complete cycle of chemotherapy to five and to cut the number of hospitalizations for infections by half or more. Amgen plans to submit a cost-analysis to the regulatory agency to demonstrate that *Neulasta* can dramatically reduce hospitalization costs for febrile neutropenia, which can run about \$25,000 per patient [*Reuters Health*, 4 February 2002].

DRUGS IN DEVELOPMENT

Promising New Agents for HIV Infection

According to researchers at the 9th Annual Conference on Retroviruses, held this year in Seattle, several new drugs seem to be very potent against HIV, including resistant strains. Among them are compounds that represent two entirely new classes of anti-HIV medication—entry inhibitors and integrase inhibitors—and a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) that is apparently effective against HIV strains that are resistant to currently available NNRTIs—efavirenz, nevirapine, and delavirdine.

NNRTIs inhibit HIV by binding to a pocket next to the enzyme's catalytic site. This deforms the site so that it cannot function. Although they are powerful anti-HIV agents, today's NNRTIs can be rendered useless by a single mutation in the binding pocket. One of the new agents discussed at the conference, TMC 125, is a flexible molecule designed to fit into the NNRTI pocket even when common mutations are present.

The new entry inhibitors generated considerable interest at the conference. To gain entry into a cell, HIV's viral envelope protein gp120 must first dock with the cell's CD4 receptor followed by fusion of the viral and cellular membranes. The next step requires the virus to bind to a second coreceptor on the cell surface. The two major coreceptors for HIV are the chemokine receptors CCR5 and CXCR4. People who have mutations in CCR5 are highly resistant to HIV infection. Therefore, researchers set out to find agents that could inhibit these coreceptors. One inhibitor, Schering-Plough's SCH-C, is in clinical studies and shows promise. Current thinking is that entry inhibitors would be used in combination with other classes of drugs. Bristol-Myers Squibb scientists reported pre-clinical data on a new compound, BMS805, which binds to the viral envelope protein gp120 and competitively inhibits the CD4/gp120 docking interaction. Also presented at the meeting were *in vitro* data on S-1360, which inhibits HIV integrase, the enzyme that inserts HIV's proviral DNA into the host cell chromosome, a crucial step in the virus's life cycle.

DRUG SAFETY

Decreased Mitochondrial DNA: Hallmark of Nucleoside Toxicity

Nucleoside analogues that inhibit HIV reverse transcriptase are a cornerstone of antiretroviral therapy. These agents inhibit HIV replication but can also inhibit human DNA polymerase γ and, thereby, replication of mitochondrial DNA, leading to depletion of mitochondrial DNA and drug toxicity. Mitochondrial toxicity is implicated in an array of adverse effects such

as lactic acidosis, myopathy, peripheral neuropathy, pancreatitis, and perhaps the lipodystrophy syndrome. Early studies of zidovudine-induced myopathy identified a decrease in total mitochondrial DNA in muscle biopsy specimens. Hyperlactatemia is well known among HIV-infected patients receiving antiretroviral therapy, particularly in those receiving stavudine.

(Continued on Supplement page 4)

DRUG SAFETY (continued)

Decreased Mitochondrial DNA: Hallmark of Nucleoside Toxicity (continued)

The definitive diagnosis of nucleoside-related mitochondrial toxicity calls for muscle or liver biopsy, but a strategy for routine screening and monitoring is needed. With this in mind, researchers have developed a novel polymerase-chain-reaction assay for mitochondrial DNA, performed on samples of venous blood, and assessed whether changes in mitochondrial DNA might serve as a marker of nucleoside toxicity in HIV-infected patients [*N Engl J Med* 2002;346:811-20].

The investigators used the new assay to evaluate blood samples from HIV-seronegative individuals (controls); HIV-infected, asymptomatic patients who had never received antiretroviral therapy; and HIV-infected patients who developed symptoms of hyperlactatemia—fatigue, rapid weight loss, and reduced anaerobic threshold during exercise tests—while receiving antiretroviral therapy that included stavudine.

The researchers found that the mitochondrial to nuclear DNA ratios were 1.28 in the controls, 0.72 in the untreated HIV-infected patients, and 0.28 in HIV-infected patients treated with antiretroviral therapy that included stavudine. Once antiretroviral therapy was interrupted, however, and even after it was reinstated in the absence of stavudine, the ratio in these patients rebounded to levels not significantly different from the antiretroviral-naïve, HIV-infected patients.

The researchers concluded, “A validated quantitative mitochondrial DNA assay could be a useful tool to monitor and evaluate mitochondrial toxicity among HIV-infected patients receiving antiretroviral therapy, as well as among patients with other diseases, such as hepatitis and cancer, which are also treated with nucleoside analogues” [*Ibid*].

Hormone Replacement Therapy and Breast Cancer Revisited

A new case-control study adds to the increasing evidence that postmenopausal women who take hormone therapy for five years or more after menopause have an increased risk of breast cancer, especially a subtype known as lobular cancer, which accounts for 5% to 10% of all breast cancers [*JAMA* 2002;287:734-41]. Based on previous studies, excess risk seems to diminish and disappear within five years of stopping hormone replacement therapy (HRT).

The report shows that women who took HRT for five years or more during the six years before diagnosis of breast cancer had an increase in risk of 60% to 85% compared with women who did not use HRT. The increase in risk for lobular breast cancer was even

greater, about three times that of women who did not take hormones. The findings applied equally to women taking estrogen alone and women taking estrogen with a progestin.

The literature suggests that in women who do not use HRT, 253 in 100,000 will develop breast cancer in a given year, including 23 lobular tumors. In those taking hormones for five years or more, 419 of 100,000 will develop breast cancer, including 70 cases of lobular cancer. Lobular tumors, which form in milk-producing cells, and the much more common ductal tumors, which grow in the ducts that carry milk, are treated in the same way, but lobular tumors are harder to detect.

DRUG EVALUATION

Vitamin B12 May Augment Folic Acid in Vascular Disease Risk Reduction

In addition to its benefits in reducing neural tube defects, consumption of folate-fortified foods or dietary supplements reduces plasma levels of homocysteine, a risk factor for vascular disease, by converting homocysteine to methionine. Remethylation of homocysteine to methionine also requires vitamin B12, but vitamin B12 has proved to be a far less effective

determinant of homocysteine levels in plasma than has folate. Hypothesizing that the reason for this conclusion is not a lack of importance of B12, but rather that its effect is usually masked by the role of folate, researchers studied the association between homocysteine and folate and vitamin B12 levels in healthy men and

(Continued on Supplement page 5)

Vitamin B12 May Augment Folic Acid (continued)

women, before and after supplementation with folic acid [*Lancet* 2001;359:227-28].

The investigators gave men folic acid at increasing doses, from 100 µg/day to 400 µg/day. Serum concentrations of folate rose and homocysteine fell with increasing daily doses of folic acid but returned to baseline after discontinuation of folate. No change in vitamin B12 concentration was observed. At baseline, a significant inverse relation was noted between homocysteine and folate concentrations, but this relationship diminished with increasing doses of folic acid. The opposite effect was seen between homocysteine and vitamin B12 concentration. A weak relationship existed

at baseline, but with increased folic acid supplementation, a stronger and statistically significant association between homocysteine and vitamin B12 emerged. A study in women confirmed these observations.

The principal investigator told *Reuters Health* [23 January 2001], “The take-away message is that you can only lower homocysteine levels so much by taking folic acid. After that, it depends on the person’s vitamin B12 status.” He added, “Co-fortifying food with vitamin B12 has two possible benefits. First, it enhances the reduction in homocysteine levels. Second . . . it appears to further decrease a woman’s risk of having a baby with neural tube defect.”

ACE Inhibitor Ramipril Prevents Strokes

Stroke is the second leading cause of death in the world. About one-half of survivors have residual disability. A person’s risk of stroke increases with blood pressure. Angiotensin converting enzyme (ACE) inhibitors block the action of the renin-angiotensin system in plasma and in the vascular wall and lower blood pressure. Recent data suggest that ACE inhibitors also reduce proliferation of vascular smooth muscle; enhance endogenous fibrinolysis; have the potential to stabilize plaques; and decrease angiotensin II-mediated atherosclerosis, plaque rupture, and vascular occlusions. Thus, ACE inhibitors have the potential to lower the risk of ischemic vascular events, including strokes, through mechanisms that are independent of lowering blood pressure.

A recent report describes the impact of the ACE inhibitor ramipril on stroke, its subtypes, and related disability [*BMJ* 2002;324:699-702]. In a randomized, placebo-controlled trial, investigators followed 9297 patients with vascular disease or diabetes plus one additional risk factor for 4.5 years. Patients were on av-

erage 66 years old and had a mean systolic blood pressure of 139 mm Hg and a mean diastolic blood pressure of 79 mm Hg.

Blood pressure reduction was modest: 3.8 mm Hg systolic and 2.8 mm Hg diastolic. Nevertheless, compared with placebo, ramipril reduced the risk of any type of stroke by 32% and the risk of fatal stroke by 61%. Benefits were consistent across baseline blood pressures, other drugs used, and subgroups defined by medical histories. Significantly fewer patients on ramipril than on placebo had cognitive or functional impairment.

The authors of the report conclude, “Patients who are at high risk of stroke should be treated with ramipril, irrespective of their initial blood pressure and in addition to other preventive treatments such as blood pressure lowering agents or aspirin” [*Ibid*]. Supporting the idea that stroke prevention somehow involves the renin-angiotensin system are recent findings that losartan, an angiotensin receptor blocker, is more effective than a beta-blocker at reducing stroke risk.

Hematologic and Cytogenetic Responses to *Gleevec* in CML

Chronic myelogenous leukemia (CML) is caused by the BCR-ABL tyrosine kinase, the product of the Philadelphia chromosome. Imatinib (*Gleevec*) is a selective inhibitor of this kinase. *Gleevec* is approved for the treatment of the chronic phase of CML and for the treatment of gastrointestinal stromal tumors. The results of the second major clinical study of imatinib in patients with CML are now available [*N Engl J Med* 2002;346:645-52].

The new report describes the evaluation of outcomes of 454 patients with chronic phase CML who were treated with imatinib 400 mg/day. All of the patients had failed treatment with interferon alfa. Imatinib induced major cytogenetic responses in 60% of patients and complete hematologic responses in 95%. Over a median of 18 months, 89% of patients had not progressed to the accelerated or blast phases of CML, and

(Continued on Supplement page 6)

DRUG EVALUATION (continued)

Responses to *Gleevec* in CML (continued)

95% of the patients were still alive. Only 2% of patients discontinued treatment because of drug-related adverse events, and no treatment-related deaths occurred.

The authors of the report state, “Regimens that combine imatinib with other agents may improve re-

sults further and ongoing clinical trials are testing the feasibility of these approaches. The activity of imatinib is also being investigated in patients with newly diagnosed CML . . . comparing imatinib with standard interferon plus low-dose cytarabine” [*Ibid*].

Amiodarone or Lidocaine for Shock-Resistant Ventricular Fibrillation

Ventricular fibrillation is the most common cause of out-of-hospital cardiac arrest. The case fatality rate for cardiac arrest outside the hospital remains very high, generally more than 95%. Guidelines recommend antiarrhythmic drugs—amiodarone or lidocaine—in the treatment of ventricular fibrillation that persists after three or more external defibrillation shocks. Although lidocaine has traditionally been used in such cases, evidence of benefit is lacking. The lack of comparative data on lidocaine and amiodarone prompted researchers to conduct a double blind, controlled trial comparing the drugs in patients with out-of-hospital ventricular fibrillation [*N Engl J Med* 2002;346:884-90].

In a total of 347 patients, the mean interval between the time at which paramedics were dispatched to the scene and time of their arrival was seven minutes, and the mean interval from dispatch to drug administration was 25 minutes. After treatment with amiodarone, 22.8% of 180 patients survived to hospital admission,

as compared with 12.0% of 167 patients treated with lidocaine. Getting antiarrhythmic therapy to the patient as soon as possible after cardiac arrest is also important. Among patients for whom the time from dispatch to drug administration was equal to or less than the median time, 27.7% of those given amiodarone and 15.3% of those given lidocaine survived to hospital admission.

Despite its potential limitations (adverse effects, complexity of administration, and cost), amiodarone led to a significant and relatively large improvement in the proportion of patients who survived to hospital admission. On the basis of this trial and other evidence, there appears to be no indication for lidocaine administration to patients with shock-resistant ventricular fibrillation in the out-of-hospital setting. Future clinical trials are needed to clarify the potential use of amiodarone earlier in the course of resuscitation from life-threatening out-of-hospital arrhythmias and its potential effect on survival to discharge from the hospital [*Ibid*].

Errata: The following is corrected text to replace the article with the same title that appeared in the April 2002 *Drug Therapy Topics Supplement*, Vol. 31 No. 4, Supplement page 6. We would like to thank Marc Takemoto, Pharm.D., clinical pharmacist in oncology, and others for bringing the error to our attention.

Irinotecan Advances Treatment of Small-Cell Lung Cancer

The topoisomerase I inhibitor, irinotecan (*Camp-tosar*), could change the way small-cell lung cancer is treated. Data reported in *The New England Journal of Medicine* [2002;346:85-91] show a significant survival advantage associated with the combination of irinotecan and cisplatin over the usual chemotherapy—cisplatin plus etoposide (CE).

In the 154-patient phase III study, average survival was 12.8 months in the irinotecan-cisplatin

arm, with a one-year survival of 60% and an 89% tumor response rate, compared with an average survival of 9.4 months, a 40% one-year survival, and a 67% response rate with standard chemotherapy. Two-year survival rates were 19.5% in the irinotecan group and 5.2% in the CE group. The incidence of myelosuppression was lower for irinotecan-cisplatin patients than for CE patients. Irinotecan is a plant-derived material marketed and widely used for the treatment of metastatic colorectal cancer.