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INSIDE

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Melphalan, Prednisone and Thalidomide: The Standard Approach for Myeloma in Elderly Patients?

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a multi-institutional randomized clinical trial, the combination of melphalan, prednisone and thalidomide (MPT) proved superior to melphalan and prednisone alone (MP) for the treatment of newly diagnosed multiple myeloma in elderly patients when measured in terms of response rate and event-free survival. Longer, and possibly larger, studies will be needed to see if overall survival is similarly affected.*

Source: Palumbo A, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomized controlled trial. *Lancet*. 2006;367:825-831.

TWO THIRDS OF CASES OF MULTIPLE MYELOMA ARE DIAGNOSED after the age of 65 years.[1] Whereas for younger patients, high-dose chemotherapy with hematopoietic reconstitution has been shown to increase the rate of complete response and extend event-free and overall survival,[2,3] for the bulk of patients with this disease, such an aggressive approach has not become standard. In fact, for older myeloma patients, no other drug regimen has exceeded outcomes achieved by melphalan/prednisone.[4,5]

Thus, improvements are sorely needed for the management of this disease in the elderly.

Thalidomide, by virtue of its cytokine inhibition, inhibition of angiogenesis, stimulation of cellular immunity or altered expression of cellular adhesion molecules has been demonstrated to have anti-tumor activity, including, notably, patients with multiple myeloma.

In the current study which was conducted by the Italian Multiple Myeloma Network, oral melphalan and prednisone (MP) was com-

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pared to MP with added daily thalidomide (MPT). Fifty-four centers throughout Italy participated in the study and 331 patients were randomized. The eligibility criteria were quite inclusive. Patients 65 years and older who were considered not to be transplant candidates and without pre-existing neuropathy were considered eligible. Patients who presented with abnormal cardiac, renal or hepatic function or chronic respiratory disease were not excluded. Experimental therapy (MPT) consisted of oral administration of melphalan at 4 mg/m^2 on days 1-7 and oral prednisone at a dose of 40 mg/m^2 on days 1-7. Each cycle was repeated every 4 weeks for a total of 6 cycles. Thalidomide was administered at 100 mg per day continuously during the 6 cycles of MPT. The control arm (MP) received melphalan and prednisone on the same schedule for 6 cycles.

Response to treatment was monitored by measurement of protein in serum and urine every 4 weeks and the response rate was determined by criteria established by the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry.[6]

Patients treated with MPT had higher response rates and longer event-free survival than those treated with standard MP. Combined complete or partial response rates were 76% for MPT and 47.6% for MP for an absolute difference in response rate of 28.3% (95% CI, 16.5%-39.1%). Two-year event-free survival rates were 54% for MPT and 27% for MP (HR for MPT, 0.51; 95% CI, 0.35-0.75; P = 0.0006). Three-year-survival rates were 80% for MPT and 64% for MP (HR for MPT, 0.68; 95% CI, 0.38-1.22; P = 0.19). Rates for grade 3 or 4 adverse events were 48% in MPT patients and 25% in MP patients (P = 0.0002). However, midway through enrollment because of an apparent association of increased thromboembolism in MPT-treated patients, enoxaparin was prescribed to those on this arm. Thereafter the rate of thromboembolic events fell from 20% to 3% (P = 0.005). Grade 3-4 neuropathy occurred in 10 MPT treated patients.

COMMENTARY

Myeloma occurs most frequently in older patients and this clinical trial is to be credited for its inclusive design, the entry criteria disallowing only 29 of 382 assessed patients. Although the findings regarding the response rate's added advantage with thalidomide are totally consistent with expectations (based upon prior reports) it was encouraging to note the manageable toxicity that some might have expected would be higher in this population. In this regard the trial highlights the importance of DVT prophylaxis when using thalidomide in myeloma patients, a problem that also might be expected to be of higher prevalence in elderly patients.

At the American Society of Clinical Oncology (ASCO) 42nd Annual Meeting to be held in Atlanta, June 2-6, 2006 the plenary session will feature a similar research presentation from the a French consortium of myeloma investigators.[7] In their trial of myeloma patients 65 years and older (n = 436), 3 regimens were examined. These were MP, MPT and an aggressive regimen of VAD × 2, cyclophosphamide 3 gm/m^2 and 2 courses of MEL-100 (including stem cell rescue). In this trial, thalidomide was escalated to a maximum of 400 mg/day (as tolerated). The data to be presented will demonstrate superiority of MPT and the suggestion will be forwarded that this approach should be the reference treatment for older myeloma patients who are considered to be ineligible for high-dose treatment. The data from both Italy and France would support this conclusion. ■

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Arsenic and ATRA for APL Induction

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

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

Synopsis: *Although highly sensitive to a variety of agents, the need for prolonged therapy, particularly with anthracyclines in APL patients, may lead to significant toxicity and be contraindicated in others. In this study, standard chemotherapy was omitted. The combination of arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) alone showed significant activity as induction and maintenance therapy for newly diagnosed low-risk (WBC < 10,000/uL) APL patients. The addition of gemtuzumab to ATO/ATRO for high-risk patients or relapse was also relatively effective. Early death remains problematic. Confirmatory studies are needed.*

Source: Estey E, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood*. 2006; 107:3469-3473.

Acute promyelocytic leukemia (APL) has distinct biologic characteristics, clinical behavior, and responsiveness relative to other variants of AML. The majority of cases harbor the t(15:17)(q22;q12) which fuses the PML gene with the retinoic-acid receptor α gene (RAR), enabling molecular diagnosis and monitoring of PML/RAR transcripts. Bone marrow morphology often is suggestive, although it may be less obvious with the t(11:17) variant. White blood cell count > 10,000/uL represents an adverse prognostic factor.

Many chemotherapy agents have considerable activity in APL including anthracyclines, gemtuzumab ozogamicin (GO), arsenic trioxide (ATO), and all trans-retinoic acid (ATRA). APL now has the best long-term outcome owing to the leukemic sensitivity to these multiple agents. ATRA with an anthracycline with or without cytarabine has become a frequently employed induction regimen. Although ATRA may be considered a non-traditional chemotherapy agent, retinoic acid syndrome (RAS) is not uncommon and can be a life-threatening toxicity. Consolidation and maintenance regimens typically add ATRA and chemotherapy[1] and employ molecular monitoring for minimal residual disease. ATO also has significant single-agent activity in newly diagnosed and relapsed patients.[2] A recent study combining ATRA with ATO demonstrated enhanced activity over either agent alone in newly diagnosed APL.

Estey and colleagues devised a risk-adapted approach to identify low-risk APL patients where chemotherapy may be safely omitted. GO was added as chemotherapy for high-risk patients defined as: WBC was > 10,000/uL at diagnosis, positive PML/RAR PCR at 3 months from CR, relapse of disease by PCR, toxicity precluding further use of ATRA or ATO. Forty-four patients were treated on this schema.

For low-risk patients, ATRA was administered at 45 mg/m^2 in 2 divided doses daily and ATO given at 0.15 mg/kg ATO intravenously over 1 hour daily on day 10. For high-risk patients at presentation GO at 9 mg/m^2 was given on day 1.

Marrow samples were obtained weekly after 1 month. Therapy was discontinued when there were < 5% blasts and no abnormal promyelocytes. Once CR was obtained as defined by neutrophil and platelet recovery, ATO was given intravenously at 0.15 mg/kg daily on Monday through Friday of weeks 1 to 4, 9 to 12, 17 to 20, and 25 to 28. ATRA was given at 45 mg/m^2 daily during weeks 1 to 2, 5 to 6, 9 to 10, 13 to 14, 17 to 18, 21 to 22, and 25 to 26. Therapy was stopped at 28 weeks after CR. PCR for PML/RAR was done every 3 months. In the event ATRA or ATO were discontinued, GO was given at 9 mg/m^2 GO once monthly until 28 weeks after CR.

In the event of molecular relapse, 9 mg/m^2 GO once monthly was given for 3 months while continuing ATO/ATRA or resuming or resuming ATO/ATRA

if therapy completed. If molecular remission obtained, 3 more months of GO plus ATRA plus ATO was given. If not, 12 mg/m^2 idarubicin daily for 3 days was substituted for GO and patients considered for allogeneic transplantation if PCR persistently positive.

The majority 39/44 achieved CR (39/44) overall, 96% in low-risk patients, and 79% in high-risk patients. Five patients had early therapy related mortality, four within 3 days of therapy. Toxicity eventually developed in 5 patients on ATO forcing discontinuation. None of the 24 low-risk patients and 3 of 15 high-risk patients relapsed. Two of the relapses were salvaged and one died from disease. Median follow-up overall was only 16 months. In patients 60 years and older, 10/12 achieved a CR; and 9 remain in molecular remission at a median of 17 months.

COMMENTARY

Estey and colleagues report a prospective approach to limit the use of chemotherapy in newly diagnosed APL patients. The results confirm a high response rate to the combination of ATRA and ATO. Low-risk patients, defined as a white blood cell count < 10,000 /uL fared relatively well and had a reasonable rate of persistent molecular remission. GO added to ATRA and ATO appeared effective as well, although several patients relapsed within a year. A promising observation was 9 of 12 patients 60 years and older remain in remission at a median of 17 months.

The relatively short follow-up limits conclusions about long-term results. Also, 5 patients died early from treatment. Although not unusual, this remains a persistent problem for therapy of APL and may be one of the most important obstacles to enhance long-term outcomes.

These data require confirmation in a larger series since this was a single-institution series. The combination of ATRA and ATO appears a promising option, particularly for low risk patients for whom anthracycline and/or cytarabine chemotherapy may be contraindicated. The schedule employed for high-risk patients may potentially be less toxic than a standard consolidation and maintenance regimen so this also warrants further study.

Even better outcomes in the future may be anticipated with improved diagnostic techniques for risk adapted strategies. Further, the recent demonstration that 43% of APL cases showed a FLT-3 mutation offers another potential treatment pathway.[3] APL remains a great success story for modern oncology and the future looks even brighter.

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ZAP-70 and CD38: Markers of Importance in CLL

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In 156 patients with B-cell chronic lymphocytic leukemia, the presence of ZAP-70 and/or CD38 on the leukemic cell surface, as determined by flow cytometry, was shown to correlate with less favorable outcomes, including reduced event-free survival. These markers are thus useful clinical predictors of CLL aggressiveness and may ultimately be used to indicate which stage 0 patients should be treated at the time of diagnosis and which patients may have their treatment safely delayed.*

Source: Hus I, et al. The clinical significance of ZAP-70 and CD38 expression in B-cell chronic lymphocytic leukaemia. *Ann Oncol.* 2006;17:683-690.

B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (B-CLL) IS a disease with a highly variable clinical course. Some patients have very indolent disease, never requiring specific therapy while in others the course is very aggressive and management may be very difficult. Although staging systems have proven very useful,[1,2] it remains difficult to predict the clinical course for those who present in the earliest stages. Thus, efforts are underway to determine other features that will help identify stable or progressive forms of CLL that might facilitate risk-adapted treatment strategies.

In the current study, lymphocytes from 156 B-CLL patients were evaluated for the expression of ZAP-70

(zeta-associated protein) and CD38 by flow cytometry. Of these, 57 (37%) were ZAP-70 positive and 52 (33%) were CD38 positive. Of the entire group, 118 patients (76%) were both ZAP-70 and CD38 concordant. Both markers had predictive value but ZAP-70 proved superior. For example, although event-free survival (EFS) was significantly longer for both ZAP-70 negative and CD38 negative patient groups, when examining those individuals who, by clinical parameters had less favorable prognosis (stage of disease, high white blood count, low platelet count, and increased LDH) the presence or absence of ZAP-70 conferred more significant prognostic information than CD38 expression. Furthermore, in patients who required chemotherapy, ZAP-70 expression was significantly higher than in still-untreated patients ($P = 0.032$), and in all patients responding to first-line chemotherapy with purine analogues, ZAP-70 expression was significantly lower than in non-responding patients ($P < 0.008$). For this group there was no significant difference in CD38 expression.

Thus, both ZAP-70 and CD38 expression were shown to predict the clinical course of B-cell CLL. However, ZAP-70 expression appeared to be more predictive, particularly with regard to defining those cases that are likely to respond or not respond to first-line chemotherapy.

COMMENTARY

ZAP-70 is a marker for IgVH mutation and has been associated with more aggressive CLL.[3,4] CD38 is also considered an indication of IgVH mutation, and its presence on the surface of CLL cells was earlier demonstrated to be a negative prognostic indicator.[5] Both measures are conveniently determined by flow cytometry and are becoming increasingly available in clinical laboratories. The data from this report would suggest that obtaining both markers would be useful for both precise prognostic classification and confirmation if one or the other markers is borderline positive. For clinicians who are presented with stage 0 CLL patients, would the presence of these markers be sufficient to initiate treatment? For this question, the answer is not yet available. Certainly this would be a question worth rigorous clinical trial. Prior to that, one would have to make the assumption that earlier treatment in patients with CLL would offer survival advantage, and this has not been clearly demonstrated. Yet, it would seem that if early treatment were to make a difference, it would be for those with aggressive disease (such as might be predicted by the presence of both ZAP-70 and CD38 on the cell surface). Hopefully, a clinical trial will soon address this question. ■

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Results of Raloxifene RUTH and STAR Trials

ABSTRACTS & COMMENTARY

By Leon Speroff, MD

Professor of Obstetrics and Gynecology, Oregon Health and Science University, Portland

Dr. Speroff is a consultant for Barr Laboratories

Synopsis: *Clinical trial results indicate that raloxifene has no effect on the risk of coronary heart disease and is equivalent to tamoxifen in reducing the risk of invasive breast cancer.*

Sources: RUTH Trial, www.newsroom.lilly.com; STAR Trial; www.cancer.gov/newscenter.

THE ELI LILLY COMPANY AND THE NATIONAL CANcer institute released preliminary results from two large clinical trials involving raloxifene. The Raloxifene Use for the Heart (RUTH) study included more than 10,000 women from 26 countries, either at high risk for myocardial infarction or with known coronary heart disease. The participants were randomized to placebo or raloxifene, 60 mg daily, and followed for up to 7 years. There was no effect of raloxifene treatment on coronary heart disease events; however, there was a small increase in stroke mortality. Invasive breast cancer was a secondary end point, and there were fewer cases in the treated group compared to placebo. The women taking raloxifene had an increase in venous thromboembolic events. The numbers for breast cancer and venous

thrombosis were not provided in the preliminary report.

The Study of Tamoxifen and Raloxifene (STAR) enrolled 19,747 women at increased risk of breast cancer who were randomized to treatment with either raloxifene, 60 mg daily, or tamoxifen, 20 mg daily, in more than 500 centers in the United States, Canada, and Puerto Rico. The results are listed in the Table.

The numbers of invasive breast cancers were identical in the 2 groups of women. It was estimated that these results were equivalent to about a 50% reduction (based on the previous results in the tamoxifen prevention trial),[1,2] but without a placebo arm, an accurate assessment was impossible. Raloxifene appears to achieve the same reduction as tamoxifen in invasive breast cancers with a lesser increase in venous thrombosis, and perhaps no increase in cataracts and uterine cancer. Fractures, as well as strokes and heart attacks, were equally prevalent in the two groups. "Quality of life" was said to be the same for both drugs.

COMMENTARY

The results of the RUTH trial are not surprising. The known favorable impact of raloxifene on the cholesterol-lipid profile was not robust enough to prevent coronary events. Tom Clarkson has been teaching for many years that based on his monkey model, prevention of coronary events requires a direct impact on coronary vascular endothelium, an effect that is greater than and independent of lipid effects. In a 2-year randomized trial in monkeys reported 8 years ago, raloxifene exerted no protection against coronary artery atherosclerosis despite changes in circulating lipids similar to those achieved in women.[3]

The day after the release of the preliminary data, an article highlighting the STAR results appeared on the first page of my morning paper. The newspaper article and the release from the National Cancer Institute emphasized the "superiority" of raloxifene over tamoxifen, pointing out a lesser rate of uterine cancers, cataracts, and venous thromboembolic events with raloxifene. A National Cancer Institute spokesperson said that the ability to strengthen bones is an added bonus. One of the study investigators said that raloxifene will be the new yardstick for measuring other cancer-fighting drugs.

But wait a minute, there are some problems:

1. Tamoxifen has been demonstrated to reduce the incidence of both lobular carcinoma-in-situ and ductal carcinoma-in-situ.[1,2] In the 7-year follow-up report of the tamoxifen for prevention study, the risk for breast cancer was 0.57 (CI = 0.46-0.79), a 43% reduction, not the 50% cited in the results above, and the risk for in-situ disease was 0.63 (CI = 0.45-0.89), a 37% reduction.[1] Not only did raloxifene not yield a reduction, the number of in-situ cancers with raloxifene was greater. What does this mean? If raloxifene is truly preventing breast cancer, this should produce a reduction in in-situ disease; the greater increase with raloxifene is inexplicable and disturbing.
2. The fracture rates in the hip, wrist, and spine in the STAR trial were similar in the two groups. In the 7-year follow-up report of the US breast cancer prevention trial with tamoxifen, osteoporotic fractures were reduced by 32%; compared with placebo, there were 11 fewer hip fractures, 13 fewer spinal fractures, and 9 fewer fractures of the radius.[1] However, even after 8 years of follow-up, no effect of raloxifene has been evident on non-vertebral fractures.[4] A similar fracture rate in the STAR trial with the 2 treatments must reflect the incidence of spinal fractures. Neither tamoxifen nor raloxifene can achieve the efficacy in preventing all fractures well-proven with both hormone therapy and bisphosphonate treatment. Raloxifene's lack of effect on the risk of hip fractures makes it less advantageous than even tamoxifen for bone protection.
3. The rate of strokes was equivalent in the 2 treatment arms; the rate of stroke was increased by 42% in the tamoxifen prevention trial (coming close, but not achieving statistical significance.[1] A small increase in stroke mortality was reported in the RUTH trial. This is a serious risk for both drugs.

And there is a new player in this field, the class of drugs known as aromatase inhibitors. Aromatase inhibitors nearly completely inhibit total body

Table

STAR Results

	Raloxifene (9745 women)	Tamoxifen (9726 women)
Invasive breast cancer	67 cases	163 cases
Breast cancer-in-situ	81	57
Deep venous thrombosis	65	87
Pulmonary embolus	35	54
Strokes	51	53
Fractures	96	104
Cataracts	313	394
Uterine cancer	23	36

production of estrogen in postmenopausal women. In clinical trials, aromatase inhibitors have been more effective and safer than tamoxifen for the treatment of estrogen-sensitive breast cancers in postmenopausal women, either for early disease or for metastatic breast cancer. The American Society of Clinical Oncology[5] and the National Comprehensive Cancer Network (www.nccn.org), based on the results of clinical trials, now make the following recommendations:

- Postmenopausal women with hormone-positive breast cancers should be treated with an aromatase inhibitor.
- Treatment options include 5 years of aromatase inhibitor treatment alone or sequential therapy with 2-3 years of tamoxifen followed by aromatase inhibitor treatment for 2-5 years.
- The optimal timing and duration of treatment have not been established.
- Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen.
- Aromatase inhibitor treatment has been associated with better response rates compared with tamoxifen in postmenopausal women with tumors overexpressing HER-2. This evidence is not strong, but should be considered.
- Women finishing 5 years of treatment with tamoxifen should consider treatment with an aromatase inhibitor (for a minimum of 2.5 years).
- There is insufficient evidence available to support the use of tamoxifen after treatment with an aromatase inhibitor.

The major problem with aromatase inhibitors has been an increase in fractures due to the profoundly low estrogen levels (nearly a 99% decrease) and the subsequent loss of bone, a risk that can probably be prevented with bisphosphonate treatment. Besides hot flushing, other side effects are arthritic complaints, reduced sexual function, and myalgia.[6] Compared with tamoxifen, there is less, if any, endometrial stimulation, less venous thromboembolism, and slightly less hot flushing.

On-going trials are comparing one aromatase inhibitor with another (with and without an inhibitor of the cyclooxygenase system), 5 years of tamoxifen alone to 5 years of aromatase inhibitors, and sequential regimens comparing tamoxifen followed by an aromatase inhibitor and vice-versa. Large trials are also assessing the value of combining aromatase inhibitor treatment with ovarian suppression in premenopausal women with breast cancer. And appropriately, trials are testing the efficacy for prevention of breast cancer.

Given the greater efficacy and safety associated with aromatase inhibitors, one can safely predict that this class of drugs will perform better in the prevention trials as well. The problem of increased fractures can be prevented with adequate calcium and vitamin D supplementation and treatment with a bisphosphonate, once a month, once every 6 months, or even only once a year.[7] It's too soon to jump on the raloxifene bandwagon. ■

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CME Questions

14. Thalidomide, when added to standard melphalan/prednisone oral chemotherapy for older patients with multiple myeloma has been associated with:

a. improved complete and partial response rates.
b. improved event-free survival.
c. increased incidence of thromboembolic events.
d. All of the above
e. None of the above

15. **What best describes the clinical characteristics of acute promyelocytic leukemia (APL)?**
    a. Worse prognosis than other AML variants
    b. Can be molecularly monitored by PCR for PML/RAR transcript
    c. The combination of all trans-retinoic acid (ATRA) and arsenic trioxide (ATO) has no toxicity
    d. Response rate is very low

16. **The following statements are true regarding tamoxifen and raloxifene *except*:**
    a. both drugs have a modest favorable effect on lipids.
    b. both drugs have no important clinical effects on the risk of coronary heart disease.
    c. neither drug increases the risk of strokes.
    d. both drugs apparently reduce the risk of invasive breast cancer.

17. **For patients with newly diagnosed B-cell chronic lymphocytic leukemia, flow cytometry determined ZAP-70 on the leukemia cell surface:**
    a. confers a favorable prognosis.
    b. confers a negative prognosis.
    c. offers no prognostic information.
    d. offers prognostic information only for patients with advanced disease.

Answers: 14 (d); 15 (b); 16 (c); 17 (d)

CME Objectives

The objectives of *Clinical Oncology Alert* are:

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- 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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Gastric Acid Secretion and the Absorption of Thyroxine

The absorption of thyroxine is strongly influenced by stomach acidity, according to new study. Researchers from Italy looked at 248 patients with multinodular goiter who were treated with thyroxine with a goal thyrotropin (TSH) level of 0.05 to 0.20 mU/L. Of these patients, 53 had *Helicobacter pylori* related gastritis and 60 had atrophic gastritis of the stomach. The reference group comprised 135 patients with multinodular goiter and no gastric disorders. The study also included 11 patients who were infected with *H. pylori* during the study and 10 patients who were treated with omeprazole and had no gastroesophageal reflux. Patients with *H. pylori*-related gastritis, atrophic gastritis, or both had a daily requirement of thyroxine that was 22-34% higher than the reference group. In the 11 patients who became infected with age by lower *H. pylori* during the study, thyrotropin levels increased significantly (P = 0 .002), an effect that was nearly reversed with eradication of *H. pylori*. Treatment with omeprazole also increased serum thyrotropin levels (median 1.70mU/L increase in thyrotropin; P = 0.002), requiring a 37% increase in thyroxine dose.

The authors conclude that normal gastric acid secretion is necessary for effective absorption of thyroxine, and factors that impair acid secretion including atrophic gastritis, *H. pylori* gastritis, and treatment with omeprazole require increased doses of thyroxine (*N Engl J Med*. 2006;354:1787-1795). This study has important implications, given millions of patients who take thyroxine, the frequency of *H. pylori* infections in this country, and frequency of use of OTC and prescription proton pump inhibitors.

Can Plavix Add to the Efficacy of Aspirin?

Does clopidogrel (Plavix) add to the efficacy of low aspirin in patients with vascular disease? No, according to new study published in the April 20th *New England Journal of Medicine*. CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) is a multinational study which randomized 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75-162 mg/d) or placebo plus low-dose aspirin for median of 28 months. The efficacy primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of this end point was 6.8% with the combined drug treatment versus 7.3% with aspirin plus placebo (P = 0.22) for the subgroup of patients with multiple risk factors, the rate of the primary end point was lower for aspirin plus placebo (5.5% aspirin plus placebo versus 6.6% aspirin plus clopidogrel; P = 0.20) and the rate of death from cardiovascular causes was also higher with clopidogrel plus aspirin vs aspirin plus placebo (3.9% versus 2.2%; P = 0.01).

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In the subgroup with clinically evident atherothrombosis, there was a slight benefit for aspirin plus clopidogrel (6.9% versus 7.9%, P = 0.46).

The authors conclude that overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease (*N Engl J Med*. 2006;354:1706-1717). An accompanying editorial acknowledges that there were many subgroups within CHARISMA that showed varying outcomes with clopidogrel plus aspirin, but cautions against differentiating patients along the lines used in the study. The editorialists find that "these data showed no significant benefit associated with long-term clopidogrel therapy in addition to aspirin." (*N Engl J Med*. 2006;354:1744-1746).

Prevention of Hypertension?

Prehypertension is defined as blood pressure in the range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Since JNC-VII, there has been increased interest in prehypertension since it has been associated with excess morbidity and deaths from cardiovascular causes. A new study suggests that pharmacologic intervention in patients with prehypertension may help prevent progression to hypertension. The Trial of Preventing Hypertension (TROPHY) looked at 809 patients with prehypertension. A total of 409 patients were randomly assigned to candesartan or placebo for 2 years, followed by 2 years of placebo for both groups. When a study participant reached the study end point of stage I hypertension, they were treated with antihypertensive agents.

Both treatment and placebo groups were instructed in lifestyle changes to reduce blood pressure throughout the trial. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 in a candesartan group ($P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 in the candesartan group (relative risk reduction 15.6%; $P < 0.007$). Serious adverse events were slightly higher in the placebo group.

The authors conclude that treatment of prehypertension with candesartan was well-tolerated and reduced the risk of incident hypertension during the study period (*N Engl J Med*. 2006;354:1685-1697). In an accompanying editorial, it is pointed out the prehypertension is present in the about 70 million Americans, and is estimated to decrease average life expectancy by as much as 5 years. Despite this, the author urges caution in recommending wholesale treatment of all patients with prehypertension until more information is available on which drugs are most effective and the best duration of therapy. In the meantime, lifestyle changes, which benefit all risk factors, should be recommended for all patients with prehypertension (*N Engl J Med*. 2006;354:1742-1744).

Estrogen Alternatives

Since publication of the Women's Health Initiative (WHI), many postmenopausal women have discontinued estrogen, and most newly menopausal women are considering alternatives. A recently published paper systematically reviews clinical trials of nonhormonal treatments for hot flashes. More than 4000 studies were considered. Forty-three trials met inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other medications, and 17 trials of isoflavone extracts. In the antidepressant group, both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were effective in decreasing the daily number of hot flashes compared to placebo (mean difference -1.13; 95% CI, -1.70 to -0.57). Clonidine was also somewhat effective (-0.95; 95% CI, -1.44 to - 0.47), as was gabapentin (-2.05; 95% CI, -2.80 to -1.30). Red clover isoflavone extracts were not effective, and mixed soy isoflavones had mixed results. The authors conclude that SSRIs, SNRIs, clonidine, and gabapentin provide evidence for some efficacy; however, none are as effective as estrogen (*JAMA*. 2006;295:2057-2071).

FDA Actions

In April, the FDA issued a statement rejecting the medical use of marijuana, citing past evaluations by several US government agencies that showed that "no animal or human data supported the safety or efficacy of marijuana for general medical use." The statement supports the Drug Enforcement Agency's approach to treating all use of marijuana as a criminal act.

Zanamivir (Relenza), GlaxoSmithKline's inhaled anti-influenza drug has received a new indication for prophylaxis of influenza in patients age 5 years and older. The approval was based on 4 large-scale, placebo-controlled trials which showed that the drug was effective in reducing spread of influenza among household members and in community outbreaks. ■