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INSIDE

Financial Disclosure:

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.

Thrombophilia and Recurrent DVT

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Division of Hematology/Oncology, University of Chicago

Dr. Artz reports no financial relationships relevant to this field of study.

Synopsis: *The risk of recurrent venous thromboembolism (VTE) during extended anticoagulant therapy for thrombophilia remains poorly defined. Investigators analyzed 661 patients with idiopathic VTE who had been randomized to extended prophylaxis after three months of initial anticoagulation using either low intensity (INR 1.5-1.9) or standard intensity (INR 2.0-3.0) anticoagulation. Thrombophilic defects were identified in 42% of patients. The rate of recurrent VTE of only 0.9% per patient year was not influenced by thrombophilic abnormalities. Antiphospholipid antibodies trended toward increased recurrence (HR, 2.9; 95% CI: 0.9- 10.5). The presence of thrombophilic defects did not increase the risk of recurrent VTE during extended anticoagulation relative to patients with idiopathic VTE without thrombophilic defects.*

Source: Kearon C, et al. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. *Blood*. 2008;112:4432-4436.

An acquired, or hereditary, thrombophilic abnormality will be identified in around 30%-60% of unprovoked (aka, idiopathic) venous thromboembolism (VTE). A variety of thrombophilic defects have been described, such as factor V Leiden, the prothrombin gene mutation, anticardiolipin antibodies, elevated factor VIII and homocysteine, as well as deficiencies of antithrombin, protein C, and protein S. Although VTE recurrence is considerable after stopping anticoagulation, thrombophilic defects do not appear to increase the risk of VTE recurrence relative to patients without such a thrombophilia.[1] Limited data have been published on whether thrombophilia influences the risk of recurrent VTE while on anticoagulation therapy.

Kearon et al evaluated extended duration anticoagulation following three months of anticoagulation for unprovoked VTE, comparing low-intensity warfarin (INR 1.5-1.9) to standard-intensity (INR

VOLUME 25 • NUMBER 1 • JANUARY 2009 • PAGES 1-8

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2.0-3.0) in the ELATE trial.[2] The data demonstrated that low-intensity extended prophylaxis was less effective in preventing recurrent VTE relative to standard-intensity treatment. The author examined this dataset for the impact of thrombophilic defects on VTE recurrence risk while on anticoagulation. Thrombophilic risk factors assessed included factor V Leiden, prothrombin gene variant 20210 G>A, anti-thrombin deficiency, lupus anticoagulant, anticardiolipin antibody, elevated homocysteine, elevated factor VIII above the 90th percentile, or elevated factor XI above the 90th percentile. In the ELATE trial, 739 patients were enrolled. Only 661 were included in the present retrospective analysis. Some patients had known anticardiolipin antibodies before screening and were excluded (2.1% of total), and some refused to participate. Thrombophilic defects included factor V Leiden in 26.5%, the prothrombin gene mutation in 9.3%, an antiphospholipid antibody in 8.2%, and antithrombin deficiency in 3.6%. Ten percent of patients had elevated factor VIII, factor XI, and homocysteine. Proteins C and S were not assessed, as patients were on warfarin. In summary, 42% had no abnormality, 41% had one abnormality, 14% had two abnormalities, and 2% had three abnormalities. The mean follow-up was 2.3 years, with a mean rate of 0.9% per year risk of recurrent DVT on warfarin. The recurrence risk was considerably higher at 1.5% in the low-intensity arm relative to 0.4% in the standard intensity arm.

Comparing patients with one of the seven identified thrombophilic defects to those without showed no increased risk of recurrence (HR, 0.7; 95% CI, 0.3-2.0). Individual defects did not confer an increased risk, although among 54 patients with anti-phospholipid antibody, three events occurred that translated into a 2.3% annual recurrence risk (HR of 2.9, 95% CI: 0.8 to 10.5).

■ COMMENTARY

The duration of anticoagulation is one of the major management challenges of venous thromboembolism (VTE). In unprovoked VTE, the authors previously confirmed that extended prophylaxis, after three months of anticoagulation using low-intensity anticoagulation (INR 1.5-1.9), increases the risk of VTE recurrence relative to standard-intensity anticoagulation (INR 2.0-3.0). For unprovoked VTE, a search for thrombophilic defects will uncover an acquired or inherited defect in a considerable portion. VTE recurrence risk, after discontinuation of anticoagulation, appears similar to those with an identified thrombophilic defect compared to those without.

In this report, Kearon et al, using the ELATE clinical trial database, found that among patients with thrombophilic defects of factor V Leiden, prothrombin gene mutation, elevated homocysteine, factor VIII and XI, or antithrombin deficiency, VTE recurrence appeared similarly low relative to those without such an identified defect. Further, harboring two or more defects did not increase VTE risk. Although the numbers were quite small (ie, three events), patients with antiphospholipid antibody showed a non-significant trend toward increased recurrence on extended prophylaxis. Of note, patients with known antibodies prior to screening for the study were excluded.

This analysis has important limitations. First, not all thrombophilic defects were assayed, such as deficiencies of proteins C and S. Second, some of the defects are relatively mild thrombophilic risk factors, such as factors XIII and XI. Most importantly, the number of recurrent VTE events was relatively small. While the relative risks appeared similar in patients receiving standard- and low-intensity anticoagulation, most events occurred in the low-intensity prophylaxis cohort. As Kearon et al point out, the recurrence risk was only 0.4% per patient year using standard-intensity anticoagulation. Thus, we must be cautious about inferences regarding recurrence risk, as standard-intensity prophylaxis is the norm in clinical practice. Similarly, there are inadequate numbers of patients having two defects for factor V Leiden (homozygosity) to draw conclusions.

These results must also be interpreted in the context of the study. Thrombophilic defects did not increase recurrence risk compared to patients with unprovoked DVT.

Clinical Oncology Alert, ISSN 0886-7186, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Russ Underwood.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
MANAGING EDITOR: Leslie Hamlin
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Clinical Oncology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $40.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
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Questions & Comments
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One can assume most patients with unprovoked VTE have a thrombophilic defect, whether identified or occult.

The findings of this study provide confidence of a low DVT recurrence risk using extended standard-intensity warfarin prophylaxis, even among subjects with a thrombophilic defect. The results are consistent with prior data showing a low recurrence rate using anticoagulation for secondary prophylaxis among patients harboring a factor V Leiden mutation[3] or uncommon thrombophilic defects.[4] The presence of an antiphospholipid antibody could heighten recurrence risk of VTE, but the data are inadequate to recommend a different prophylactic strategy (eg, INR of 2.5-3.5). ■

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Bisphosphonates and Long-term Survival in Breast Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *The role of bisphosphonates in the treatment and prevention of bone metastases remains incompletely characterized. In the current report, Diel et al detail long-term survival data on patients with known microscopic bone disease more than eight years after adjuvant treatment with clodronate. Although other favorable markers such as reduced bone metastases and disease-free survival, present at earlier analyses, were no longer evident, those who were treated with clodronate continued to have improved overall survival.*

Source: Diel IJ, et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. *Ann Oncol*. 2008;19:2007-2011.

BISPHOSPHONATES, ADMINISTERED EITHER ORALLY OR intravenously, are known to accumulate within the bone microenvironment and inhibit osteoclast activity. Furthermore, it has been speculated that drugs in this class inhibit tumor cell adhesion to bone and enhance tumor cell apoptosis.[1,2] Because of these potential beneficial effects, bisphosphonates have been evaluated for the treatment and prevention of bone metastases in women with breast cancer.[3] Early results indicate that adding oral clodronate (Ostac®, Boehringer Mannheim/Roche) to postoperative adjuvant breast cancer therapy significantly improves disease-free survival (DFS) and overall survival (OS).[4] In the current report, long-term follow-up data from a prospective, randomized, controlled study are reported.

Primary breast cancer patients were enrolled in the study conducted at the University of Heidelberg between 1990 and 1995. Patients (n = 302) with immunocytochemical evidence of at least one tumor cell per million cells in the bone marrow, but without confirmed distant metastases, including to the bone, were randomized to receive either clodronate 1600 mg/day for two years (treatment group) or standard follow-up (control group). All patients in both groups received standard surgical treatment and customary adjuvant endocrine therapy or chemotherapy with or without radiotherapy. Follow-up evaluations were carried out every 3-4 months during the two-year treatment period.

The current analysis includes a total of 290 of the original 302 patients after a median time of 103 ± 12 months. Earlier reports from this cohort described differences in the incidence of bone and visceral metastases and disease-free survival in the clodronate group (at 36 months [4] and 55 months [5]), but these differences were no longer significant at 103 months. However, the significant improvement in overall survival for those in the clodronate group was maintained, with death occurring in 20.4% of the clodronate-treated patients and 40.7% of controls ($p = 0.049$).

■ **COMMENTARY**

Other studies have examined the role of bisphosphonate treatment in breast cancer. A study by Powles et al[6] in which patients with stage I-III breast cancer received oral clodronate or placebo for two years reported better overall survival in the treatment group. In this study, patients were not required to have evidence of tumor cells within the bone marrow. However, they showed that those at highest risk of recurrence experienced the greatest benefit from adjuvant bisphosphonate therapy. In contrast, Saarto et al reported increased bone metastases and reduced survival in clodronate-treated breast cancer patients at both 5[7] and 10 years[8] of follow-up. There were, however, methodological concerns in that study, including imbalanced randomization with more hormone-negative patients in the treatment arm and a fairly large number of protocol violations.

Currently, several trials[9] of adjuvant bisphosphonate treatment in patients with breast cancer are recruiting, or have completed patient recruitment, and await data analysis. A study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP B34) has recruited more than 3,000 patients with primary stages I and II breast cancer to compare the efficacy of oral clodronate with or without chemotherapy and/or hormone therapy in the prevention of bone metastases. The Southwest Oncology Group study (SWOG) is actively recruiting patients (expected accrual of 6,000 patients) to compare the efficacy of oral clodronate, ibandronate, and zoledronic acid in preventing bone metastases in patients who have undergone surgery for stages I-III breast cancer. And, the UK AZURE trial, which has recruited 3,356 patients, was designed to determine whether adjuvant treatment with zoledronic acid plus (neo)adjuvant chemotherapy and/or (neo)adjuvant endocrine therapy is superior to (neo)adjuvant chemotherapy and/or (neo)adjuvant endocrine therapy alone in improving the DFS and bone metastasis-free survival of patients with stages II and III breast cancer. Furthermore, the longer intervals of treatment in the AZURE trial may indicate whether a normalization of bone metabolism leads to a reduction of bone metastases and whether an intravenous application is as effective as an oral one.

Thus, the long-term data presented in the current report suggest an active role for bisphosphonates administered in the adjuvant setting for women with breast cancer. Hopefully, the larger trials will provide the needed data from which clinicians may be guided regarding which patients to treat and for how long. ■

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Prevalent vs Incident PSA Screen-detected Prostate Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Among patients who undergo screening and are diagnosed with prostate cancer, there is a dichotomy between those who are diagnosed after their initial screening (prevalent cases) and those who have cancer detected after subsequent screenings (incident cases). In the current analysis, "prevalent" cases were found to have a poorer outcome after radical prostatectomy than "incident" cases. This finding may be of clinical value, in conjunction with other prognostic factors, in the estimation of risk of recurrence and determining treatment strategies.*

Source: Nguyen PL, et al. Biochemical recurrence after radical prostatectomy for prevalent versus incident cases of prostate cancer: implications for management. *Cancer*. 2008; 113:3146-3152.

Prostate cancer (PC) screening remains controversial, and whether regular screening can decrease cancer-specific and overall mortality rates remains to be determined. However, it is clear that screening has led to a downward migration in age at diagnosis and lower stage and Gleason scores, all of which are associated with a lower PSA level at the time of diagnosis.[1] Among screened populations, it is unknown whether men with PC diagnosed at the initial screening (prevalent cases) have a different outcome than men who are diagnosed at subsequent screenings (incident cases) after adjusting for known prognostic factors. One study indicated that prevalent cases tend to consist of more poorly differentiated and higher volume tumors than incident cases,[2] whereas another found that patients who were diagnosed on their initial screening had a higher mean PSA, more advanced clinical tumor (T) classification, and had a greater proportion of high Gleason scores than patients who were diagnosed in subsequent rounds of screening.[3]

The current study was undertaken to determine if the risk of biochemical recurrence is greater for "prevalent" vs "incident" cases, after adjusting for other prognostic factors. The study cohort was comprised of 1,923 men from a prospective PC screening study who underwent radical prostatectomy (RP) between September 19, 1989 and May 22, 2002. Cox regression multivariate analysis was used to determine whether having prevalent PC vs incident PC was associated with the time-to-failure after RP, after adjusting for PSA level, Gleason score, clinical tumor (T) classification, and year of RP.

As expected, men with prevalent PC had higher PSA levels ($p < .001$) and more advanced clinical T classification ($p < .001$) than men with incident PC. After a median follow-up of 6.1 years, factors that were associated with a significantly shorter time to PSA failure after RP were prevalent PC (adjusted hazard ratio [AHR], 1.8; 95% confidence interval [95% CI], 1.3-2.6; $p = .0005$), baseline PSA (AHR, 1.07; 95%CI, 1.04-1.09; $p < .001$), Gleason 7 disease (AHR, 2.5; 95% CI, 1.9-3.3; $p < .001$), Gleason 8-10 disease (AHR, 2.3; 95%CI, 1.5-3.5; $p < .001$), and the year of RP (AHR, 0.92; 95%CI, 0.86-0.97; $p = .003$). Men with prevalent PC also had worse outcomes after adjusting for their more advanced pathologic features.

■ COMMENTARY

The main finding from this study is that after adjusting for PSA, T classification, and Gleason score, having a prevalent case (ie, prostate cancer) meant shorter time to PSA failure after radical prostatectomy. The clinical implication of this finding is that among screened men who are being considered for surgery, whether their cancer is a prevalent or incident case, should be factored into the calculation of their risk of recurrence in addition to the usual clinical features of PSA, T classification, and Gleason score. Whether prevalent cases would benefit from a more aggressive treatment regimen remains speculative at this time, but could be explored in future trials. Detected as a result of an elevated PSA at the first screening determination (ie, prevalent case) rather than an incident case was significantly associated with known prognostic factors, men with prevalent PC had a poorer outcome after RP than men with incident PC. Nguyen et al believe that this finding should be taken into consideration when weighing the risk of recurrence and treatment options for men who are diagnosed with PC on their initial screening.

These results and conclusions do not fully address the fundamental issue at the heart of the screening controversy. Although the finding that diagnosis after serial screening was associated with a lower recurrence rate than diagnosis after initial screening, is consistent with the hypothesis that earlier and more widespread screening could improve overall outcomes, there is the issue of lead-time bias that tends to inflate the apparent survival of screened patients. Thus, the benefits of screening would best be demonstrated by a randomized trial, two of which are currently underway (one in North America and one in Europe). ■

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FLOT: An Effective Regimen for Gastric or Gastro-esophageal Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *A new regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel [FLOT]) was tested in a phase II trial in 54 patients with gastric or gastro-esophageal cancer. Response rates were comparable, or perhaps even a little better than those published for other combinations; the toxicity profile appears favorable.*

Source: Al-Batran SE, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol*. 2008;19:1882-1887.

Systemic chemotherapy offers palliation and improved overall survival for patients with advanced gastric cancer.[1] Fluorouracil (FU) and cisplatin are commonly employed alone or in combination. Recently, a phase III trial demonstrated the addition of docetaxel to cisplatin and FU (DCF) was superior to cisplatin and FU (CF) in terms of quality of life, response rate, time to progression, and overall survival.[2] Despite the improvements observed, enthusiasm for this combination is tempered by the high level of toxicity observed, including grade 3/4 neutropenia, which occurred in more than 80% of those on the phase III trial, and substantial other toxicities, including stomatitis (21%), diarrhea (19%) and vomiting (14%). In recognition of this, other combinations, including docetaxel, have been tested. The current study was designed to incorporate docetaxel into a tolerable bi-weekly, oxaliplatin-based chemotherapy regimen.

Patients with measurable, metastatic adenocarcinoma of the stomach or esophagogastric junction and no prior chemotherapy received oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and fluorouracil 2600 mg/m^2 as a 24-hour infusion in combination with docetaxel 50 mg/m^2 (FLOT) on day 1 every two weeks. Prophylactic growth factors were not administered.

Fifty-nine patients were enrolled; 54 received treatment. Patients had a median age of 60 years (range 29-76), and most (93%) had metastatic disease. Objective responses were observed in 57.7% of patients with a median time-to-treatment response of 1.54 months. Median progression-free survival (PFS) and overall survival were 5.2 and 11.1 months, respectively. Twenty-five percent of patients experienced prolonged (> 12 months) PFS. Frequent (> 10%) grade 3 or 4 toxic effects included neutropenia in 26 (48.1%), leucopenia in 15 (27.8%), diarrhea in 8 (14.8%), and fatigue in 6 (11.1%) patients. Complicated neutropenia was observed in two (3.8%) patients only.

■ COMMENTARY

Compared to earlier regimens, the results established by the V-325 trial for the DCF regimen set a high bar for response rates in the treatment of gastric carcinoma.[2] Acknowledging the risks of interstudy comparison, it's difficult to resist contrasting the FLOT response rate of 57.7%, PFS of 5.2 months, one-year survival rate of 42%, and OS of 11.1 months with those same parameters achieved with DCF (response rate 37%, PFS 5.6 months; OS 9.6 months; one-year survival rate of 40%). But what is more impressive is the lower rate of both hematological and non-hematological toxicity. Adverse reactions included what might be expected from these drugs (docetaxel, FU, and oxaliplatin), and included grade 3 or 4 neutropenia in 48% of those treated. However, only two patients experienced "complicated" neutropenia, and again, this contrasts favorably when compared with DCF (grade 3 or 4 neutropenia, 82%; "complicated" neutropenia, 29%). FLOT was also associated with lower rates of non-hematological toxicity (diarrhea in 15% and neuropathy in 9%).

It might be premature to adapt FLOT as primary therapy for those with gastric or gastro-esophageal cancer, but certainly this combination deserves additional study. A phase III trial comparing the two regimens (FLOT vs DCF) would be a logical next step. ■

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Thalidomide-rituximab for Waldenstrom Macroglobulinemia

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Thalidomide-rituximab was administered to 25 symptomatic patients (20 previously untreated) with Waldenstrom macroglobulinemia. The overall response rate was 72%, and the median time-to-progression for responders was 38 months. Peripheral neuropathy to thalidomide was the most common adverse event, occurring in 11 patients. Thus, thalidomide-rituximab is an active regimen, and may prove a less toxic alternative than combination chemotherapy when treatment is required for this disorder.*

Source: Treon SP, et al. Thalidomide and rituximab in Waldenstrom macroglobulinemia. *Blood*. 2008;112:4452-4457.

Waldenstrom macroglobulinemia (WM) cells express CD20[1] and, accordingly, are suitable targets for rituximab, a therapeutic monoclonal antibody directed at the CD20 molecule. When used as a single agent at standard dose and schedule, rituximab induces an overall response rate of 27%-35% and median durations of response from 8-27 months.[2,3] When used on a more extended schedule, response rates and durations of response are improved to a small degree.[4] Factors that predict a less than optimal rituximab response include serum IgM level above 6,000 mg/dL and beta-2 microglobulin (B2M) greater than 3 mg/L.[4] When combined with chemotherapy such as cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP-R), or with dexamethasone and cyclophosphamide (DC-R), response rates approach 90% and the median time-to-progression, in excess of three years, has been reported.[5,6] Although impressive, these regimens are associated with prolonged neutropenia, occasional disease transformation, and the potential for secondary myelodysplasia and acute leukemia.

In an effort to avoid the complications of cytotoxic chemotherapy, the current phase II study was undertaken to assess the combination of rituximab with thalidomide. The rationale for this was based upon the observation that thalidomide enhances rituximab-mediated, antibody-dependent, cell-mediated cytotoxicity.[7,8] Patients with symptomatic WM who had not previously been treated with either rituximab or thalidomide were treated with daily thalidomide (200 mg for two weeks, then 400 mg for 50 weeks) and rituximab (375 mg/m^2 per week) administered on weeks 2 to 5 and 13 to 16. Twenty-five patients were enrolled, 20 of whom had been previously untreated. In total, one patient demonstrated a complete response, 16 patients achieved a major response, and two patients received a minor response, for overall and major response rates of 72% and 64%, respectively. Median serum IgM decreased from 3,670 to 1,590 mg/dL ($p <$ .001), whereas median hematocrit rose from 33.0% to 37.6% (p = .004) at best response. Median time-to-progression for responders was 38 months. Peripheral neuropathy to thalidomide was the most common adverse event. Among 11 patients experiencing grade 2 or greater neuropathy, 10 resolved to grade 1 or less at a median of 6.7 months.

■ COMMENTARY

Thus, it is apparent that thalidomide, in combination with rituximab, is active, and produces long-term responses in WM. The combination was generally well tolerated, and the response rates and duration of responses were comparable to those seen with CHOP-R or DC-R. Additional study is warranted to determine whether lower doses of thalidomide (ie, < 200 mg/day) would be similarly efficacious in light of the relatively high frequency of treatment-related neuropathy in this patient population.

Two further clinical notes are worth mentioning. First, abrupt increases in serum IgM have been known to occur with the use of rituximab in patients with WM, and, although transient, this can aggravate hyperviscosity and contribute to hyperviscosity-related symptoms. In this study, six patients with very high pre-treatment serum viscosity (3.5 CP or higher) received prophylactic plasmapheresis. Of the remaining 17 patients, nine experienced a rise in serum IgM after rituximab infusion and five had a rise in IgM of greater than 25%. Of the 21 patients who received a second course of rituximab, one required pre-treatment plasmapheresis, seven had a rise in IgM after rituximab, but only one had a rise greater than 25%.

A second note is that, unlike multiple myeloma, for which the thalidomide analogue lenalidomide has proven very effective, and with considerably less neurotoxicity, its use in WM has been problematic. In a prior clinical trial from this same group of investigators with lenalidomide in combination with rituximab, there has been the unexpected and curious development of an acute, non-hemolytic anemia and, furthermore, response durations for those who tolerated the lenalidomide treatment were shorter than those described for thalidomide-rituximab

(*Clinical Cancer Research*, in press). Thus, clinicians should resist the temptation to substitute lenalidomide for thalidomide when considering WM treatment. Perhaps, the exploration of newer thalidomide analogues will provide some clues as to why there is this unexpected difference in response to lenalidomide in WM patients. ■

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CME Questions

1. **The FLOT chemotherapy regimen for gastric cancer appears to be:**
   a. comparably effective to DCF (docetaxel, cisplatin, fluorouracil) in terms of response rates and survival.
   b. less toxic (hematologic and non-hematologic) than DCF.
   c. Both
   d. Neither

2. **Men who have prostate cancer diagnosed after their initial PSA was found to be elevated, compared to men who were diagnosed after serial screening PSA determinations, are more likely to have:**
   a. a larger tumor volume.
   b. a higher Gleason score.
   c. positive tumor involvement at the margins of the surgical resection.
   d. a shorter time to PSA recurrence.
   e. All of the above

3. **From the recent update of adjuvant clodronate treatment, after a median of 103 months, which of the following breast cancer outcomes were demonstrable in those treated with clodronate compared to those in the control group?**
   a. Reduced rate of bone metastases
   b. Improved disease-free survival
   c. Improved overall survival
   d. All of the above
   e. None of the above

4. **Thrombophilic defects, such as factor V Leiden, showed what impact on venous thromboembolism (VTE) recurrence while on extended warfarin prophylaxis for unprovoked VTE?**
   a. VTE recurrence was dramatically increased for patients with a thrombophilic defect compared to those without.
   b. The risk of bleeding using extended duration anticoagulation was prohibitive and thus should not be used.
   c. VTE recurrence for patients with a thrombophilic defect was not increased compared to those without.
   d. Antiphospholipid antibodies interfered with monitoring the INR on warfarin.

5. **The combination of thalidomide and rituximab is associated with overall response rates in patients with Waldenstrom macroglobulinemia that are comparable to:**
   a. rituximab alone.
   b. CHOP-rituximab.
   c. lenalidomide-rituximab.
   d. All of the above
   e. None of the above

Answers: 1. (c); 2. (e); 3. (c); 4. (c); 5. (b)

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.

In Future Issues: **Breast Cancer in Young Women: New Data**

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 14, NUMBER 1 PAGES 1-2 JANUARY 2009

Effective Combination Therapy for Acne

Source: Thiboutot D, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for once-daily treatment of moderate to severe acne vulgaris. *J Am Acad Dermatol* 2008;59:792-800.

TOPICAL AGENTS, BOTH AS MONOTHERapy and in combination, have shown efficacy in management of acne. Benzoyl peroxide (BPO) is one of the most commonly used agents, but despite excellent efficacy, the side effects of skin dryness, burning, erythema, and peeling are sometimes limiting effects of treatment.

Clinical trials of clindamycin phosphate (CMP) 1% + BPO have demonstrated that the combination is more effective than either agent alone, but traditional BPO concentrations (5%-10%) have been associated with dryness and irritation. Monotherapy comparisons of BPO 2.5% with BPO 5%-10% indicate similar efficacy, with better tolerability. Hence a clinical trial to establish the relative efficacy of CMP, BPO 2.5%, and the combination was a sensible next step.

Thiboutot et al randomized adolescents and adults (n = 2813) with moderate-to-severe acne to CMP 1%, BPO 2.5%, CMP + BPO, or placebo. Subjects were followed for 12 weeks. Outcomes included facial acne lesion counts as well as tolerability evaluation.

CMP + BPO was statistically significantly superior to CMP, BPO, and placebo at the conclusion of the trial. The tolerability of CMP + BPO was essentially the same as placebo (vehicle), and when adverse effects were reported, 97% were mild to moderate. My on-line search (Nov. 23, 2008) does not yet show availability of a CMP 1% + BMP 2.5% product, but FDA approval of this product (Acanya) occurred Nov. 20, 2008. ■

Genotypes associated with CRP elevations

Source: Zacho J, et al. Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med* 2008; 359:1897-1908.

IT REMAINS UNCERTAIN WHETHER THE observed relationship between elevated CRP levels and adverse cardiovascular outcomes is causal. The question remains whether elevated CRP simply reflects the presence of inflammation or instead is etiologic in increasing the risk of endpoints. One way to elucidate the relationship is to evaluate persons who have gene polymorphisms that lead to elevated CRP levels.

Danish investigators identified genotypes associated with elevated CRP; a high-sensitivity CRP level of > 3.0 was defined as high. Several populations were available for comparison: the Copenhagen City Heart Study (n = 10, 276); the Copenhagen General Population Study (n = 37,690); and the Copenhagen Ischemic Heart Disease Study (n = 2238).

Overall, an elevated CRP was associated with an increased risk of ischemic heart disease (2.2 relative risk). However, when the population of individuals with genetic polymorphisms leading to elevated CRP was evaluated, there was no increased CV risk identified. If elevated CRP levels were causal in CVD endpoints, one would expect that persons with genetically influenced elevations would show a similar risk relationship as study groups with known CVD. The concluding statement of the authors summarizes their findings: "…the risk of ischemic vascular disease associated with higher plasma CRP levels observed in epidemiologic studies may not be causal, but rather that increased CRP levels are simply a marker for atherosclerosis and ischemic vascular disease." ■

Benefits of Extended Duration Detoxification

Source: Woody GE, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth. *JAMA* 2008;300:2003-2011.

MISUSE OF PHARMACEUTICAL OPIOIDS is increasing. Data from 2004 indicate that as many as 10% of high school seniors acknowledge prescription opioid use in the prior year. Although the majority of opioid misuse is sporadic, a substantial minority of young adults suffer opioid addiction, for which short-term (14 days) buprenorphine combined with naloxone (s-B/N) has shown some detoxification benefit. Whether a more extended e-B/N (e-B/N) program could reduce opioid addiction relapse was the object of this study.

Woody et al randomized opioid-addicted adults (n = 153) to either s-B/N (14 days) or e-B/N (12 weeks). The primary outcomes measure was the number of patients with opioid-positive urine drug testing (UDT) at week 12.

UDT was opioid-positive in 51% of s-B/N subjects, compared with 43% of the e-B/N group. Post-treatment outcomes at months 6, 9, and 12 showed no statistically significant difference in use

of opioids, alcohol, or marijuana between the groups; on the other hand, cocaine use was approximately half as common in the e-B/N group. Extending the duration of B/N treatment merits further study, based upon the favorable results of this trial. ■

CPAP for OSA in Metabolic Syndrome

Source: Dorkova Z, et al. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. *Chest* 2008;134: 686-692.

The association of obstructive sleep apnea (OSA) with adverse cardiovascular (CV) outcomes is strong. Encouraging data from persons with OSA who have been treated with continuous positive airway pressure (CPAP) have demonstrated that effective CPAP treatment reduces blood pressure. Whether CPAP might have favorable effects on other CV risk factors such as glucose, lipids, and markers of inflammation is less clear. Individuals with metabolic syndrome, who are at increased risk for CV events, provide an appropriate population to study the impact of CPAP treatment for OSA upon CV risk factors.

Dorkova et al studied 32 metabolic syndrome patients with OSA. At baseline and after 8 weeks of CPAP for OSA, risk factors associated with CVD were measured and compared: BP, cholesterol, triglycerides, HDL, fibrinogen, CRP, insulin resistance, and others. Subjects who used their CPAP for at least 4 hours nightly were considered compliant.

Compliant CPAP users enjoyed reduced BP, cholesterol, and insulin resistance. Non-compliant CPAP subjects (i.e., < 4 hrs/night) did not demonstrate these favorable changes. CPAP has been shown, in the high-risk group of patients with metabolic syndrome, to improve the CV risk factor profile. ■

Clinical Briefs in Primary Care is published monthly by AHC Media LLC.

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

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Uric Acid and CV Risk: Not Ready Yet

Source: Feig DI, et al. Uric acid and cardiovascular risk. *N Engl J Med* 2008; 359:1811-1821.

The relationship between uric acid (URA) and cardiovascular (CV) risk has been the subject of controversy for decades. Even if one were to fully accept that the various associations between URA and unfavorable CV outcomes have a causal relationship, the hurdle of prospectively proving that reduction of URA will improve outcomes has yet to be addressed.

URA elevation has been identified as a harbinger of hypertension, as well as obesity, diabetes, and kidney disease, but that may only be part of the story. For instance, that renal disease develops disproportionately in gouty patients is certainly true, but so does hypertension, which is more often the cause of renal disease than uric acid stones or urate nephropathy. The Framingham Heart Study suggests that the relationship of URA and CV risk is not independent of hypertension, hence, it does not qualify as an independent risk factor.

URA may play an etiologic role in development of metabolic syndrome. Even though insulin resistance is regarded by some as a *sine qua non* of metabolic syndrome, URA often precedes the insulin resistance; indeed, animal studies suggest that decreasing URA forestalls metabolic syndrome.

URA is also associated with vascular disease in the carotids and peripheral circulation. Some even attribute favorable CV effects seen in the LIFE study (utilizing losartan) to its favorable effects on lowering uric acid (losartan is the only antihypertensive agent known to lower uric acid).

The pathophysiologic underpinnings linking URA to CV misadventure have some plausibility. All-in-all, the relationship between URA and CV risk is tantalizingly close to compelling. However, even though we have expanded the old aphorism that "close only counts in horse shoes and hand grenades" to include archery, darts, lawn bowling, etc., close still doesn't count in science. ■

Documentation of Coronary Ischemia Prior to PCI

Source: Lin GA, et al. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA* 2008;300:1765-1773.

For the sake of discussion, let's momentarily agree that percutaneous coronary intervention (PCI) is an appropriate step for persons suffering symptomatic coronary artery disease. The reason to establish this premise is that whether PCI actually offers any meaningful advantage over simple medical management is a matter of great debate. Indeed, the majority of PCIs in the United States are performed for patients with stable coronary disease, despite lack of evidence that outcomes with PCI in this setting are superior to intensive risk factor modification combined with medical therapy. Guidelines for PCI in stable CAD patients suggest that documentation of ischemia (most commonly by treadmill testing) should be obtained prior to PCI.

This study looked at Medicare beneficiaries undergoing elective PCI to see how often PCI had been preceded by stress testing. Of 23,887 Medicare recipients who underwent PCI in 2004, slightly less than half had any record of stress testing within the 90 days immediately preceding their PCI. The authors comment that in the absence of corroboration of ischemia, PCI may have been performed in patients who may not have benefited. ■

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*.

JUPITER: C-reactive Protein a Marker for CV Events?

In this issue: The JUPITER trial causes a stir; ACP practice guideline for antidepressant use; testosterone for low libido; continued shortage of Hib vaccine; FDA Actions.

The JUPITER trial causes a stir

Elevated high-sensitivity C-reactive protein (CRP) may help identify otherwise healthy patients with normal cholesterol levels who will benefit from statin therapy, according to the JUPITER trial published in November. Researchers randomized nearly 18,000 healthy men and women with normal cholesterol levels (LDL < 130 mg/dL) with CRP levels of 2.0 mg/L or greater to rosuvastatin (Crestor) 20 mg daily or placebo. The combined primary endpoint was myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular cause. The trial was stopped early at 1.9 years when the rate of the primary endpoint was found to be 0.77 per 100 person-years in the treatment group vs 1.36 per 100 person-years in the placebo (HR 0.56; 95% CI, 0.46-0.69; $P < 0.00001$). Overall, the rate of events was low in both groups: 142 of 8901 in the treatment group vs 251 of 8901 in the placebo group. The individual endpoints of myocardial infarction, stroke, and revascularization or unstable angina were all reduced by approximately 50% in the rosuvastatin group, LDL cholesterol levels were decreased by 50%, and CRP levels were decreased 37%. There was not a significant increase in myopathy or cancer in the treatment group, but there was a higher incidence of physician-reported diabetes. The authors conclude that in apparently healthy persons without hyperlipidemia but with elevated CRPs, rosuvastatin significantly reduced the incidence of major cardiovascular events (*N Engl J Med* 2008;359:2195-2207).

In an accompanying editorial, Mark Hlatky, MD, Stanford University School of Medicine, points out that although the relative risk reductions in the JUPITER trial were clearly significant, the absolute difference in risk was less impressive with 120 participants treated for 1.9 years to prevent one event. It is also difficult to know the role of CRP in risk stratification since patients with normal CRP levels were not treated and it is possible that lowering cholesterol with statins may benefit even those with low CRP levels. CRP may have a role in deciding whether to treat patients with intermediate risk, but it may be too early to use it to recommend treatment for those at low risk. Hlatky writes that "guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and long-term safety and cost" (*N Engl J Med* 2008;359:2280-2282). It is safe to say that JUPITER has been the subject of many lively discussions in hospital lunchrooms

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

across the country. Whether the benefit of rosuvastatin can be generalized to all statins, whether CRP should be a standard part of yearly blood panels for adults patients, and whether everyone with an elevated CRP should be offered treatment with a statin are all questions that are being hotly debated and will need further evaluation.

ACP treatment guideline for antidepressants

The American College of Physicians has issued a practice guideline for the use of antidepressants to treat depressive disorders. The guideline encompasses the use of newer "second-generation antidepressants," including the SSRIs: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and fluvoxamine (Luvox). Also included were the SNRIs venlafaxine (Effexor), and duloxetine (Cymbalta), as well as other drugs such as mirtazapine (Remeron), bupropion (Wellbutrin), nefazodone, and trazadone. After reviewing 203 clinical trials, the guideline group concluded that there were no significant differences between the drugs with regard to efficacy. The guideline group recommends that second-generation antidepressants should be selected on the basis of adverse effect profiles, cost, and patient preference. They further recommend that clinicians should assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1-2 weeks of initiation of therapy and that treatment should be modified if the patient does not have an adequate response to pharmacotherapy within 6-8 weeks. Finally, they recommend that clinicians continue treatment for 4-9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients with history of depression, a longer duration of therapy may be beneficial (*Ann Intern Med* 2008;149:725-733).

Testosterone for low libido: Questions remain

Low sexual desire is commonly reported by postmenopausal women. A new study suggests that testosterone replacement may be of benefit. Researchers randomized 814 postmenopausal women with hypoactive sexual desire or disorder to testosterone patches delivering 150 or 300 mg of testosterone per day or placebo. The primary endpoint was change from baseline to week 24 in the 4-week frequency of satisfying sexual episodes. Safety outcomes were followed out to one year. At 24 weeks the primary endpoint was significantly greater in the group receiving 300 mg of testosterone per day than placebo (increase in sexually satisfied episodes of 2.1 vs 0.7, $P < 0.001$) but not in the group receiving 150 mg per day. Both doses of testosterone were associated with significant increases in desire and decreases in distress. The rate of androgenic side effects including unwanted hair growth was higher in the group receiving 300 mg per day. Breast cancer was diagnosed in 4 women who received testosterone vs none in the placebo group. The authors conclude that a testosterone patch delivering 300 mg per day results in modest but meaningful improvement in sexual function although the long-term effects of testosterone including effects on the breasts remain uncertain (*N Engl J Med* 2008;359:2005-2017). This study confirms previous reports that testosterone has a positive effect on sexuality in women. The rate of breast cancer, although not reaching statistical significance in this study, raises concern.

Continued shortage for Hib vaccine

The continued shortage of the *Haemophilus influenza* type b (Hib) vaccine has not led to an increase in *Haemophilus* infections according to the *MMWR*. It has been a year since the CDC recommended deferring the fourth dose of the Hib vaccine in healthy children (at 12-15 months of age) because of a shortage due to contamination concerns in the manufacturing process. Merck & Co. now reports that mid-2009 is a realistic date for normal production. The CDC has undertaken national surveillance for Hib infections including 748 cases in children < 5 years old. Of these, only 6% were clearly identified as serotype b (the most invasive strain of *Haemophilus*), although serotyping information was missing in nearly 40% of cases. The CDC is concerned because antibody levels fall 12 months after vaccination in children. In the U.K., where the fourth booster was not initially recommended, Hib infections rebounded after 12-15 months. CDC is recommending vigilance on the part of pediatricians and also is emphasizing that state and hospital labs should perform serotyping on all *Haemophilus* infections.

FDA Actions

The FDA has approved fesoterodine fumarate for the treatment of overactive bladder. The drug relaxes smooth muscle of the bladder reducing urinary frequency, urge to urinate, and sudden urinary incontinence. Fesoterodine fumarate will be available in 4 mg and 8 mg strengths for use once daily. The drug is manufactured by Schwartz Pharma and will be marketed as Toviaz . ■