Providing Evidence-based Clinical Information for 18 Years

CLINICAL ONCOLOGY ALERT

A monthly update of developments in cancer treatment and research

Thomson American Health Consultants Home Page—http://www.ahcpub.com **CME for Physicians**—http://www.cmeweb.com

THOMSON AMERICAN HEALTH CONSULTANTS

INSIDE

Prophylactic G-CSF for elderly lymphoma patients ***page 83***

Extrapleural pneumonectomy ***page 84***

CML treatment in the elderly ***page 85***

Maintenance paclitaxel with advanced ovarian cancer ***page 86***

Palonosetron Improves Prevention of Chemotherapy-Induced Nausea and Vomiting Following Moderately Emetogenic Chemotherapy

ABSTRACT & COMMENTARY

Synopsis: *A single i.v. dose of palonosetron 0.25 mg was significantly superior to i.v. ondansetron 32 mg in the prevention of acute and delayed CINV.*

Source: Gralla R, et al. *Ann Oncol*. 2003;14:1570-1577.

The prevention of acute chemotherapy-induced nausea and vomiting (CINV) has improved dramatically in the past decade. Three selective 5-HT3 (serotonin-3) receptor antagonists—dolasetron, ondansetron, and granisetron—are available in the United States for this use. Despite some minor variations in pharmacology, these differences have not resulted in any clinically meaningful differences. According to current consensus guidelines, these medications are equivalent with regard to efficacy and are therapeutically interchangeable when used at equipotent doses.[1] The efficacy of these drugs is high with reported response rates of 50-70% in the prevention of acute CINV. There is a significant clinical problem in the prevention of delayed CINV. Palonosetron is a highly potent, selective, second-generation 5-HT3 receptor antagonist with a binding affinity that is ~100 fold higher than other drugs of the same class. It has an extended plasma elimination half-life of ~40 hours, which is significantly longer than others in its class. The present study was designed to determine the efficacy of this drug in the prevention of acute and delayed CINV following administration of moderately emetogenic chemotherapy.

■ COMMENT BY STUART M. LICHTMAN, MD, FACP

Patients older than age 18 scheduled to receive moderately emetogenic chemotherapy were selected. The chemotherapy included any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan or mitoxantrone; methotrexate > 250 mg/m^2; or cisplatin > 50 mg/m^2; cyclophosphamide > 1500 mg/m^2; or doxorubicin > 25

VOLUME 18 • NUMBER 11 • NOVEMBER 2003 • PAGES 81-88

mg/m^2. Patients were to receive a single intravenous dose of palonosetron 0.25 mg, palonosetron 0.75 mg, or ondansetron 32 mg.

Corticosteroids were not used in this trial. A complete response (CR) was defined as no emetic episode and no use of rescue medication during the first 24 hours following chemotherapy administration. Secondary end points included the proportion of patients achieving a CR during the delayed 24-120 hour time period and the cumulative 120-hour time period. Complete control was defined as no emetic episode, no need for rescue medication, and no more than mild nausea. Various quality-of-life parameters were also used.

The study had 563 patients evaluable for efficacy. The rate of CR with palonosetron 0.25 mg was superior to palonosetron 0.75 mg and ondansetron 32 mg in the prevention of acute (81% vs 73.5% vs 68.6%), delayed (74.1% vs 64.6% vs 55.1%), and overall (69.3% vs 58.7% vs 50.3%) CINV. Palonosetron produced significantly higher complete control rates compared with ondansetron during the delayed interval (66.7% vs 50.3%) and the overall interval (63.0% vs 44.9%). Time-to-treatment failure was significantly longer following treatment with palonosetron than treatment with ondansetron (46.5 hours vs 19.5 hours). Palonosetron 0.25 mg was superior to ondansetron in the number of emetic episodes during the acute, delayed, and overall intervals as well as on study days 2 and 3. Subset analysis showed than males had higher CR and complete control rates, less severe nausea, longer time to treatment failure, longer time to first emetic episode, and less rescue medication. Chemotherapy-naive patients tended to have less severe nausea than non-naive patients. The most common adverse reaction reported was headache in all groups (~5%).

The results of this study suggest that the binding affinity difference of palonosetron translates into improved control of CINV in patients receiving moderately emetogenic chemotherapy. This single-dose study showed the superiority of palonosetron over ondansetron in preventing delayed CINV, as measured by CR and complete control rates, as well as respect to number of emetic episodes, percent of patients with no nausea, and time to treatment failure. A similar trial of palonosetron and dolasetron in patients receiving moderately emetogenic chemotherapy showed similar results.[2]

This is an important clinical observation, as other 5-HT3 receptor antagonists do not demonstrate substantial efficacy in delayed emesis, despite repeated dosing and concomitant use with corticosteroids. There is currently available a novel neurokinin 1 antagonist, aprepitant, that has been shown to improve control of CINV when added to a standard antiemetic regimen of 5-HT3 receptors antagonists plus a corticosteroid.[2] Aprpeitant can produce moderate inhibition of CYP3A4, which can potentially produce clinically significant drug interactions.[3]

There are now a number of newer and more efficacious medications for the prevention of acute and delayed CINV. Palonosetron may have an advantage in that it can be used as a single-dose medication, which does not require corticosteroids for efficacy. Further studies will elucidate the role of the second-generation 5-HT3 receptor antagonists and neurokinin 1 antagonists in the treatment of our patients. ■

References

1. Gralla RJ, et al. *J Clin Oncol*. 1999;17:2971-2994.
2. Poli-Bigelli S, et al. *Cancer*. 2003;97:3090-3098.
3. Majumdar AK, et al. *Clin Pharmacol Ther*. 2003;74: 150-156.

Clinical Oncology Alert, ISSN 0886-7186, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina.

GST Registration Number: R128870672. Periodicals postage paid at Atlanta, GA.

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.
This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail Address:
customerservice@ahcpub.com

Editorial E-Mail Address:
robert.kimball@ahcpub.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $239
(Student/Resident rate: $120).

Multiple Copies
1-9 additional copies: $215 each; 10 or more copies: $191 each.

Canada
Add GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517 or **Robert Kimball,** Assistant Managing Editor, at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Ershler is on the speaker's bureau for Wyeth and does research for Ortho Biotech. Drs. Hawkins, Kaplan, Kotz, and Morris report no relationships related to this field of study. Drs. Canellos, Chabner, Einhorn, Goodman, Lippman, Pinedo, and Sutton did not return financial disclosures.

Prophylactic G-CSF for Elderly Lymphoma Patients: Negative Findings

ABSTRACT & COMMENTARY

Synopsis: *In a trial of elderly patients with non-Hodgkin's lymphoma, the prophylactic use of granulocyte colony-stimulating factor did not improve clinical outcomes, including hospitalization rate and survival. The findings run counter to an emerging clinical trend toward the use of prophylaxis with colony-stimulating factors in susceptible populations. Certain concerns are raised about the current trial, but the findings are of great importance and need to be confirmed by additional clinical investigation before we abandon the concept of primary prophylaxis in chemotherapy-treated elderly patients.*

Source: Doorduijn JK, et al. *J Clin Oncol*. 2003;21: 3041-3050.

THE DUTCH-BELGIAN HEMATO-ONCOLOGY Cooperative Group undertook an investigation to determine whether the relative dose-intense cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy could be improved by prophylactic administration of granulocyte colony-stimulating factor (G-CSF) in elderly patients with aggressive non-Hodgkin's lymphoma (NHL). For this, patients aged 65-90 years with aggressive histology NHL were randomly assigned to receive standard CHOP chemotherapy every 3 weeks or CHOP plus G-CSF, with the G-CSF administered on days 2-11 of each cycle.

In 389 eligible patients, the relative dose intensity of cyclophosphamide (median, 96.3% vs 93.9%; P = .01) and doxorubicin (median, 95.4% vs 93.3%; P = .04) were higher in patients with CHOP plus G-CSF. The complete response rates were 55% and 52% for CHOP and CHOP plus G-CSF, respectively (P = .63). Actuarial survival at 5 years was 22% with CHOP alone, compared with 24% with CHOP plus G-CSF (P = 0.76) at a median follow-up of 33 months. Patients treated with CHOP plus G-CSF had an identical incidence of infections and only cumulative days with antibiotics were fewer with CHOP plus G-CSF (median, 0 vs 6 days; P = .006) than with CHOP alone. The number of hospital admissions and the number of days in the hospital were not different.

COMMENT BY WILLIAM B. ERSHLER, MD

Occasionally in clinical medicine, a seemingly logical approach makes its way into common practice, only to have careful clinical investigation challenge its tenets. In this report, the prophylactic use of G-CSF to prevent infection, and thereby enhance survival, in elderly lymphoma patients was examined. The elderly represent a particularly susceptible at-risk population for febrile neutropenia and infection after treatment with chemotherapy with moderately intensive regimens, such as CHOP. For that reason, ASCO and NCCN guidelines have recommend that this population receive prophylactic G-CSF.[1] The current trial certainly brings that recommendation into question.

Doorduijn and colleagues in the Dutch-Belgian Hemato-Oncology Cooperative Group should be congratulated for completing a difficult and challenging trial. There are concerns, however, about interpretation of their data, warranting some caution before clinicians abandon the concept of primary prophylaxis for this group of patients.

The overall survival for the population studied was less than would be expected based upon the data from other groups.[2-4] Secondly, as Doorduijn et al state, patients in the G-CSF group had a higher prevalence of bulky disease, which might alone account for the lack of difference in treatment outcomes. In fact, twice as many patients in the G-CSF group had progressive disease forcing them off protocol, while 40% in the non-G-CSF group left the protocol because of chemotherapy-induced toxicity. Another concern was the higher incidence of infections, number of antibiotic days, and frequency of serious infections after the first course of chemotherapy in the non-G-CSF group. Of note, after the first course of treatment there was a puzzling decline in the number of infections in both groups, raising the question of whether the sickest patients were withdrawn from study due either to toxicity or progressive disease. Finally, the incidence of infections in the whole group was much lower than reported in other studies of older lymphoma patients. For example, in one report involving a number of US practices, the incidence of infection without growth factors was close to 40%, double the rate found in the growth factor-treated group.[5] Furthermore, the common use of Rituxan® with CHOP, currently considered standard therapy for elderly patients with aggressive lymphomas, may render treated patients even more susceptible to infection.

With these concerns stated, the current results still deserve the highest consideration, as oncologists are, and will be, managing an increasing number of elderly cancer patients undergoing chemotherapy treatment.

However, the aforementioned considerations, most of which were out of the control of the investigative team, should be further clarified. The findings from this group need to be confirmed before clinical practice or the current NCCN guidelines, which call for the use of growth factors with first-cycle chemotherapy in individuals aged 65 and older can be modified. ■

References

1. Balducci L, Yates J. *Oncology*. 2000;14:221-227.
2. Vose JM, et al. *J Clin Oncol*. 1988;6:1838-1844.
3. Zinzani P, et al. *Blood*. 1999;94:33-38.
4. Osby E, et al. *Blood*. 2003;101:3840-3848.
5. Morrison VA, et al. *Clin Lymphoma*. 2001;2:47-56.

Extrapleural Pneumonectomy Permits More Effective Radiotherapy Dose Delivery for Malignant Pleural Mesothelioma

ABSTRACT & COMMENTARY

Synopsis: *Malignant pleural mesothelioma (MPM) is an uncommon tumor that carries a dismal prognosis. Its incidence is rising and is expected to continue climbing as more patients reach the end of the 35-40-year lag period between asbestos exposure and tumor development. Local failures occur early, and patients typically die of pulmonary complications. In contrast to the limited radiation dose that patients undergoing pleurectomy/decortication can receive by virtue of their remaining lung tissue, investigators at MSKCC found that removal of the entire contents of the affected hemithorax via extrapleural pneumonectomy (EPP) enabled them to deliver tumoricidal doses while limiting the dose to nearby critical structures. This, in turn, resulted in better local control rates.*

Source: Yajnik S, et al. *Int J Radiat Oncol Biol Phys*. 2003;56:1319-1326.

Malignant pleural mesothelioma is a disease that typically is associated with up to an 80% local recurrence rate. Median survival is on the order of 4-18 months. Surgery alone does not control the disease. Efforts at resecting all gross disease by pleurectomy and decortication, followed by chemotherapy and/or radiotherapy, have not improved outcomes. Intrapleural chemotherapy and brachytherapy at sites of residual disease have not helped much. It has been widely recognized that external beam radiotherapy doses to the tumor bed in the lung were limited by the presence of residual ipsilateral lung tissue, making RT ineffective. Once the Lung Cancer Study Group reported that extrapleural pneumonectomy (EPP) offered a survival benefit over pleurectomy/decortication in 1991, it became possible to increase the adjuvant RT dose.[1] This is because, using the EPP technique, the entire lung along with the pleura, diaphragm, and ipsilateral pericardium are removed, and a mediastinal lymph node dissection is usually performed. The ipsilateral chest wall, bronchial stump, diaphragmatic insertion points, mediastinum, and pericardium are then at risk for local recurrence and serve as the target structures for postoperative RT.

Yajnik and colleagues reported on 35 patients who were treated at Memorial Sloan-Kettering Cancer Center (MSKCC) from 1991-2001 with EPP and radiotherapy. Three-quarters of the patients had epithelioid tumors, while the remainder had other types of MPM. Mean age was 60 years (range, 9-75 years). Four patients had Stage I tumors, 11 Stage II, 19 Stage III, and 1 Stage IV. Radiotherapy commenced 3-6 weeks postsurgery and consisted of mixed electrons and 6 MV photons given AP/PA at 1.8 Gy per fraction for 30 fractions to a dose of 54 Gy (range, 45-54 Gy). The upper border was at the thoracic inlet (T1), the lower border was at the inferior aspect of L2, the lateral border was flashing the skin, and the medial border was either at the contralateral edge of the vertebral column if there were no positive lymph nodes, or 1.5-2 cm lateral to the edge if there was disease in the lymph nodes. The stomach and liver were blocked from the outset, and those portions of the thoracic cavity extending into the blocked area were covered with electrons. The heart was blocked after 19.8 Gy for tumors on the left, and electrons were used as above to cover the chest wall and diaphragm. Finally, the spinal cord was blocked at 41.4 Gy, and the remainder of the field was treated for an additional 12.6 Gy to 54 Gy.

At a median follow-up of 55 months (range, 17-85 months), there were 13/35 local failures (37%), including 2 chest wall failures and 3 skin failures away from drainage sites or scars. Five patients (14%) were alive without disease, 26 (74%) died of disease, 2 (6%) were alive with disease, and 2 (6%) were lost to follow-up. Toxicities were limited, with 6 patients requiring intravenous hydration during RT. One patient developed a bronchopulmonary fistula and empyema.

Yajnik et al concluded that EPP and RT to adequate

doses are feasible and lead to higher local control than reported in the literature, while at the same time limiting the doses to critical structures such as the spinal cord, liver, stomach, esophagus, and heart. Diaphragmatic reconstruction must be anatomically correct so that the entire preoperative volume at risk is included within the fields. The single patient at MSKCC who was treated to T12 rather than L2 failed in the posterior costophrenic angle. Given the success of the above technique, a pilot trial testing the efficacy of induction chemotherapy is now being conducted, according to Yajnik et al.

■ **COMMENT BY EDWARD J. KAPLAN, MD**

In general, the obstacles to delivering an effective dose of radiation to structures inside the hemithorax are: limitations posed by the tolerance doses of the critical structures listed above, particularly the lung; intact mobile diaphragms; and proper delineation of the target volume. Following EPP, the removal of all ipsilateral lung tissue virtually eliminates the potential for pneumonitis, and reconstructed Gore-tex diaphragms exhibit no real respiratory excursion. This leaves target delineation as the last hurdle.

Ahamad and colleagues from M.D. Anderson Cancer Center (MDACC) recently published their institutional experience with a pilot study involving 7 MPM patients who were treated using an intensity-modulated radiotherapy (IMRT) approach.[2] They collaborated directly with their thoracic surgeons, who had clipped areas within the hemithorax for RT targeting purposes. In contrast to the MSKCC study where clips were not routinely used, the MDACC paper pointed out that the surgeons adjusted their clipping patterns in a dynamic fashion as problems were encountered during CT-target identification with their radiation oncology colleagues. The MDACC investigators delivered 50 Gy with 6 MV photons to the hemithorax, followed by a boost to 60 Gy to areas with residual disease or positive margins. Acute toxicity was quite manageable. They found "better than expected" local control, with no local failures at a median follow-up of 13 months. Interestingly, they determined that it is fruitless to attempt to spare the ipsilateral kidney based on its proximity to the target volume. In a companion paper from MDACC by Forster et al,[3] the MSKCC technique was criticized for only "occasionally" including the upper pole of one kidney. Like the MSKCC team, they cautioned against "abdominalizing" the pre-EPP diaphragmatic insertion in order to avoid truncating the RT target volume (ie, a "geographic miss").

It is encouraging to see that higher doses of RT can now be delivered safely to the hemithorax in patients who undergo EPP. As always, meticulous attention must be paid to designing the RT fields, both to avoid geographic misses and to avoid toxicity to critical structures. Undoubtedly, we will continue to learn more as data are accrued and the various planning and treatment techniques are refined. ■

References

1. Rusch VW, et al. *J Thorac Cardiovasc Surg*. 1991; 102:1-9.
2. Ahamad A, et al. *Int J Radiat Oncol Biol Phys.* 2003; 55:768-775.
3. Forster KM, et al. *Int J Radiat Oncol Biol Phys*. 2003; 55:606-616.

CML Treatment in the Elderly

ABSTRACT & COMMENTARY

Synopsis: *In a 4-year review of chronic myelogenous treatment responses with imatinib mesylate at a single institution, older patients were found to have comparable outcomes to younger patients. An implication of this finding is that this disorder is not biologically more resistant in the elderly and that nontoxic and effective treatment, such as with imatinib mesylate, is likely to produce meaningful responses at all ages.*

Source: Cortes J, et al. *Cancer*. 2003;98:1105-1113.

Older age has been considered a negative prognostic factor in patients with Philadelphia chromosome (Ph)-positive chronic myelogenous leukemia (CML), either due to inherent biological differences in the disease in older patients or a perceived or real inability of older patients to receive adequate treatment. However, with the availability of imatinib mesylate as first-line therapy, a larger number of older patients are receiving this less toxic, but effective, therapy. The current report is a retrospective analysis of recently treated elderly CML patients in an effort to determine if there remains an age disadvantage in survival.

Of a total of 747 patients with CML evaluated and treated (from 1999 to date) with imatinib mesylate in the Leukemia Department of the University of Texas M.D. Anderson Cancer Center, approximately one-third were considered in the "older" age group (age 60 years and older). Of these, 187 patients had newly diagnosed, early chronic-phase CML; 351 patients had chronic phase CML after interferon α failure; 133 patients had

accelerated-phase CML; and, 76 patients had blastic phase CML. Imatinib mesylate was used in doses ranging from 400 mg to 800 mg daily, depending on the phase of disease and prior treatments. Of the 187 patients with newly diagnosed, early chronic-phase disease, 49 (26%) were in the older age group. The older patients had similar cytogenetic response rates and survival when compared with younger patients. Among 351 patients with late chronic-phase CML after interferon α failure, 120 patients (34%) were in the older age group. Although the older patients had a lower incidence of achievement of complete cytogenetic response by univariate analysis (56% vs 44%; $P = .05$), age was not found to be an independent poor prognostic factor in the multivariate analysis. Similarly, older age was not an adverse prognostic factor for survival in this group. Of the 133 patients with accelerated phase disease, 42 (32%) were in the older group. By univariate analysis, the incidence of any cytogenetic response was less in this group (53% vs 33%; $P = .04$), but age was not an independent adverse prognostic indicator by multivariate analysis. Of the 76 patients in blastic phase, 28 (37%) were in the older age group, and older age was not a significant prognostic factor either for achieving response or for survival.

■ **COMMENT BY WILLIAM B. ERSHLER, MD**

Chronic myelogenous leukemia is a disease that occurs most frequently in older people, and survival has been found to be reduced in patients of advanced age.[1,2] Among the reasons that might explain this, 2 seem most likely. Like acute myelogenous leukemia (AML), the disease might actually be somewhat different in older people, and perhaps more resistant to chemotherapy. Older individuals with AML more typically present with an antecedent myelodysplastic syndrome, cytopenias and marrow cytogenetic abnormalities.[3] Cytoreductive treatment in these patients has been unsatisfactory and is generally not recommended, unless in an investigational setting.[4] Thus, it is conceivable that similar factors explain the negative effect of age on CML outcomes. The current report, however, would speak to another explanation. In this review, it is apparent that older patients, treated with the less toxic imatinib mesylate, fared comparably well as younger patients. Although there were differences detected in univariate analysis, these turned out to be not a factor of age when analyzed by multivariate methodology, perhaps reflecting the influence of age-associated comorbidities.

This report is a good reflection of what is likely to be found with other tumors in older patients. The tumors are not *a priore*, more resistant in older patients. Instead, the differences in survival may result from less therapy, either because of a presumed likely greater toxicity, or for some other bias that precludes effective management in geriatric cancer patients. ■

References

1. Sokal J, et al. *Blood*. 1984;63:789-799.
2. Hasford J, et al. *J Natl Cancer Inst* 1998;90:850-858.
3. Taylor P, et al. *Leukemia*. 1995;9:231-237.
4. Burnett AK, Eden OB. *Lancet*. 1997;349:270-275.

12 vs 3 Months of Maintenance Paclitaxel in Patients with Advanced Ovarian Cancer after Platinum and Paclitaxel-Based Chemotherapy

ABSTRACT & COMMENTARY

Synopsis: *Twelve cycles of single-agent paclitaxel administered to women with advanced ovarian cancer who attain a clinically defined complete response to initial platinum/paclitaxel-based chemotherapy significantly prolongs the duration of progression-free survival.*

Source: Markman M, et al. *J Clin Oncol*. 2003;21:2460-2465.

Markman and colleagues conducted a study of the Gynecologic Oncology Group in which patients were randomly assigned to either 3 or 12 cycles of single-agent paclitaxel administered every 28 days and were then followed up for progression-free survival and overall survival. The primary objective of this study was to determine whether continuing paclitaxel for an extended time period in women with advanced ovarian cancer who had achieved a clinically defined complete response to a platinum/paclitaxel-based chemotherapy regimen could prolong subsequent progression-free survival and overall survival. Two hundred seventy-seven patients entered the trial at the time of the analysis, with a total of 54 progression-free survival events having developed among 222 patients with follow-up data. With the exception of peripheral neuropathy, there were no major differences in toxicity between the regimens. The median pro-

gression-free survivals were 21 and 28 months in the 3-cycle and 12-cycle paclitaxel arms, respectively. The Cox model-adjusted 3-cycle vs the 12-cycle progression hazard ratio was estimated to be 2.31 (99% confidence interval, 1.08-4.94). This preliminary analysis led the Southwest Oncology Group Data Safety Monitoring Committee to discontinue the trial. As of the date of study closure, there was no difference in overall survival between the treatment arms. Markman et al concluded that 12 cycles of single-agent paclitaxel administered to women with advanced ovarian cancer who attain a clinically defined complete response to initial platinum-paclitaxel-based chemotherapy significantly prolongs the duration of progression-free survival.

■ **COMMENT BY DAVID M. GERSHENSON, MD**

Standard management of patients who are disease-free at completion of primary surgery/chemotherapy for advanced epithelial ovarian cancer is discontinuation of treatment and subsequent surveillance. While the findings of this randomized, clinical trial are provocative and suggest that there are benefits in prolonged chemotherapy in patients who are clinically disease-free at the completion of primary chemotherapy for advanced ovarian cancer, this study has resulted in considerable controversy. Prior randomized studies focusing on this topic had not demonstrated any benefits. However, they were grossly underpowered and poorly designed. A retrospective study from M.D. Anderson Cancer Center had previously suggested a benefit in progression-free survival associated with prolonged chemotherapy. This prospective study confirms those findings. Previous breast cancer studies had also found a delay in disease progression associated with prolonged chemotherapy. This study is controversial for the following reasons: 1) The early termination of the trial by the Data Safety Monitoring Committee was not felt to be justified by several experts; 2) The 12-cycle arm was associated with excessive neurotoxicity; 3) No benefit in overall survival was demonstrated in this study; and; 4) The difference in disease progression was less than the increased length of maintenance treatment. In addition, the investigators were compelled to reduce the dose of maintenance paclitaxel from 175 mg/m^2 to 135 mg/m^2. Further studies will be needed to elucidate the true benefits of maintenance or prolonged chemotherapy after completion of primary treatment. In the interim, oncologists need to apprise their patients who are disease-free after primary treatment for advanced epithelial ovarian cancer of the various management options, including prolonged chemotherapy. ■

Dr. Gershenson is Professor and Chairman, Department of Gynecology, M.D. Anderson Cancer Center, Houston, Tex.

CME Questions

17. Extrapleural pneumonectomy includes all of the following *except*:

a. resection of the ipsilateral pericardium.
b. abdominalizing the diaphragmatic insertion points.
c. removal of the pleura.
d. reconstruction of the diaphragm.

18. Efforts to increase local control in malignant pleural mesothelioma:

a. have failed despite increases in RT dose.
b. have succeeded primarily based on the use of radiosensitizing chemotherapy.
c. are doomed to fail because of the inherent radioresistance of MPM.
d. appear to be succeeding based on the use of higher RT doses and meticulous target delineation.

19. MPM patients:

a. usually succumb to pulmonary complications related to local failure.
b. usually exhibit significant responses to induction chemotherapy.
c. will invariably require dialysis after completion of RT.
d. are declining in number.

20. Which of the following was found in the Dutch-Belgian trial of primary prophylaxis with granulocyte colony stimulating factor in elderly patients with lymphoma?

a. Those treated with granulocyte colony stimulating factor used less antibiotics.
b. Those treated with granulocyte colony stimulating factor had fewer hospitalizations.
c. Those treated with granulocyte colony stimulating factor had better survival.
d. All of the above
e. None of the above

21. Which of the following statements about treatment of chronic myelogenous leukemia in older patients is true?

a. Interferon based regimens result in response rates that are equivalent in young and old patients.
b. Imatinib mesylate, when combined with interferon and cytosine arabinoside, is effective in the management of elderly patients with chronic phase disease.
c. Imatinib mesylate results in response rates that are equivalent in young and old patients.
d. Interferon has proven superior to imatinib mesylate in elderly chronic phase patients, but the reverse is true in younger patients.

Answers: 17 (b); 18 (d); 19 (a); 20 (a); 21 (c)

Attention Readers . . .

American Health Consultants is happy to announce that we are opening up our *Primary Care Reports* author process to our readers. A biweekly newsletter with approximately 5000 readers, each issue is a fully referenced, peer-reviewed monograph.

Monographs range from 25-35 Microsoft Word document, double-spaced pages. Each article is thoroughly peer reviewed by colleagues and physicians specializing in the topic being covered. Once the idea for an article has been approved, deadlines and other details will be arranged. Authors will be compensated upon publication.

As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ■

Annual Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Clinical Oncology Alert	0 8 8 6 - 7 1 8 6	10/1/03
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$249.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Robin Salet; Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Rob Kimball, same as above

Managing Editor *(Name and Complete Mailing Address)*: Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Thomson American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thomson Healthcare, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

13. Publication Name: Clinical Oncology Alert

14. Issue Date for Circulation Data Below: September 2003

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1489	1359
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1010	796
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	5	2
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	80	35
	(4)	Other Classes Mailed Through the USPS	42	25
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2))*			1137	858
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	15	20
	(2)	In-County as Stated on Form 3541	1	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			25	25
f. Total Free Distribution *(Sum of 15d and 15e)*			41	45
g. Total Distribution *(Sum of 15c and 15f)*			1177	903
h. Copies Not Distributed			311	456
i. Total *(Sum of 15g, and h.*			1489	1359
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			97	95

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2003 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Brenda L. Mooney Publisher — Date: 9/30/03

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

In Future Issues:

IL-6 and Prostate Cancer

PHARMACOLOGY WATCH

Generic Paxil Scheduled to Hit Market this Fall

A generic form of paroxetine (Paxil—GlaxoSmithKline) will soon be on the market. The drug marks the second SSRI antidepressant to go generic after fluoxetine (Prozac) last year. US sales of Paxil reached $2.23 billion last year, and the approval of a generic is a blow to GSK's bottom-line but is welcome news to consumers. Generic paroxetine will be launched by Canadian drugmaker Apotex almost a year earlier than most analysts had anticipated because of continued legal wrangling over patents. If generic companies launch a drug that is later found in violation of the branded drugs patents, they are liable for treble damages, a threat that has impeded generic competition in the past. In this case, Apotex feels it has a strong legal basis for defending any claims by GSK, a pattern that is being seen more frequently among generic companies in the last year. Generic paroxetine should be available this fall in 4 different dosing strengths.

New Study Questions CHD and C pneumoniae

An association between *Chlamydia pneumoniae* infection and coronary heart disease has been suggested by several lines of evidence; however, a new, large, multicenter study fails to confirm this association. Nearly 8000 adults with a recent myocardial infarction and positive *C pneumoniae* titers were randomized to 12 weeks of azithromycin (600 mg/d for 3 days then 600 mg/wk through week 12) or placebo. The primary outcomes were death from any cause, nonfatal reinfarction, coronary revascularization, or hospitalization for angina. After a median of 14 months of follow-up, there was no significant risk reduction with azithromycin vs placebo (any primary event 7% risk reduction with azithromycin, P =.23). Adverse reactions to the study drug occurred in 13.2% of patients randomized to azithromycin and were generally mild—predominately diarrhea. The study represents the largest antibiotic trial to date for the eradication of *C pneumoniae*, and although there were indications that there might be an early benefit, this was not sustained at 14 weeks. The authors suggest that there's no justification for the use of antibiotics in treating patients with coronary disease (*JAMA*. 2003;290:1459-1466).

Warfarin Patients: Limit Cranberry Juice

Cranberry juice may increase the risk of hemorrhage in patients taking warfarin according to British researchers. The British Committee on Safety of Medicines recommended patients taking warfarin should limit or avoid drinking cranberry juice until they can sort out 5 reports of hemorrhage associated with the combination, including 1 death. In all cases, increases in INR were noted when patients who had been stabilized on warfarin started drinking cranberry juice. The committee postulates that the juice inhibits cytochrome P450 activity, thus slowing metabolism of warfarin. Cranberry juice has been touted in recent years for its antioxidant proper-

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. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. 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.

ties as well as its purported ability to prevent or treat urinary tract infections.

Therapeutic Magnets Put to Test

A randomized double-blind trial has finally put therapeutic magnets to the test for the treatment of foot pain. Researchers at the Mayo Clinic randomized 101 adults with the diagnosis of plantar heel pain to treatment with cushioned insoles with bipolar magnets and sham magnets. The insoles were worn daily for 8 weeks. The main outcome was reported average daily for pain and the effect of the insoles on work performance and enjoyment. Again, at 8 weeks no significant difference was noted between the 2 groups, with both groups reporting significant improvements in foot pain (33% improvement nonmagnetic group, 35% improvement magnetic group [P = .78]). The authors conclude that embedded bipolar magnets to add nothing to cushioned insoles and the treatment of plantar heel pain (*JAMA*. 2003;290:1474-1478).

St. John's wort Might Block Certain Medications

St. John's wort, the popular herbal product that is widely used to self-treat depression may significantly reduce the effectiveness of at least 50% of all marketed medications. A new study looked at the effect of St. John's wort on cytochrome P450 (CYP) enzymes. Twelve healthy volunteers (6 men and 6 women) were given St. John's wort for 14 days. Participants were given dextromethorphan and alprazolam before and after administration of St. John's wort to assess plasma pharmacokinetics. After 14 days use of St. John's wort, a 2-fold decreased area under the curve for alprazolam plasma concentration and a 2-fold increase in alprazolam clearance was found as well as an elimination half-life that decrease from 12.4 h to 6.0 h suggesting a significantly induced activity of CYP 3A4 (all findings significant at $P <$ .001). Dextromethorphan metabolism, a measure of CYP 2D6, was unchanged. The effect of St. John's wort on CYP 3A4 is quite significant, however, since at least 50% of all medications currently on the market are at least partially metabolized by this enzyme. This, coupled with 2 recent multicenter double-blind, placebo-controlled studies questioning the effectiveness of St. John's wort for the treatment of depression, should alert clinicians to question their patients about their use of herbal medications, especially St. John's wort (*JAMA*. 2003;290:1500-1504).

Parathyroid Hormone and Alendronate Offer No Improved Osteoporosis Treatment

Parathyroid hormone and alendronate in combination offer no advantage and may in fact be less effective than either drug alone in treating osteoporosis according to 2 studies in the Sept. 25 issue of *New England Journal of Medicine*. In a study of 83 men with low bone density, 28 were randomized to receive alendronate 10 mg/d, 27 received parathyroid hormone 40 mg subcutaneously daily, while 28 men received both. The bone mineral density of the lumbar spine, proximal femur, radial shaft, and total body was measured every 6 months and trabecular bone mineral density of the lumbar spine was measured at baseline and 30 months. The most effective treatment was parathyroid hormone alone ($P < 0.001$ for both comparisons), and it appeared that alendronate impaired the ability of parathyroid hormone to increase bone mineral density at the lumbar spine and femoral neck. In the second study, 238 postmenopausal women with low bone mineral density at the hip or spine were randomly assigned to daily treatment with parathyroid hormone 100 mg/d (119 women), alendronate 10 mg/d (60 women), or both (59 women). After 12 months of follow-up, bone mineral density was assessed at the spine and hip. Bone mineral density increased in all treatment groups, but the volumetric density of trabecular bone in his spine increase substantially more in the parathyroid hormone group than either of the other groups. The authors suggest that there is no evidence of synergy between parathyroid hormone and alendronate and there may be evidence that alendronate reduces the anabolic effects of parathyroid hormone in the study group (*N Engl J Med*. 2003;349:1207-1215, 1216-1226).

FDA Actions

Barr laboratories has received approval to market an extended-cycle birth control pill that cuts the number of a women's menstrual cycles from 13 to 4 per year. Marketed under the trade name "Seasonale," the product is a 91-day ethinyl estradiol/levonorgestrel oral contraceptive regimen that includes 84 days of active hormones and 7 days of placebo. The new product seems to be as effective as other oral contraceptives; however, the label does note that the longer interval between menstrual periods may allow for unintended pregnancies to go undetected for longer period of time. ■