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INSIDE

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Metronomic Cyclophosphamide Adds Value to Neoadjuvant Hormonal Therapy for Elderly Breast Cancer Patients

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a trial in elderly women with breast cancer, primary systemic (neoadjuvant) therapy with letrozole with or without low dose daily oral cyclophosphamide was shown to increase overall clinical response. Furthermore, at the time of surgical resection, residual breast tumor tissue had reduced Ki67 and VEGF immunostaining in samples from those treated with the combined letrozole-cyclophosphamide regimen, suggesting the added cytotoxic drug may be inhibiting endothelial cell proliferation and angiogenic response.*

Source: Bottini A, et al. Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. *J Clin Oncol*. 2006:24:3623-3628.

PRIMARY SYSTEMIC THERAPY (PST) HAS BECOME INCREASINGLY utilized as a method of determining sensitivity of breast cancer to chemotherapy and hormonal manipulation. For example, in hormone receptor positive postmenopausal women, endocrine treatment has been shown to significantly reduce tumor volume prior to surgical resection.[1,2] In the current report, the addition of low-dose, oral daily cyclophosphamide to hormonal therapy was tested in elderly women with breast cancer. The trial was conducted at various centers in Italy and included 114 consecutive elderly women with clinically determined T2-4, N0-1, ER positive breast cancer. Patients were enrolled who were older than 70 years of age, or 65-69 years but considered unfit for systemic chemotherapy on the basis of clinical evaluation.

All patients were ECOG performance status 0-2 with adequate marrow reserve, hepatic and renal function. Patients were randomized

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to letrozole (LET) alone (n = 57) or LET plus cyclophosphamide (LET-CYC) (n = 57). LET was administered at a dose of 2.5 mg/day and CYC at a dose of 50 mg/day.

Of the 114 patients, 104 completed the planned 6 months of therapy (n = 52 in each arm). The overall response rate was 50 of 57 (87.7%; 95% CI, 78.6-96.2) in the LET-CYC arm and 41 of 57 (71.9%; 95% CI, 60.8-83.8) in the LET arm. There were 25 (43.8%) complete clinical responses in the LET-CYC group compared with 23 (40.3%) for those receiving LET alone. Somewhat disappointingly, however, pathologic responses (no evident tumor at the time of surgical excision) were observed in only two patients, one in each treatment arm. Yet, overall the combined treatment was associated with a 2.79 (95% CI, 1.05-7.42) increased odds of response when compared with LET alone ($P = 0.04$).

Of note, Ki67 expression was measured in 88 matched cases. At baseline, no difference in Ki67 immunostaining was observed and both LET and LET-CYC treatments resulted in a significant reduction in Ki67 expression. At post-chemotherapy assessment, Ki67 expression was lower in samples from the LET-CYC patients. Similarly, vascular endothelial growth factor (VEGF) immunostaining was significantly lower in samples from the LET-CYC patients ($P < 0.002$). Specifically, 35.5% of patients in the LET-CYC group had their VEGF staining become negative compared to 7.9% in the LET alone group.

COMMENTARY

Thus, both letrozole and letrozole plus cyclophosphamide treatments were active as primary systemic therapy in elderly patients with breast cancer. The data would suggest that the added low-dose oral cyclophosphamide increases overall and complete clinical response rate and this may be as a result of an antiangiogenic response as indicated by the significant reduction in VEGF immunostaining.

There has been increasing interest in the concept of 'metronomic' chemotherapy (eg, low dose but daily cytotoxic drug administration) as this approach may theoretically target tumor cells by inhibiting endothelial cell proliferation.[3,4] Indeed, in this trial, the reduction in VEGF staining by added low-dose cyclophosphamide would seem to support this contention. The enhanced effect may be more than this; however, since Ki67, a marker of tumor cell proliferation, was also reduced by the added cyclophosphamide.

As mentioned, there were disappointingly few pCRs in this trial, not unlike prior experience of hormonal therapy in the neoadjuvant setting.[2,5,6] Thus, the overall value of neoadjuvant hormonal therapy with or without added metronomic chemotherapy remains to be determined pending additional relevant clinical outcomes such as disease free, and overall survival.

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

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Resecting the Primary When Patients Present with Metastatic Breast Cancer: The Swiss Experience

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *When a woman presents with metastatic breast cancer, the question of surgical excision of the primary tumor often arises. In a series of 300 consecutive patients reported to the Geneva Cancer Registry with primary breast cancer and distant metastases at the time of diagnosis, survival was found to be significantly better for those who had their primary tumor resected. Although this was true for patients with metastatic disease at all sites, the findings were most remarkable for those with skeletal metastases.*

Source: Rapiti E, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol*. 2006;24:2743-2749.

THE ROLE OF PRIMARY TUMOR RESECTION FOR THOSE who present with disseminated breast cancer has not been established. Rapiti and colleagues performed a population-based study to determine the impact of local surgery on survival in women with breast cancer who, at the time of initial presentation, were known to have distant metastases. They examined all patients recorded at the Geneva Cancer Registry between the years 1977 and 1996. Of the 4,485 women with invasive breast cancer reported during this period, 317 (7%) presented with distant metastases at diagnosis. Of these, 17 were registered at the time of death and were excluded from analysis, leaving a total of 300 patients with distant metastases at the time of initial diagnosis.

Overall, 173 patients (58%) did not receive any kind of resection of their primary tumor, whereas 127 (42%) had either mastectomy (n = 87) or tumorectomy (n = 40). Among women who underwent surgery, 48% (n = 61) had negative surgical margins, 26% (n = 33) had positive margins, and 26% (n = 33) had unknown margins. Women who had complete excision of the primary with negative margins had a 40% reduced risk of breast cancer-related death compared to women who did not have surgery. This mortality reduction was not significantly different among patients with different sites of metastases, but in the stratified analysis the effect was particularly evident for women with bone metastasis only (hazard ratio, 0.2; 95% confidence interval, 0.1-0.4; $P = 0.001$). In contrast, mortality did not differ significantly between patients who underwent surgery and had positive surgical margins and those who did not undergo surgery. Thus, if a complete (margin-free) excision is possible, and particularly if the metastatic disease is in bone, primary resection for those presenting with metastatic disease should be considered on the basis of these findings.

COMMENTARY

Metastatic breast cancer remains an unmet challenge with systemic therapy the mainstay. For patients who present with distant metastasis, the value of primary resection has been debated for decades without resolution. In some cases it seems warranted to prevent local complications, but some have argued that tumor excision might stimulate growth of metastatic lesions[1,2] or that resection does little to alter the natural history of the disease. The current observational study would suggest that survival might actually be enhanced by primary resection; a concept that has not received much attention and one that is worthy of investigation.

The survival advantage was most notable for those with metastatic disease confined to bone, a group that generally has a more favorable prognosis compared to patients with disease at other sites.[3,4] Perhaps the value of primary resection for those with incident metastatic disease will be realized to the greatest extent in those who have more indolent disease, such as favorable histological features, hormone receptors and without expression of Her2/neu. In these individuals the natural history is such that the residual primary might be the origin of later-to-come metastatic foci, and resection a preventative measure. For those with the markers of aggressive disease, resection might be predicted to have little value. These, of course, are hypotheses that would optimally be tested in a well constructed, multi-center randomized clinical trial.

This report is an excellent example of the utility of epidemiological studies to debunk unsubstantiated dogma (eg, more aggressive disease is observed after primary resection) and to generate hypotheses worthy of more in-depth probing. However, without evidence derived from clinical trial, the practicing oncologist considering treatment options for a patient with newly diagnosed disseminated breast cancer must rely on clinical judgment regarding the

benefit to be gained from primary tumor resection.

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KIT Mutations Confer Worse Prognosis in Core Binding Factor Leukemias

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Section of Hematology/Oncology, University of Chicago

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

Synopsis: *Core binding factor (CBF) AML (eg, inversion 16 and translocation 8;21) has generally been considered favorable risk although the 50% long-term survival demonstrates the need for better delineating high-risk subsets. In this study, pre-treatment samples from 110 CBF AML patients enrolled in CALGB trials were analyzed for mutations at exon 8 and 17 of the KIT gene. The authors found an increased relapse risk associated with mutated KIT, primarily related to exon 17 mutations. Survival was worse for the subset with inv(16) but not t(8;21). Although the data require validation, mutated KIT holds promise to identify a high-risk subset of CBF AML.*

Source: Paschka P, et al. Adverse prognostic significance of KIT mutations in Adult Acute Myeloid Leukemia with inv(16) and t(8;21): A Cancer and Leukemia Group B Study. *J Clin Oncol*. 2006;24:3904-3911.

THE PROGNOSTIC HETEROGENEITY FOR ACUTE myeloid leukemia (AML) has lead to various strategies to assign risk. Among those, pre-treatment chromosomal abnormalities detected by cytogenetic analysis have gained widespread acceptance, especially to direct post-remission therapy.[1] Genetic abnormalities leading to aberrant subunits of core-binding factor (CBF), such as inv(16)(p13;q22), t(16;16)(p13;q22), and t(8;21)(q22;22)[2] are relatively frequent and confer a relatively favorable outcome. Nevertheless, the 5-year survival of 50% among CBF AML indicates a substantial number of patients still succumb to the disease,[3] demonstrating a need to further delineate adverse prognostic subsets among CBF AML. Recent data suggest a mutated KIT gene (mutKIT) as a candidate in identifying a high-risk subset.[4] Common sites for mutKIT in CBF AML include exon 17 and exon 8.

Paschka and colleagues analyzed 110 patients with AML harboring the core binding factor mutations of inv16 and t(8;21) who were enrolled in several CALGB treatment protocols. In general, patients received fairly uniform induction (cytarabine, +/- etoposide) and consolidation (high-dose cytarabine). KIT mutations in exon 17 and 8 were identified by HPLC and confirmed by direct sequencing.

KIT gene mutations were identified in 29 of 110 patients. Specifically, 18/61 (29.5%) with inv16 and 11/49 (22%) with t(8;21) harbored mutKIT. MutKIT was associated with older age, male sex, and peripheral blood blasts in inv(16) but not in t(8;21). The median age was 38 years for wild-type KIT and 49 years for mutKIT ($P = 0.001$). Although the CR rates were not lower for mutKIT, the cumulative incidence of relapse was significantly worse for mutKIT in inv16 ($P = 0.05$) and t(8;21) ($P = 0.017$). MutKIT predicted for inferior survival among inv16 ($P = 0.009$) but not t(8;21). The increase in relapse for inv 16 arose primarily from mutKIT in exon 17 as opposed to exon 8.

COMMENTARY

This study of a relatively large number of AML patients harboring the core binding factor mutations of inv(16) and t(8;21) shows an association with increased relapse and possibly inferior survival for those with concurrent mutations in KIT. Although both exon 17 and exon 8 were analyzed, the data suggest most of the adverse impact is related to exon 17 mutations. The relapse rate was six times higher for mutKIT at exon 17 compared to non-mutated KIT for inv(16). The relapse rates were also higher among the t(8;21) patients with mutKIT, of whom 9/11 had exon 17 mutations. The data are consistent with another recent study suggested the adverse impact of mutKIT may primarily relate to exon 17 mutations.[4]

One strategy should the results be validated would

be to consider more aggressive post-remission therapy, such as hematopoietic transplant. This may be particularly appealing to the extent the initial complete remission rates were not affected by mutational status. Targeted therapy may be an even more appealing approach. KIT mutations result in a tyrosine kinase gain of function and thus represent obvious targets for tyrosine kinase inhibitors. Dampening some enthusiasm, the authors note that activity of TK inhibitors vary depending on the precise mutation which may be a major challenge for designing clinical trials.

An important limitation in this study is the limited adjustment for age. Most of the multivariable analysis only adjusted for peripheral blood blasts and sex. Older age is strongly associated with adverse prognosis in AML, even among good-risk cytogenetic subgroups. The median age was one decade greater in the mutKIT patients. It may be that the adverse impact of age is due to mutated KIT or, alternatively, older age confounds the association and that mutKIT may not necessarily have any independent adverse impact once considering older age. While the authors propose screening for mutated KIT among CBF AML, the prognostic relevance still requires validation in larger studies employing adequate multivariate adjustment. These limitations notwithstanding, KIT mutation analysis holds promise to add to the growing arsenal of genetic mutations enabling more accurate disease characterization of AML and possibly targeting therapies. ■

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Adding Rituximab to CHOP for HIV-Lymphoma: Do the Benefits Outweigh the Risks?

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Patients with HIV-associated non-Hodgkin's lymphoma have been successfully treated with chemotherapy since the advent of more effective anti-retroviral combinations. The question remains whether the additional value of rituximab to the CHOP combination would be countered by its immunosuppressive effects and risk of infection. In the current phase II trial from France, 61 patients with HIV-NHL were treated with R-CHOP and the results in terms of complete response rate and survival are quite encouraging. However, the patients included in this trial did not have advanced AIDS or low CD4 counts and, thus, the current findings do not reflect the full spectrum of HIV-NHL and should not be generalized with regard to treatment recommendations.*

Source: Boue F, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol*. 2006;24:4123-4128.

PRIOR TO THE ADVENT OF HIGHLY ACTIVE ANTIretroviral therapy (HAART) the occurrence of non-Hodgkin's lymphoma (NHL) was a strongly negative prognostic factor and lymphoma treatment success was unusual. For example, in various clinical trials the median survival was 8 months and only 10% survived two years after lymphoma onset.[1] However, since the occurrence of HAART, prognosis for HIV-NHL patients has improved considerably.[2] The current study was undertaken in 1998 in a French multicenter trial to address the concern whether the addition of the monoclonal anti-CD20 rituximab would, due to its immunosuppressive effects, adversely affect clinical outcomes for HIV patients with NHL.

HIV-seropositive patients with high-grade lymphoma of B-cell origin were eligible if their CD4 cell count was > 100/ L, they were without prior history of opportunistic infection and were of reasonably good performance status (ECOG, 0-2). All of the enrolled patients (n = 61) were evaluable with

regard to safety and in 52 tumor responses could be assessed. The median age was 41 years and the median CD4 count was 172/L. The histologic types included diffuse large B-cell lymphoma (n = 42), immunoblastic (n = 2), Burkitt lymphoma (n = 16) and plasmablastic (n = 1). Forty-two patients had stage III/IV disease and the International Prognostic Index (IPI) was 0 to 1 in 31 patients and 2 to 3 in 27 patients. Rituximab was administered at a dose of 375 mg/m^2 followed (next day) by CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 [maximum 2 mg], and prednisone 40 mg/m^2 orally for 5 days).

Grade 3 or 4 toxicity consisted of febrile neutropenia in 9 patients, anemia in 16 patients, and thrombocytopenia in 5 patients. Complete remission (CR) was achieved in 40 of the 52 assessable patients, partial remission in 5 patients and disease progression in 7 patients. At a median of 33 months, 43 patients were alive and the estimated 2-year overall survival rate was 75% (95% CI, 64%-86%). In the 18 patients who had died, lymphoma was the primary cause in 16, HIV encephalitis in 1 and infection in 1.

Thus, the authors concluded that rituximab could be safely added to CHOP chemotherapy for selected patients with HIV-associated NHL in an effort to optimize response rate and overall survival.

COMMENTARY

In this Phase II study, rituximab added to the standard CHOP regimen produced quite favorable results (77% CR rate, 75% two-year survival), numbers that are most encouraging in this setting. Yet, the numbers are in stark contrast to that from the AIDS-Malignancies Consortium trial (AMC 010).[3] In that randomized trial, there were 16 infection-related deaths and 15 of these occurred in the rituximab arm. However, in the AMC trial patients with more advanced HIV infection were included, whereas the current trial excluded patients who, at the time of enrollment, had CD4 counts < 100/L and any history of opportunistic infection.

Accordingly, this report adds significant positive information with regard to which HIV-NHL patients can be safely treated with R-CHOP. The data suggest for HIV patients with good performance status and CD4 counts above 100/L, rituximab can be safely used in lymphoma treatment schemas. For patients with active AIDS, low CD4 counts or poor performance status, reservations regarding rituximab use would still seem appropriate. ■

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Breast Cancer Risk in the WHI Estrogen-Progestin Trial Arm

ABSTRACT & COMMENTARY

By Leon Speroff, MD

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

Dr. Speroff is a consultant for Barr Laboratories

Synopsis: *The WHI reports an increase in breast cancer is concentrated in prior hormone users, but the overall adjusted risk of breast cancer is not statistically significant.*

Source: Anderson GL, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas.* 2006 Jun 29; [Epub ahead of print];www.sciencedirect.com.

ANDERSON AND COLLEAGUES FROM THE WHI PERformed subgroup analyses focusing on how prior hormone therapy use influenced the risk of breast cancer found in the estrogen-progestin trial arm.[1] Prior hormone users totaled 4311 participants (26%), with 42% reporting less than 2 years of use (17% used hormones 5 to 10 years previously, and 26% more than 10 years before enrolling in the WHI study). Prior users had an increased hazard ratio compared to placebo (1.96; CI = 1.17-3.27) in contrast to no increase among never users (1.02; CI = 0.77-1.36). The WHI concluded that this difference could reflect an increasing risk with cumulative exposure to hormone therapy. The subgroup analysis suggested that no increase in breast cancer was seen in never users, perhaps because of insufficient duration of exposure.

COMMENTARY

Many of the factors associated with a reduced risk of breast cancer were slightly but significantly more prevalent in the group of prior hormone users, such as younger age, more education, lower body mass, and more physically active. On the other hand, some factors associated with an increased risk of breast cancer were more common in prior users (smoking, alcohol use, vasomotor symptoms, and lower bone density). The overall risk of breast cancer in the treated estrogen-progestin group was the same as previously reported by the WHI (1.24; CI = 1.02-1.50).[1] However, after adjusting for the multiple factors recognized to influence the risk of breast cancer, the hazard ratio was 1.20, and no longer statistically significant, CI = 0.94-1.53). Remarkably, the authors comment that the adjustment "did not substantially alter this risk estimate." Is it not substantial if the risk goes from significant to nonsignificant? Is it appropriate for the WHI in its conclusion to say "the significant increase in breast cancer risk found in the trial overall . . . ?"

A year-by-year analysis of prior users and never users is provided in a Figure. Every single line in this figure, with one exception, crosses 1.0, is not statistically significant, and the confidence intervals are very wide. The only statistically significant line is for prior users at year 5 of the study, and this confidence interval is the widest of all, 1.18-10.73. When the adjusted overall risk is no longer statistically significant, how confident can we be in the results of subgroup analyses with smaller numbers?

This report from the WHI is promoting the idea that increasing duration of exposure is necessary for an increasing risk. Yet, they provide this result: "Duration of prior hormone therapy use, and specifically duration of prior combined hormone use, did not significantly modify the risk of breast cancer."

How does all this fit with the idea that the data reflect the effect of hormone therapy on pre-existing tumors. Interestingly, the prior users who ended up in the placebo group had a lower incidence of breast cancer per year compared to the women without prior exposure. After adjustment for the various risk factors, this reduction was not statistically significant (0.66; CI = 0.41-1.05). The WHI recognized that this was a "puzzle." It seems to me that this is tantalizing, a result consistent with early detection of pre-existing tumors. The WHI concludes that the results are consistent with the hypothesis that the risk of breast cancer increases with longer exposure; however, the data do not answer the question: are we seeing effects on pre-existing tumors.

Most importantly, the overall result of an increased risk of breast cancer in the estrogen-progestin arm was no longer statistically significant after adjusting for risk factors. This is good news! The WHI results are not consistent with a large effect, and the findings are finding it hard to escape the influence of differences in risk factors and personal characteristics. ■

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CME Questions

14. In the French multicenter Phase II trial of R-CHOP demonstrating encouraging results with regard to complete response rate and overall survival, which of the patients were *not* included:

a. Patients with poor performance status (eg, ECOG PS > 2)
b. Patients with history of opportunistic infection
c. Patients with CD4 counts of < 100/ L
d. All of the above

15. In the Swiss registry study regarding the advisability of primary tumor resection for women who present with (distant) metastatic breast cancer and metastatic disease, which site was associated with the most significant improvement by successful (margin-free) resection?

a. liver
b. lung
c. skeleton
d. brain

16. The addition of low-dose ('metronomic') cyclophosphamide to letrozole administered in the neoadjuvant setting in elderly breast cancer patients was associated with:

a. a greater number of clinical complete responses.
b. a greater number of pathological responses.
c. higher level of immunostaining for Ki67.
d. higher level of immunostaining for VEGF.
e. All of the above.

17. In this study of core bind factor AML, what mutations were associated with a worse prognosis?

a. KIT gene
b. Flt-3
c. Complex cytogenetics
d. Deletions of chromosome 5

18. The following statements regarding estrogen-progestin therapy and the risk of breast cancer in the WHI are true except:

a. Prior hormone users differ from never users in many ways.

b. The WHI analyses suggest that increasing risk follows longer exposure.
c. The overall risk of breast cancer in the estrogen-progestin arm is a significant 1.20.
d. Subgroup analyses are limited by small numbers.

Answers: 14 (d); 15 (c); 16 (a); 17 (a) 18 (c)

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:

Fludara/Rituxan and the Risk of Infection

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.

The Indictment of Pharma Industry Marketing Practices

A team from UCSF recently reviewed company documents that were entered into the public record as a result of litigation over the promotion of gabapentin (Neurontin) between 1994 and 1998. The result, a rather scathing indictment of the pharmaceutical industry's marketing practices, is published in the August 15 *Annals of Internal Medicine*.

The authors had access to thousands of pages of inside company documents from Pfizer, Parke-Davis, and Warner-Lambert regarding the marketing of gabapentin during a time that the drug was a blockbuster, with sales in the hundreds of millions of dollars.

The primary focus of the litigation was the promotion of off-label indications of gabapentin by Parke-Davis. The paper highlights the company's marketing strategy, which included identifying groups of physicians for targeted marketing. Local champion physicians were identified and trained as "peer-to-peer selling" program leaders. The company also identified physician thought leaders in academic medicine who were given large honoraria, research grants, and educational grants to promote the drug. Resident physicians were also targeted, and large sums of money were given to residency programs. Medical education was one of the cornerstones of the marketing plan.

Physician lectures, teleconferences, and other meetings were set up discuss treatment of epilepsy, but also to discuss off-label use of the drug. Parke-Davis employees frequently surreptitiously listened in on these meetings electronically, in part to gauge the effectiveness of the presentation. Physician moderators were paid well for their participation.

Parke-Davis also developed speaker's bureaus and created academic neurologic lecture series for the neurology community. Department chairs and clinical training program directors were frequently on the speakers lists of these programs. The company also gave unrestricted grants through third-party medical education companies which allowed speakers to legally discuss off label use of gabapentin and to grant CME credits.

A Parke-Davis memo describes these activities as a "growth opportunity" for off-label use of the drug. Physician advisory boards were also well paid to attend meetings where promotional activities were discussed. Research was also directed by the company, and there are indications that studies that gave favorable outcomes were more likely to be published than studies that were not favorable to the drug.

The company also promoted review articles and letters to the editor of journals regarding gabapentin for as much as the $18,000 per article. The authors point out that activities "traditionally considered independent of promotional intent" such as CME and research were corner-

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stones of marketing efforts, and when run through a third party, were legal marketing forums for off-label uses of the drug. The authors call for new strategies to "ensure a clear separation between scientific and commercial activity" (*Ann Int Med*. 2006;145:284-293). This paper is a must read for anyone involved in formulary management, cost effective prescribing processes, or medical education.

TNF Blockers: Should You Be Concerned?

The use of TNF blockers for treatment of rheumatoid arthritis has always been clouded by the potential risk of lymphoma or solid cancers. A new study suggests that the concern may be unfounded.

Researchers from Harvard and University of British Columbia performed a cohort study pooling data from 1152 RA patients who received a biologic DMARD (the TNF blockers etanercept, infliximab, adalimumab, or anakinra) and 7306 patients who received methotrexate. Both groups of patients had elevated risks of cancer compared to the general population, but the overall hazard ratio for hematologic and solid tumors for patients receiving a biologic DMARDs vs methotrexate was 0.98 (1.11 lymphoproliferative cancers 1.37 for hematologic malignancies, and 0.91 for solid tumors).

The authors conclude that biologic agents are unlikely to have a substantial increase in the risk of hematologic malignancies and solid tumors as compared with methotrexate users (*Arthritis Rheum*. 2006;54:2757-2764).

FDA Actions

The FDA has approved over-the-counter access for Plan B, the so-called morning-after pill. Over-the-counter sales of Plan B have been a contentious issue on Capitol Hill throughout the Bush presidency, and it took a change in leadership in the FDA to bring about the change in position. Plan B will be available for women ages 18 and older without a prescription; however, a prescription is still required for women ages 17 and younger. Plan B is marketed by Duramed, a subsidiary of Barr Pharmaceuticals.

Several SSRI antidepressants have made the switch to generic, including fluoxetine, paroxetine, citalopram, and sertraline. Now the first generic serotonin/norepinephrine reuptake inhibitor has been approved. Venlafaxine (marketed as Effexor) was approved for generic switch in August in 25 mg, 37.5 mg, 50 mg, 75 mg, and 100 mg strengths. TEVA pharmaceuticals have exclusivity on the generic for 180 days.

The FDA has approved the use of clopidogrel (Plavix -Bristol-Myers Squibb) in patients with ST segment elevation myocardial infarction (STEMI) who are not going to have coronary artery interventions. The new indication for the drug was based on the findings of 2 studies (COMMIT and CLARITY), which showed improved outcomes with use of the drug in STEMI patients, including those who had initial thrombolytic therapy.

In related news, a somewhat bizarre patent battle over clopidogrel is raging between Bristol-Myers Squibb and Canadian generic maker Apotex. The Canadian company challenged the patent, and introduced generic clopidogrel to the American market on August 8. On August 31, a federal judge in New York issued a restraining order to block distribution of the generic version of the drug; however, she did not require a recall of the generic pills already on the market. Bristol-Myers, which derives 30% of its yearly profit from sales of Plavix, is unsure how much generic product was distributed in 4 weeks; most estimates are approximately 3 months supply. Meanwhile, the patent trial is scheduled to begin in January.

The FDA's Center for Drug Evaluation and Research has issued a warning regarding concomitant use of ibuprofen and aspirin for patients who are taking aspirin for cardioprotection. Functional studies have shown that ibuprofen blocks the effect of aspirin on platelets if the 2 drugs are taken at the same time. Both drugs inhibit cyclooxygenase on platelets. Aspirin's effect is irreversible for the life of the platelet, whereas ibuprofen and other NSAIDs cause reversible inhibition. If ibuprofen is taken before or concomitantly with aspirin, the receptor site is occupied and aspirin is unable to exert its effect. However, if aspirin is taken 30 minutes before ibuprofen or 8 hours after, there is no competitive inhibition. The FDA is recommending that physicians be aware of the timing of ibuprofen and, perhaps, other NSAIDs when used with aspirin, and specifically recommend that aspirin be given 30 minutes prior to ibuprofen or 8 hours later. Recommendations regarding enteric-coated aspirin are unavailable at this time. ■