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INSIDE

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Multiplicity of Benign Breast Cancer Lesions: Risk for Progression to Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In an analysis of benign breast disease evaluated and treated within the Henry Ford Health system over a thirteen year period, the question of breast cancer risk was determined in the context of the number of benign breast lesions. Patient age and the histologic presence of "atypia" conferred increased risk of later breast cancer, as did the presence of multiple lesions, with or without histological "atypia" and when adjusted for age.*

Source: Worsham MJ, et al. Multiplicity of benign breast lesions is a risk factor for progression to breast cancer. *Clin Cancer Res.* 2007;13:5474-5479.

Benign breast lesions are quite heterogeneous but of these, the best characterized premalignant lesions are atypical ductal hyperplasia, atypical lobular hyperplasia and lobular carcinoma *in situ*.[1] Prior studies of benign breast disease have focused on the risks for subsequent breast cancer associated with benign lesions classified into one of three broad histopathologic categories: nonproliferative, proliferative, or proliferative with atypia.[2-4] When concurrent lesions occur, the biopsy is usually classified in terms of the most serious of these three outcome categories. What remains uncertain, however, is whether the absolute number of benign lesions predicts a malignant outcome.

To address this, Worsham and colleagues examined data from a cohort of 4,544 patients evaluated within the Henry Ford Health system within the period from January 1981 through December 1994, with BBD lesions from which 4.5% (n=201) developed breast cancer during an average follow-up period of 10.3 years. From the univariate Poisson regression analysis of 19 variables, 11 individual risk factors were significant predictors

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The survey demonstrated that the majority (70%) of BBD subjects had more than one breast lesion. Concurrent multiple nonproliferative or proliferative BBD lesions with or without atypia in a BBD biopsy and age turned out to be significant predictors of risk for progression of BBD to breast cancer. The presence of atypical hyperplasia in a BBD biopsy alone or in conjunction with other lesions without atypia conferred higher risks. Women with fibrosis had a reduced risk for progression to beast cancer. Race was not a significant predictor of progression to breast cancer. The effect of age, fibrosis and multiple lesions (whether nonproliferative, proliferative, or atypia) on breast cancer progression was not influenced by race.

COMMENTARY

The current report provides useful additional predictive information for women with benign breast lesions regarding the risk for breast cancer. As demonstrated in prior reports, [5,6] benign lesions in women over the age of 50 years or lesions with demonstrable atypia were once again shown to confer increased risk for the development of breast cancer. However, a new finding was an increased risk for those with multiple concurrent lesions, whether atypia was present or not. This increased risk with multiplicity was not statistically significant at 5 years after breast biopsy but was at 10 years. The presence of atypical hyperplasia in a breast biopsy solely or in conjunction with other nonatypical hyperplasia conferred higher risks, corroborating other studies which indicate the risk of developing breast cancer is directly related to the degree of epithelial atypia. With regard to number of breast lesions, the data is very thin. In one previously reported series, 38% of women with low-grade benign disease contained more than one lesion.[7] In the current comprehensive review the percentage with multiple lesions was high (70%), and women with multiple nonproliferative or proliferative lesions with or without atypia were at an increased risk. Furthermore, these findings remained significant after adjusting for age. Thus, efforts to improve risk estimates for women with benign breast disease should include both qualitative and quantitative information. Hopefully, before long more precise indicators will become evident through advances in genomic and proteonomic technologies. ■

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Eltrombopag for Chronic ITP

ABSTRACT & COMMENTARY

By Andrew Artz, MD, MS

Division of Hematology/Oncology, University of Chicago, Chicago, IL

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

Synopsis: *Recent studies have shown that thrombopoiesis stimulating molecules improve platelet counts in chronic refractory idiopathic thrombocytopenic purpura (ITP). Busser and colleagues performed a randomized dose escalating trial of eltrombopag, an oral thrombopoietin stimulating agent, vs placebo for chronic ITP. The three doses of 30 mg, 50 mg, and 75 mg daily that were investigated led to platelet counts above 50,000 per uL in 28%, 70% and 81% respectively. Toxicities were similar to placebo. Eltrombopag is an oral thrombomimetic with considerable activity in chronic ITP that warrants further clinical study.*

Source: J. Bussel, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl. J. Med.* 2007. 357: 2237-2247.

Idiopathic (or immune) thrombocytopenic purpura (ITP) is an acquired platelet disorder diagnosed by exclusion.[1] ITP has been classically described as a condition of platelet destruction. However, impaired megakaryopoiesis and/or reduced thrombopoietin levels (a platelet growth factor) have spurred interest in molecules that bind the thrombopoietin receptor, thereby enhancing megakaryopoiesis. Recent data employing AMG 531, a novel subcutaneously administered thrombopoiesis stimulating molecule showed considerable activity in chronic refractory ITP.[2] In this study, Bussel and colleagues report on the activity of eltrombopag, an oral small molecule non-peptide thrombopoietin-receptor agonist, for refractory ITP in adults.

Investigators enrolled adults at 44 sites internationally with chronic refractory ITP and a platelet count < 30,000/uL. ITP considered secondary to another disease was excluded including HIV, systemic lupus erythematosus, and hepatitis C virus. Study drug was administered in a double-blind placebo fashion with random assignment to 30 mg, 50 mg, or 75 mg po daily of study drug or daily placebo for up to 6 weeks. A platelet count > 200,000/uL required discontinuation of study drug. The study was supported GlaxoSmithKline.

Among the 153 patients screened, 118 underwent randomization and 117 were treated over the 10 month period the study was open. The study design allotted for 272 patients with two planned interim analyses. The study was discontinued early when the efficacy endpoints were met early as per the prespecified early stopping rules. The median age was 50 years, 62% were women, and 47% had undergone prior splenectomy. The primary endpoint of a platelet count of 50,000/uL or more by day 43 was achieved in 11% (3/27) of placebo patients, 28% (8/29) at 30 mg of drug, 70% (19/27) at 50 mg of drug, and 81% (21/26) at 75 mg of Eltrombopag. Significantly more patients in the 50 mg and 75 mg of eltrombopag reached the platelet count threshold compared to placebo ($p < 0.002$ and $p < .001$, respectively). By day 15, the second study visit, 88% of patients taking the 50mg dose and 81% taking the 75 mg dose had a platelet count > 50,000/uL. Finally, a platelet count > 200,000 /uL occurred in 4% of placebo patients and 15%, 37% and 50% at doses of 30, 50, and 75 mg. Adverse events were similar across study groups. One patient in the 50mg Eltrombopag died from cardiopulmonary failure. The patient had multiple cardiac risk factors.

COMMENTARY

In adults, ITP is often a recurrent clinical problem. Initial therapy involves glucocorticoids, IGIV and/or Anti-D (WinRho). A variety of interventions have been used for relapsed disease including agents used in upfront therapy, splenectomy, rituximab, and other immunosuppressive agents. Because of the chronic nature of ITP and cumulative toxicities of long-term therapy, a conservative approach has been advocated where treatment is generally reserved for a platelet count < 20,000-30,000/uL for asymptomatic individuals. More tolerable and effective treatments are clearly needed for chronic refractory ITP.

This study by Bussel and colleagues builds upon ongoing research into new ITP treatments based on stimulating megakaryopoiesis rather than immunosuppression. The initial enthusiasm using PEG-MGDF, a recombinant form of thrombopoietin, was erased when severe thrombocytopenia occurred related to thrombopoietin antibodies. A new generation of smaller, less immunogeneic molecules that are agonists for the thrombopoietin receptor but have a structure distinct from native thrombopoietin have been developed, reducing the risk of antibody formation. One year ago, promising results with the subcutaneously administered thrombopoiesis stimulating protein AMG 531 were reported. In this study, another thrombopoiesis stimulating protein, eltrombopag, showed highly promising activity with platelet counts

exceeding 50,000/uL in 70% and 81% of the two higher study doses, compared to only 11% of placebo. Moreover, most of these responses had occurred by day 15 and almost half of the highest dose cohort achieved a platelet count of > 200,000 /uL.

As in early phase investigation, further study will be required. Long term follow-up will be needed to exclude antibody development, determine the results of re-exposure to drug, and dissect uncommon or late toxicities. Since studies using AMG-531 have shown marrow fibrosis, future trials would benefit from bone marrow evaluation. As an orally administered non-immunosuppressive drug, eltrombopag may have clinical advantages over further immunosuppression or subcutaneous preparations of thrombopoiesis stimulating molecules. Potentially even more interesting will be whether eltrombopag and other thrombopoiesis stimulating proteins are effective in thrombocytopenia from other conditions such as chemotherapy and hepatitis treatment.

In conclusion, daily doses of 50 mg and 75 mg orally of eltrombopag raise platelet counts in chronic refractory ITP and should be a high priority for future study. ■

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Testing a New Regimen for Metastatic Colorectal Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Rather than infusional 5 fluorouracil, the use of capecitabine in combination with irinotecan and oxaliplatin (COI) was explored to establish appropriate dose (of irinotecan) and efficacy in terms of response rate and progression-free survival. Toxicity was primarily gastrointestinal and was manageable with no episodes of severe neutropenia or neutropenic fever and response rates were comparable to published phase II reports of FOLFOXIRI.*

Source: Bajetta E, et al. *Ann Oncol.* 2007;18:1810-1816.

ALTHOUGH THERE HAVE BEEN SIGNIFICANT advances in the management of metastatic colorectal cancer, there remains plenty of room for improvement in terms of response rates and toxicity. Phase II trials combining irinotecan and oxaliplatin concurrently with 5FU infusion (FOLFOXIRI) showed promising activity in the first-line setting, achieving response rates of 58-69%, median time to progression of 10-11 months and overall survival of 22-26 months.[1,2] The 5FU infusion, however, is cumbersome, requiring an indwelling central venous catheter and portable infusion pump. Because Capecitabine, an oral fluoropyrimidine pro-drug that achieves tumor-selective generation of 5FU through exploitation of the higher activity of the thymidine phosphorylase enzyme in tumors, compared with healthy tissue[3] has the additional advantage of oral formulation, efforts have been made to substitute it for infusional 5FU in newer regimens.[4-6] The current report from Milan details one such new regimen utilizing capecitabine, oxaliplatin and irinotecan (COI) in a novel schedule.

The study consisted of a phase I, open-label, dose-finding part followed by a phase II trial. The primary objective was to determine the maximum-tolerated dose (MTD) of irinotecan when administered concurrently with oxaliplatin and Capecitabine in close sequence in a 6-day schedule biweekly. Patients received irinotecan on day 1, oxaliplatin (85 mg/m2) on day 2 and Capecitabine 1000 mg/m2 orally twice daily) on days 2-6 of a biweekly cycle. Three dose levels ranging from 150 to 180 mg/m2 were explored for irinotecan in sequential cohorts of three to six patients. The recommended dose for irinotecan was 180 mg/m2.

A total of 38 patients received a median of six cycles. The majority of patients (76%) completed six or more cycles and early discontinuation due to dose-limiting gastrointestinal toxicity occurred in only two patients. Four patients discontinued therapy to undergo resection of metastases. Toxicity was present but manageable and included diarrhea (grade 3 or 4 in 9 patients [24%]) and nausea (grade 1 or 2 in 6 patients [16%]). Grade 3 or 4 neutropenia did not occur and one patient had grade 3 or 4 thrombocytopenia and another grade 3 or 4 anemia.

Of 27 assessable patients treated at the recommended dose, 17 achieved a partial response (overall response rate [ORR] 63%; 95% confidence interval [CI], 44 to 78%) with a total of eight patients undergoing metastasectomy. Estimated progression-free survival and overall median survival were 8.5 and 23.5 months, respectively.

COMMENTARY

Thus, Bajetta and colleagues have provided an alternative to FOLFOXIRI; one that is both more convenient (two days of intravenous chemotherapy per cycle, compared with one day and a five day infusion) and less myelosuppressive (with no patients experiencing grade 3/4 neutropenia or neutropenic fever). The lack of neutropenia compares favorably with FOLFOXIRI during which severe neutropenia occurs in the majority of treated patients.[1,2]

Regarding efficacy, it appears that COI is comparable to FOLFOXIRI as well as with FOLFIRI[7] in terms of both response rate and progression-free survival. However, to be confident of this would require a randomized trial. Nonetheless, the current data are promising, and the regimen may prove particularly useful for downsizing hepatic colorectal metastases before curative surgery.

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Obesity and Prostate Cancer Mortality

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a review of a large, multicenter trial of radiation and androgen deprivation therapy for men with locally advanced prostate cancer, patients with BMI of >25 but < than 30, or >30 were found to have a higher rate of prostate-cancer specific mortality. This prospective data is in agreement with previously published population studies indicating a higher death rate from prostate cancer in obese individuals.*

Source: Efstathiou JA, et al. Obesity and mortality in men with locally advanced prostate cancer: Analysis of RTOG 85-31. *Cancer.* 2007;110:2691-2699.

Approximately one third of American men are obese[1] and although the extent to which obesity contributes to development of prostate cancer remains unresolved,[2-4] there have been reports of an association of high BMI with features of more aggressive disease.[5, 6] Yet, survival after radical prostatectomy may be unaffected by BMI.[7] It is not clear, however, if BMI affects outcomes for those receiving radiation or androgen deprivation therapy. In the current report, Efstathiou and colleagues present data from the Radiation Therapy Oncology Group (RTOG) addressing the question of whether BMI is associated with prostate cancer-specific mortality (PCSM) among men treated on RTOG protocol 85-31.

This Phase III trial, conducted between the years 1987 and 1992, randomized patients with locally-advanced prostate cancer to RT (external beam) followed by androgen deprivation therapy (ADT) either in the adjuvant setting or at the time of recurrence. For ADT, patients were administered goserelin (gonadotropin-releasing hormone [GnRH] agonist) 3.6 mg subcutaneously each month. For those in the adjuvant treatment arm the goserelin was started during the last week of RT. For those in the non-adjuvant group, goserelin treatment was initiated at the first sign of recurrence. For both arms, the monthly treatments were continued indefinitely or until sign of disease progression. For the 788 (of a total of 945), enrolled patients for whom height and weight data were available, Cox regression analyses were performed to evaluate possible associations between BMI and all cause (ACM) and

prostate cancer-specific mortality (PCSM). Examined covariates included age, race, treatment arm, history of prostatectomy, nodal involvement, Gleason score, clinical stage and BMI.

The 5-year PCSM rate for men with BMI <25 kg/m2 was 6.5%, compared with 13.1% and 12.2% in men with BMI >25 to <30 and BMI >30, respectively ($P = 0.005$). In multivariate analysis, greater BMI was significantly associated with higher PCSM (for BMI >25 to <30, hazard ratio [HR] 1.53, 95% confidence interval [CI], 1.02-2.27, $P = 0.04$; for BMI >30, HR 1.64, 95% CI, 1.01-2.66, $P = 0.04$). Of note, non prostate cancer-specific mortality and all cause mortality were not different among the three BMI groups.

COMMENTARY

The long-term data from this large, multicenter trial are quite compelling and indicate that a greater baseline BMI is independently associated with higher cancer specific mortality in men with prostate cancer. This supports conclusions made from epidemiological studies from both Europe[8] and the United States[9] that indicate a greater risk of dying from prostate cancer in obese men. Potential explanatory mechanisms include the greater difficulty in staging as well as delivering external beam radiotherapy to obese individuals. Certainly, to the extent that more extensive disease is more difficult to recognize and thereby results in understaging, the finding might be a technical artifact. However, obesity alone is associated with hormonal and metabolic alterations, such as elevated estradiol, reduced testosterone, insulin resistance, elevated insulin like growth factors as well as elevated leptin and reduced adiponectin levels, all of which have been associated with more aggressive prostate cancers or other negative prostate cancer outcomes. Furthermore, despite lower testosterone levels at baseline, ADT has been shown to be less effective in obese men.[10]

Thus, baseline BMI is independently associated with higher cancer-specific mortality in patients with locally-advanced prostate cancer. Additional studies would be required to determine whether deliberate weight reduction after prostate cancer diagnosis would modify the negative influence of obesity at time of diagnosis.

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Assessing 'Cure' in AML

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Two recent reports provide information regarding durability of complete remission for those treated for acute myeloid leukemia. The rapidity with which blasts are cleared from the peripheral blood turns out to be an excellent predictor of relapse free survival. For those who remain in complete remission at 3 years, cytogenetic features and patient age remain predictors of relapse.*

Sources: Yanada M, et al. Potential cure of acute myeloid leukemia: Analysis of 1069 consecutive patients in first complete remission. *Cancer.* 2007;110:2756-2760.

Elliott MA, et al. *Blood.* 2007;110:4172-4174.

ALTHOUGH THE MAJORITY OF PATIENTS WITH ACUTE myeloid leukemia (AML) achieve complete remis-

sion following standard induction chemotherapy with agents such as daunorubicin and cytosine arabinoside, most will relapse and relatively few are cured. Clinicians are well aware that cytogenetic abnormalities and advancing age are predictive factors, as well as the number of cycles it takes to induce remission, but two recent reports indicate additional useful prognostic information.

Rate of Blast Clearance Elliott and colleagues from the Mayo Clinic in Rochester, Minnesota examined the outcomes of 86 adult AML (excluding acute promyelocytic leukemia) patients achieving complete remission (CR) during the years 1994 to 2006. All patients received standard induction chemotherapy (idarubicin at 12 mg/m2 per day [n=70] or daunorubicin at 45 mg/m2 per day [n=16] on days 1-3 in conjunction with continuous infusion cytarabine at 100 mg/m2 per day on days 1 to 7) followed by consolidation therapy which was most typically one repeat of the induction regimen followed by three cycles of high-dose cytarabine (3g/m2 q12 hours on days 1, 3 and 5). Patients over the age of 60 years received the same schedule but the dose of cytarabine during consolidation was 1.5 g/m2. The majority of patients (83%) completed at least 3 cycles of consolidation. At the time of analysis, 37 (43%) had died, primarily of relapsed leukemia (97%). Of the remainder, the median survival of surviving patients was 42.5 months (range 8-133). The median overall survival (OS) and relapse free survival (RFS) were 30.2 months (range 5.5-133) and 14 months (range 2-131.5), respectively.

Of the 86 patients, 73 had circulating peripheral blood blasts (PBB). PBB clearance was defined as the interval in days from the first day of induction chemotherapy until the day that PBB were not detected in the peripheral blood. The median time to PBB clearance was 5 days (range 2-10). The rate of relapse for those who cleared PBB on or before day 5 (n=45) was less than that for those who took greater than 5 days for blast clearance (33% vs 79%, respectively; $P<0.001$). Furthermore, RFS and OS were better for those who cleared PBB by or on day 5. The prognosis for those who cleared blasts by day 3 was even better, with a relapse rate of 12.5%, compared with 47% for those who cleared on days 4 or 5, or 78% for those who cleared on days 6 or beyond. In univariate analysis, clearance of PBB gave the strongest prediction of RFS and OS. Other factors which significantly influenced these parameters was the necessity for two induction cycles to achieve CR and unfavorable cytogenetics. A number of other factors were tested, but did not reach significance. These included age, gender, FAB group, de novo vs secondary AML, leukocyte count, platelet count, marrow blast %, and LDH. By multivariate analysis, clearance of PBB was the only independent factor that retained prognostic value with regard to RFS ($P=0.001$).

Cures Yanada and colleagues report the experience from M.D. Anderson Cancer Center regarding late relapse of AML was also recently published. This analysis included data from 1069 consecutive AML patients in CR (between 1991 and 2003) for whom factors associated with late relapse were examined. For the group as a whole, the failure rate (recurrence or nonrecurrence mortality per 100 years of patient follow-up) was 69.1, 37.7, 17.0, 7.6, and 6.6 for years 1, 2, 3, 4, 5 respectively. Age at diagnosis and cytogenetics both influenced long-term survival. However, the effect of cytogenetics on RFS was constant throughout the first 3 years whereas the effect of age increased with time. The probability of RFS for patients alive at 3 years was 84% that they would remain alive through 6 years. For those with "favorable" cytogenetics (22%, including t(8:21), inv(16), and t(15:17)) the serial 5 year survival rates were 30.9, 30.9, 5.8, 2.5, and 2.5. For those with "intermediate" cytogenetics (including normal, -Y, 11q23, or others), or "adverse" cytogenetics (including monosomy or deletion of long arm of chromosome 5 and/or 7) long-term RFS was less certain. For those with intermediate cytogenetics alive at 3 years, those <60 years old had excellent outcomes but for those 60 years and older there remained a substantial risk for relapse, even after 3 years of CR (failure rate by 6 years of 43.5%). Thus, this analysis demonstrates that the risk of treatment failure differs over time, according to both cytogenetic profile and age.

COMMENTARY

These are two reports that should prove useful to those immersed in clinical practice. Although there are a number of new laboratory findings, such as the identification of the molecular mutation *NUCLEOPHOSMIN-1* which show promise as useful prognostic tools, these tests are not readily available.[1] Yet, the findings from these reports provide confidence for those relying on clinical intuition. We learned from the Mayo Clinic series that those who achieve rapid blast clearance have the most durable CRs with significantly improved RFS and OS. Although a relatively small series, the patients were all treated similarly and carefully followed. It was remarkable that of all the factors, including age and cytogenetics, the rate of blast clearance provided the most useful information.

From the larger but less well described M.D. Anderson series (with regard to treatments received), additional useful information was presented. The take-home message was that the relapse rate after 3 years of CR was very low for those with "favorable" cytogenetics (any age) and for those younger than 60 years with "intermediate" cytogenetics.

With the increasing availability and utilization of allo-

geneic stem cell transplant for patients with AML in CR, including those beyond age 60 at some Centers, these reports might prove useful in guiding decision making. ■

Reference

1. Mrozek K, et al. *Curr Opin Hematol.* 2007;14(2):106-114.

CME Questions

1. **In estimating the risk of subsequent breast cancer for women with benign breast lesions, which of the following factors does NOT provide predictive value:**
   a. age
   b. race
   c. hisotologic evidence of "atypia"
   d. number of lesions

2. **What did Bussel and colleagues demonstrate regarding Eltrombopag, an oral thrombopoiesis stimulating molecule, for chronic refractory Immune Thrombocytopenic Purpura (ITP)?**
   a. increased platelet count > 50,000/uL in the majority of patients receiving the 50 and 75 mg doses
   b. no increase in the platelet count
   c. excessive toxicity
   d. the development of leukemia

3. **When compared with prior reports of the FOLFOXIRI regimen administered for metastatic colorectal cancer, COI (capecitabine, oxaliplatin and irinotecan) was notable for significantly less:**
   a. nausea
   b. diarrhea
   c. hand foot syndrome
   d. neutropenia

Answers: 1 (b); 2 (a); 3 (d)

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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:

CT Colonography vs Colonoscopy

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.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

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drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■