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A monthly update of developments in cancer treatment and research [ALERT]

ILLUSTRATIVE CASE SERIES

Endocrine Tumors

By Jerome Yates, MD
Hematology/Immunology Unit, National Institute on Aging, NIH
Dr. Yates reports no financial relationships relevant to this field of study.

A 55-YEAR-OLD WOMAN PRESENTS TO HER PRIMARY physician with worsening diarrhea and abdominal discomfort. Symptoms first occurred 3 months prior to presentation, and were mild. However, for the prior month, the diarrhea had become moderate-to-severe, and was associated with abdominal cramping. She was employed as a medical receptionist, but for the two weeks prior to her visit, she had not been able to work. She had not travelled, and had no unusual change in her diet prior to her illness. No one in her family (husband, children, and grandchildren) was ill. She thought she was experiencing fever, but when she measured her temperature, it was always lower than 99°F. Physical exam in the office revealed a normal blood pressure, heart sounds, lung sounds, and abdominal exam. There was no tenderness, palpable organomegaly, or mass. A complete blood count and serum chemistries were normal.

She was referred to a gastroenterologist, who undertook an evaluation. Colonoscopy and upper endoscopy were normal. Chest, abdominal, and pelvic CT scans revealed two masses within the liver, one in the right lobe measuring 5 cm in diameter and the other in the left lobe measuring 3 cm in diameter. Ultrasound-guided needle biopsy of the lesion in the right lobe revealed a well-differentiated neuroendocrine tumor consistent with carcinoid.

The 24-hour urine 5-hydroxyindolacetic acid (5HIAA) level and serum chromagranin (CGa) were both elevated. The patient was referred to a medical oncologist for additional evaluation and recommendations regarding management.

CASE DISCUSSION

This patient has a well-differentiated endocrine tumor, presumably carcinoid, and her symptoms are most likely the result of sporadic release of serotonin or other substances, such as tachykinins, prostaglan-

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dins, and bradykinins into the circulation. These tumors are uncommon, occurring in approximately 1 in 100,000 per year, and account for approximately 25% of all the neuroendocrine tumors of the upper intestinal tract.[1-3] Most of these tumors are well-differentiated and have an indolent course. However, despite this, most are metastatic at the time of diagnosis.

In the current case, it would be reasonable to attempt to define and resect the primary lesion so as to prevent local complications, such as bowel obstruction or vascular compromise. To this end, imaging studies, including MRI and somatostatin receptor scintigraphy, could be very instructive,[4] as would capsule endoscopy and/or double balloon enteroscopy.[4] Also, an echocardiogram is warranted to determine cardiac involvement, as it occurs in almost 50% of patients.

There have been few clinical trials on which to base therapy, and because there is great variability in clinical presentation, treatment approaches must be tailored for each individual. That stated, there is general agreement that for those with carcinoid syndrome (flushing, diarrhea, bronchospasm, etc.), treatment with somatostatin analogs is a first priority. Once these symptoms are controlled, treatment directed at the tumor, per se, may be undertaken.

Somatostatin analogs, including octreotide and lanreotide, are generally effective in controlling tumor-related symptoms in about 50%-80% of patients.[5] Such treatment should be undertaken before any debulking procedure to prevent "carcinoid crisis." For example, continuous-infusion octreotide, at a dose of 50 mg/hour, starting 12 hours before surgery and continuing a minimum of 48 hours post-operatively, has been recommended.[6] Long-acting octreotide is currently available, and newer analogs, such as SOM-230, are currently under evaluation for patients who are refractory to octreotide.

With regard to anti-tumor approaches, surgery remains the greatest chance for extending life. However, as mentioned, most patients present with metastatic disease, and curative approaches are infrequent. For patients such as the current case, an exploratory laparotomy might be required to find the primary lesion. In addition to excision of the primary lesion, lymphadenectomy should be undertaken, as well as cholecystectomy in anticipation of future use of somatostatin analogs and hepatic arterial embolization. For patients with one or two approachable hepatic lesions, and a presurgical evaluation which indicates no extrahepatic tumor deposits, surgical resection of the metastatic deposits may provide improved survival.[7]

Hepatic metastases also may be approached successfully by interventional radiologists using trans-catheter arterial embolization (TAE) or chemoembolization (TACE).[8] Such approaches have resulted in objective tumor response rates in up to 86% of cases.[8-10] Similarly, radiofrequency ablation (RFA) has a role in the management of liver involvement, particularly if the lesions are few in number and between 3 and 5 cm in diameter.[11] In fact, RFA has been used successfully in patients in whom TAE has failed.[12]

Systemic treatment with chemotherapy, including agents such as 5FU, streptozotocin, thalidomide, temozolomide, and doxorubicin has been variably tried, but response rates are generally low, in the 15% range in most studies. Interferon, angiogenesis, and tyrosine-kinase inhibitors may offer improved response rates, and these alone or in combination are under investigation.

With this as a background, my recommended approach for the current patient would be to treat initially with octreotide. Once symptoms have abated, I would recheck the 5HIAA urinary level and then proceed to surgery. It is likely, although not definite, that the primary lesion will be found in the jejunum or ileum and, if so, it should be excised to the extent possible, and the surgical specimen should include as many nodes as possible. If exploration (including lymph node histopathology) indicates no other extra-hepatic sites, the lesions in the liver could be addressed by a second surgery or either TAE or RFA. Postoperatively, 5HIAA should be followed, but expectation would be that survival would be 5 years or more. ■

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RAPID REVIEW

Castleman's Disease and Interleukin-6

By William B. Ershler, MD

CASTLEMAN'S DISEASE (CD), ANGIOFOLLICULAR LYMPH-node hyperplasia, was initially described a half century ago in asymptomatic patients with a mediastinal mass.[1] Since then, a number of variants have been described, including hyaline-vascular, plasmacytic, mixed-cellularity, and plasmablastic.[2] CD is further defined as localized (unicentric) or systemic (multicentric). Unicentric CD is commonly cured by surgical excision, although, if this is not possible, radiation and/or chemotherapy have been used successfully.[3] Multicentric CD (MCD) is a systemic disorder more commonly observed with advancing age, characterized by both nodal disease and hepatosplenomegaly and the appearance of constitutional symptoms, including fever, night sweats, and weight loss.[4-6] The disorder is known to occur in patients with HIV infection and, in that case, is most often associated with HHV-8 co-infection. In patients who are HIV negative, evidence for HHV-8 infection is present in approximately 40% of cases in some series.[6,7] MCD also has been associated with Epstein-Barr virus, although this is not commonly observed.

Most, but not all, cases of MCD are polyclonal. It has long been recognized that interleukin-6 (IL-6) is of pathogenetic importance, and vascular endothelial growth factor may be as well.[8,9] In fact, the bulk of constitutional symptoms associated with CD have been attributed to IL-6.[2,3]

There is no standard approach to the treatment of MCD, and numerous modalities, including steroids, radiation therapy, and chemotherapeutic agents,[10,11] have been used with success. Antiviral therapy with ganciclovir has resulted in regression of disease for some, but not all HHV-8/HIV MCD patients.[12] Rituximab® also has been variably successful, but has resulted in exacerbation in Kaposi's sarcoma and is, therefore, not generally advised for HIV-positive patients.[13]

Inasmuch as dysregulated IL-6 is considered central to the pathogenesis of CD, it has long been considered a target for novel therapies. Treatment with murine anti-IL-6 monoclonal antibody re-

sulted in clinical improvement in patients with CD, although efficacy was transient because of development of neutralizing anti-murine antibody.[14] Subsequently, the use of a humanized anti-IL6-receptor antibody was found to result in symptomatic relief and partial or complete regression of the adenopathy in patients with MCD.[15] Most recently, CNTO 328 (Siltuximab®), a chimeric, human-murine monoclonal antibody that binds and neutralizes IL-6, was reported to be effective in patients with CD.[16] Of 23 patients, 18 obtained clinical benefit and 12 had objective tumor regression. This was a dose-escalation study, and all 11 patients treated with the highest dose (12 mg/kg at variable ([1, 2, or 3] weekly intervals) achieved benefit, with 8 patients demonstrating clinical regression of tumor. Of note, there were no patients enrolled on this study with HIV- or HHV-8-associated disease. This was an interim report, and 15 of the enrolled 23 patients remained on study at the time of publication. That stated, there was no dose-limiting toxicity observed, and the majority (87%) experienced no toxicity greater than grade 2, and no significant adverse events were attributable to the antibody treatment.

CONCLUSION

CD is a heterogeneous diagnosis ranging from localized benign tumor masses to extremely aggressive disseminated proliferations. Although histologic variants have some features in common, the subtypes are substantially distinct, such that a common therapeutic approach is unlikely to be successful. For multicentric CD, including the recently described plasmablastic variant, dysregulated IL-6 appears to be a common feature in pathogenesis, and targeting this cytokine is of demonstrable clinical benefit. Notably, HIV and HHV-8 are associated with multicentric CD, and appropriate anti-viral therapies should be highly considered in this subset. ■

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ABSTRACT & COMMENTARY

Alcohol Consumption and Breast Cancer Recurrence

By William B. Ershler, MD

Synopsis: *Consumption of alcohol among women who had received primary treatment for breast cancer was not associated with increased risk of breast cancer recurrence. In fact, for non-obese patients, alcohol intake was associated with other favorable prognostic factors and improved overall survival.*

Source: Flatt SW, et al. Low to moderate alcohol is not associated with increased mortality after breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2010;19:681-688.

There have been conflicting reports about alcohol intake and breast cancer risk. It is apparent that there is a higher risk of developing breast cancer among consumers.[1-3] However, recent reports have suggested that recurrence rates are lower among those who consume low-to-moderate amounts when compared to those who abstain.[4,5] Yet, this finding of a protection conferred by moderate alcohol consumption is somewhat controversial, as others, particularly from Europe, have found no effect.[6,7] It is possible that the observed differences might relate to the lower level of alcohol consumed in the United States and/or differences in confounding variables, such as the presence or absence of obesity. Thus, to address this issue, Flatt and co-investigators from the Women's Healthy Eating and Living (WHEL) study examined the roles of alcohol intake and obesity as predictors of additional breast cancer events and all-cause mortality in a large cohort of breast cancer survivors. This was a randomized dietary intervention trial[8,9] that did not include modifying alcohol intake as a variable, although alcohol consumption was determined prior to and during the course of the study.

Thus, alcohol intake (beer, wine, and spirits) was examined in their cohort of 3,088 women who had previously been diagnosed and treated for breast cancer. Factors associated with baseline alcohol intake were included in Cox proportional hazards models for recurrence and mortality. They found that alcohol intake was significantly associated with higher-education and physical-activity levels. Neither light alcohol intake nor obesity was significantly associated with breast cancer recurrence, but moderate alcohol intake > 300 g/mo (i.e., approximately one drink per day) was protective against all-cause mortality (hazard ratio, 0.69; 95% confidence intervals, 0.49-0.97) in a proportional hazards model adjusted for obesity. Obese women were 61% more likely to be non-drinkers than drinkers and 76% more likely to be light drinkers than moderate/heavy drinkers. In non-obese women, alcohol intake > 10 g/mo was associated with lower risk of all-cause mortality (hazard ratio, 0.68; 95% confidence intervals, 0.51-0.91).

■ COMMENTARY

Thus, it appears that light alcohol intake, regardless of body weight, did not increase the risk of breast cancer recurrence or all-cause mortality in this cohort of middle-aged women previously diagnosed with breast cancer. In fact, a moderate level of alcohol consumption (approximately one alcoholic drink per day) was associated with reduced all-cause mortality, particularly among women who were not obese).

It remains unclear whether alcohol itself influences breast cancer directly. Certain bioactive constituents in beer and wine, such as flavonoids and polyphenols, have been postulated to reduce cancer mortality,[10] but clearly other mechanisms might be at play. Nonetheless, it is equally likely that the effect relates more to correlates of alcohol intake. In the current study, non-obese women with higher education and physical activity were more likely to consume moderate amounts of alcohol, and it is fairly well established that those of higher socioeconomic status are more likely to have improved health outcomes.

Thus, although there is sound evidence that alcohol consumption is a risk factor for incident breast cancer, moderate use among survivors of primary therapy is not associated with a higher recurrence rate and may be associated with overall improved survival. ■

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ABSTRACT & COMMENTARY

Imatinib Withdrawal in CML Patients After Molecular Remission

By Andrew Artz, MD

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

Synopsis: *Imatinib results in significant and durable responses for CML. The safety of discontinuation has not been rigorously tested. In a prospective study, imatinib was discontinued among CML patients in a complete molecular remission (CMR) for 2 years or more. Among 69 patients with at least one year of follow-up, 61% relapsed by molecular analysis, almost all by 6 months. After imatinib reintroduction, all 42 relapsing patients responded, of which 26 (62%) entered CMR again. High Sokal score at baseline, female sex, and shorter period of CMR predicted for relapse on imatinib discontinuation. Around 40% of patients with CML in prolonged CMR on imatinib do not relapse at least one year after stopping the drug.*

Source: Mahon F, et al. Discontinuation of imatinib in patients with chronic myeloid leukemia who have maintained complete molecular remission for at least 2 years: The prospective, multicenter STOP Imatinib (STIM) trial. *Lancet Oncology*. 2010;11:1029-1035.

IMATINIB MESYLATE, GLEEVEC, AN ORAL INHIBITOR OF *BCR/ABL* tyrosine-kinase activity, results in frequent and durable remissions, as documented in the seminal international randomized study of interferon vs STI571 (IRIS) trial.[1] Follow-up data indicate 85% estimated survival at 8 years. Although cytogenetic remission remains an important milestone indicating a low likelihood of future progression, molecular monitoring of *BCR/ABL* transcripts enables determination of deeper responses. A 3-log reduction, as assessed by RT-PCR for *BCR/ABL,* indicates a major molecular response (MMR), and undetectable disease by quantitative RT-PCR is considered a complete molecular remission (CMR).[2] At present, indefinite therapy is recommended. In a study of 12 patients who achieved CMR for 2 years, imatinib discontinuation resulted in molecular relapse in 50%.[3] The authors now embarked on a larger trial to determine whether some CML patients in CMR on imatinib may safely discontinue therapy.

In this multi-institutional trial, patients 18 years and older with CML in chronic or accelerated phase on imatinib therapy for 3 years, and in sustained CMR for at least 2 years, were eligible. The authors report on 69 patients with at least 1 year of follow-up. After imatinib discontinuation, molecular relapse was established in 42 patients (60.8%). Almost all relapses occurred within 6 months, with two relapses occurring at 7 months and 19 months, respectively. Two patients with molecular relapse had a declining transcript levels by the second molecular analysis and eventually re-entered CMR without imatinib therapy.

Prognostic factors for relapse included women (70% vs. 46%), shorter CMR prior to discontinuation, and higher Sokal risk score in multivariable analysis. Specifically, molecular relapse occurred in 17 of 35 in the low-risk Sokal group, 15 of 23 in the intermediate-risk Sokal group, and 7 of 8 patients in the high-risk Sokal group. Treatment of molecular relapse by imatinib 400 mg daily enabled 16 (38%) to have reductions and 26 (62%) to achieve CMR. No hematologic progression or mutant *BCR/ABL* phenotype has occurred, although follow-up is limited.

■ COMMENTARY

The advent of tyrosine-kinase inhibitors (TKIs) has turned CML from a slowly lethal condition into a highly treatable illness. Specifically, imatinib mesylate results in high response rates, and a fraction of patients achieve a major molecular remission if not CMR. Traditionally, an allogeneic hematopoietic transplant was considered the only curative treatment. The question emerges whether a high level of sustained CMR, induced by imatinib, has eradicated the malignant clone or reduced the disease adequately to discontinue therapy. In a pilot study of 12 patients, around 50% of patients with CML in CMR experienced a molecular relapse after stopping imatinib.

In this prospective French study, the authors report interim data from 69 patients in CMR for 2 years or greater and with 1 year of follow-up after imatinib discontinuation. The authors found 39% at year 1 remained in CMR after imatinib discontinuation. Of the 61% (n = 42) who developed a molecular relapse after stopping imatinib, all but 2 relapsed by 6 months. Risk factors for relapse after imatinib discontinuation included higher Sokal risk group (7 of 8 in the high-risk Sokal group at baseline relapsed), female sex, and shorter CMR duration at the time of discontinuation. Importantly, the strategy did not induce resistance, as all patients responded to imatinib reintroduction, with 26 of 42 re-entering CMR and 16 showing decreased *BCR-ABL* levels.

These data, although provocative, are clearly too early to change the recommended approach of indefinite therapy. The follow-up for such patients is short. We must also recognize the eligible population of those entering CMR after imatinib is quite small. Still, there are patients right now for whom imatinib interruption may be advisable or necessary, such as pregnancy, drug cost, non-adherence, or temporary inability to tolerate pills (e.g., surgery). These data provide reassurance that at least for those in CMR, especially if after a prolonged period of CMR, discontinuation for a short period of time may not be harmful. The fact that relapses tended to occur early suggests that at the time of discontinuation, early and aggressive monitoring would be needed.

The advent of second-generation TKIs, such as dasatinib and nilotinib, as front-line therapy, and the associated higher molecular responses, raise the possibility of a much larger population entering CMR, and might even promote more rapid uptake of such drugs in preference to imatinib as initial treatment. For example, nilotinib and dasatinib induce a 1-year molecular response rate of 43%-46% compared to 22%-28% for imatinib.[4,5] The notion of a clinical trial assessing if discontinuation identifies patients that might benefit from second-generation TKIs or closer long-term monitoring is intuitively appealing. Further, CML subsets may be characterized for whom initial TKI therapy is curative without an

allogeneic hematopoietic transplant.

In summary, 61% of CML patients in complete molecular remission on imatinib relapsed after drug discontinuation with 1 year of follow-up. Higher Sokal risk group at diagnosis, shorter period in molecular remission, and female sex were associated with a greater relapse risk. Longer follow-up will establish the viability of TKI discontinuation for CML. ■

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CME Questions

13. Among middle-aged women who had been treated for primary breast cancer, moderate alcohol consumption was demonstrated in the WHEL study to be associate with:

a. a reduction in the rate of breast cancer recurrence.
b. no increase in rate of breast cancer recurrence.
c. an increase in breast cancer recurrence.
d. no change in the rate of breast cancer recurrence but a higher overall mortality.

14. Which of the following therapies have been demonstrably effective for patients with multicentric Castleman's disease?

b. Antiviral therapy (e.g., gancyclovir)
c. Monoclonal anti-IL6 receptor antibody
d. Monoclonal anti-IL6
e. All of the above

15. What are the results for imatinib discontinuation for CML patients in complete molecular remission at the time of imatinib withdrawal?

a. Proven cure in most at 10 years.
b. Molecular relapse in approximately 61% mostly by 6 months.
c. Men are more likely to relapse after imatinib discontinuation.
d. Frequent development of T315I mutations.

Answers: 13. (b); 14. (e); 15. (b)

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

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How to Improve Office-based Colon Cancer Screening?

Source: Nadel MR, et al. Fecal occult blood testing beliefs and practices of U.S. primary care physicians: Serious deviations from evidence-based recommendations. *J Gen Intern Med* 2010;25:833-839.

COLON CANCER SCREENING (CCS), WHEN properly done, has been shown to improve outcomes. Unfortunately, available screening methods suffer from underutilization, misinterpretation, and inappropriate follow-up.

Nadel et al compared data obtained from the National Survey of Primary Care Physicians' Recommendations and Practices for Cancer Screening during two time intervals (1999-2000 and 2006-2007), compiling responses from PCPs (n = 1134).

Before exploring the results, it is important to note recommendations about CCS. First, in-office screening of samples obtained through digital rectal examination (DRE) is not a recommended strategy; a single, in-office fecal occult blood testing subsequent to DRE will miss 95% of advanced neoplasia. Rather, annual CCS by means of three separate stool samples collected at home is appropriate: ACS guidelines suggest annual screening by three out-of-office samples tested with high-sensitivity guaiac or FIT.

One-fourth of primary care physicians reported using a single in-office sample in 2006-2007, down from one-third in 1999-2000. Low-sensitivity guaiac utilization decreased in the same interval from 77.4% to 61.1%. ■

Extended-release Carvedilol + Lisinopril in Hypertension

Source: Bakris GL, et al. Effect of combining extended-release carvedilol and lisinopril in hypertension. *J Clin Hypertens* 2010;12:678-686.

SINCE THE PUBLICATION OF THE ALLHAT TRIal, clinicians have progressively relied upon diuretic-based regimens to manage hypertension (HTN). On the other hand, in the ALLHAT trial, overall mortality was similar with diuretic, calcium channel blocker, or ACE inhibitor, lending credence to the idea that any of the treatment choices is reasonable, at least for the endpoint of all-cause mortality. There was no beta blocker arm in the ALLHAT trial; instead, beta blockers were used as add-on treatment.

Ultimately, only a small minority (about 25%) of patients with HTN are able to be controlled with monotherapy. Hence, clinicians must feel comfortable taking best advantage of available combinations of treatment. The COSMOS Study (Coreg and Lisinopril Combination Therapy in Hypertensive Subjects) randomized 656 hypertensive patients to treatment with extended-release carvedilol, lisinopril (LIS), or both. Each agent, as monotherapy or in combination, was used in the full range of therapeutic doses (e.g., LIS 10 mg, 20 mg, and 40 mg).

Although perhaps counter-intuitive, it was only when the highest doses of combination therapy were compared with highest-dose monotherapy that an advantageous differential of diastolic BP lowering was seen. This is the first clinical trial to combine these specific agents, and the fact that simultaneous initiation of both medications was very well tolerated is reassuring. ■

Aspirin Resistance and Established Hypertension

Source: Ozben B, et al. Aspirin resistance in hypertensive adults. *J Clin Hypertens* 2010;12:714-720.

THE PROPHYLACTIC USE OF ASPIRIN (ASA) provides risk reduction when used for secondary prophylaxis. Nonetheless, the protective effects of ASA are imperfect, which is to some degree explained by the concept of ASA resistance, variously measured by failure of aspirin to reduce thromboxane production, platelet activation, or platelet aggregation. Because various methodologies have been used to measure antithrombotic activity of ASA (such as platelet aggregability or thromboxane), the prevalence of ASA resistance in the literature is widely variant. ASA resistance has not been the subject of much study, specifically in hypertensive patients.

Ozben et al used a device called the Ultegra Rapid Platelet Function Assay-ASA to measure the degree of platelet aggregation reduction attained in persons with established hypertension receiving 100-300 mg/d of ASA. The Ultegra device measures light transmission in whole blood to which a platelet activator has been added: If ASA is doing its job, platelets will not activate. If ASA is not doing its job, fibrinogen will agglutinate with platelets, obscuring light transmission. Patients who were taking any other

agents that might influence platelet aggregation were excluded from the trial (e.g., clopidogrel).

In the 200 study subjects, ASA resistance was found in 21%. ASA resistance was more common in uncontrolled hypertension, women, chronic kidney disease, and persons with lower platelet counts. Measurement of ASA resistance is not yet a readily applied clinical tool. Whether persons with ASA resistance merit higher doses of ASA, alternative pharmacotherapy (e.g., clopidogrel), or other intervention is unclear. ■

Dementia and Aggressive Behavior

Source: Kunik ME, et al. Causes of aggressive behavior in patients with dementia. *J Clin Psych* 2010;71:1145-1152.

METRICS DESIGNED TO MEASURE AGGRESsion in dementia patients list activities such as spitting, verbal aggression, hitting, kicking, pushing, biting, and making inappropriate sexual advances either verbally or physically. Because such behaviors can be highly disruptive, it would be helpful to shed light on factors associated with aggressive behavior.

To be included in the trial, subjects had to be free of a history of aggressive behaviors for the previous 12 months. Factors that were measured included depression (Hamilton Depression Scale), pain, caregiver burden (based upon a validated scoring system that measures psychological, physical, emotional, financial, and social impact of being a caregiver), and an item titled "mutuality," which measures the positive qualities of the caregiver-to-care-receiver relationship, including frequency of contact, positive interactions, degree of attachment, and emotional support. The authors looked at data from 215 patients with dementia, of whom 41% developed aggression over a 2-year interval.

Predictors of increased risk for aggression were low baseline mutuality, high caregiver burden, pain, and depression. Although some of the predictors for aggression may be difficult or impossible to modify, others are clearly modifiable and might reduce likelihood for aggression. ■

Dabigatran vs Warfarin for AFib

Source: Wallentin L, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation. *Lancet* 2010; 376:975-983.

WARFARIN (WAR) DOES AN IMPRESSIVE job of stroke reduction in patients with atrial fibrillation (AFib): Clinical trials indicate a relative risk reduction of 65%. Unfortunately, chronic WAR therapy is not without obstacles, including need for ongoing monitoring, expense, vigilance to diet and pharmacotherapy, etc. Dabigatran is an orally administered direct thrombin inhibitor that does not require routine monitoring, and is not significantly affected by vitamin K content in food. In October 2010, the FDA approved dabigatran for reduction of risk of stroke in persons with AFib.

The RE-LY trial randomized AFib patients (n = 18,113) to anticoagulation with warfarin (target INR, 2.0-3.0) or dabigatran. Dabigatran was administered as either 110 mg bid or 150 mg bid. Patients were followed for 2 years.

Initial reporting of RE-LY results found that lower-dose dabigatran (110 mg bid) was non-inferior to warfarin, and that higher-dose dabigatran (150 mg bid) was superior to warfarin. This article further examined whether trial results were impacted by the degree of success with which study sites were able to keep patients within the therapeutic range with warfarin.

Ultimately, the efficacy of dabigatran 150 mg bid relative to WAR for stroke prevention was found not to be dependent upon the efficacy with which clinical trial centers maintained INR within the therapeutic range. On the other hand, for the endpoints of all vascular events, nonhemorrhagic events, and mortality, differences between dabigatran and WAR were greater at study sites with less efficacy at maintaining in-range INR. Dabigatran appears to be at least as effective as WAR, although some advantages of dabigatran are magnified by inconsistencies in maintaining good INR control. ■

When Should a Non-diabetic A1c Be Rechecked?

Source: Takahashi O, et al. A1c to detect diabetes in healthy adults: When should we recheck? *Diabetes Care* 2010;33: 2016-2017.

RECENTLY, THE ADA HAS ADVOCATED THE use of A1c to diagnose diabetes, indicating that we may now make a diagnosis of diabetes with an A1c ≥ 6.5. We do not have explicit guidance about the frequency with which persons whose A1c falls below the diagnostic threshold should be rechecked.

Takahashi et al followed all adults participating in preventive health checkups (n = 16,313) at the Center for Preventive Medicine at St. Luke's International Hospital, Tokyo, from 2005 to 2008. Three years after enrollment, among those without diabetes at baseline, 3.2% had reached an A1c ≥ 6.5. However, the likelihood of progressing to diabetes varied widely and was dependent upon the baseline non-diabetic A1c: Only 0.05% of persons with an A1c < 5% became diabetic vs 20% of those with an A1c 6.0%-6.4% at baseline.

Based upon their observations, the authors suggest that if baseline A1c is < 6.0%, rescreening is unlikely to be valuable in less than 3 years. On the other hand, the high frequency of A1c progression when baseline A1c is 6.0%-6.4% merits consideration of annual rescreening. ■

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Tiotropium for Uncontrolled Asthma

In this issue: Tiotropium for uncontrolled asthma, sibutramine pulled from market, incidence and mortality data from WHI, FDA Actions.

Tiotropium for uncontrolled asthma

Tiotropium, a long-acting anticholinergic inhaler, is approved for treatment of chronic obstructive pulmonary disease. A new study suggests that it may also be effective for patients with asthma.

In a study of 210 adults with asthma with inadequate control with inhaled glucocorticoids, tiotropium was compared to doubling the dose of glucocorticoids, and was also compared to the addition of salmeterol, a long-acting beta agonist (LABA). Tiotropium was superior to doubling the dose of inhaled glucocorticoid as assessed by measuring the morning peak expiratory flow (PEF) ($P < 0.001$). It also improved evening PEF, asthma control days, and FEV1, as well as daily symptom scores. The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and was superior to salmeterol in measures of prebronchodilator FEV1 ($P = 0.003$).

The authors conclude that tiotropium is superior to doubling the dose of glucocorticoid in patients with inadequately controlled asthma, and is equivalent to the addition of salmeterol in the same patient group (published online *N Engl J Med* Sept. 19, 2010). This study is important because it may result in options for patients with poorly controlled asthma beyond adding a LABA. Recently, asthma experts and the FDA have questioned the safety of LABA therapy (FDA Drug Safety Communication June 2, 2010), and a recent meta-analysis suggests that use of LABAs without concomitant inhaled corticosteroids increase the risk for intubation or death (*Am J Med* 2010;123:322-328). ■

Sibutramine pulled from market

Abbott Laboratories announced in October that it is withdrawing the weight-loss drug sibutramine (Meridia®) from the market. The move comes a month after the FDA finished a review of the drug and found that patients with cardiovascular disease or diabetes given sibutramine had a significantly higher rate of serious cardiovascular events compared to placebo. The drug was originally approved in 1997. In a news release, the FDA states "physicians are advised to stop prescribing Meridia to their patients and patients should stop taking this medication." *The Wall Street Journal* reports that while Meridia may be off the market, sibutramine is still available illegally in many weight-loss nutritional supplements, most of which are available via the Internet from oversee suppliers. The supplements are marketed as "all-natural" and their labels list only herbal ingredients. The FDA recently advised consumers that Slimming Beauty Bitter Orange Slimming Capsules contains sibutramine, and last year published a list of more than 50 other supplements containing the banned drug. For complete list of supplements containing sibutramine go to: www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm136187.htm. ■

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Incidence and mortality data from WHI

In 2002, the Women's Health Initiative (WHI) study was stopped early after 5.6 years when data showed that combination estrogen and progesterone therapy increased the risk of breast cancer. Mortality data had never been reported from WHI, however, and other studies have suggested that hormone therapy-associated breast cancers might have a more favorable prognosis than other breast cancers. A new analysis of WHI data dispels that notion.

The current study is a follow-up study of more than 16,000 women enrolled in WHI who were randomized to conjugated equine estrogen 0.65 mg per day plus medroxyprogesterone 2.5 mg per day (Prempro®) or placebo. Participants were followed for an average of 11 years with the main outcome measure being breast cancer incidence and breast cancer mortality. Women on hormone therapy had a higher rate of breast cancer compared to women on placebo (0.42% vs 0.34% per year; hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.07-1.46; $P = 0.004$) and breast cancers in the hormone group were more likely to be node-positive (23.7% vs 16.2%; HR, 1.78; 95% CI, 1.23-2.58; $P = 0.03$). The death rate associated with breast cancer was higher in the hormone group (0.03% vs 0.01% per year; HR, 1.96; 95% CI, 1.00-4.04; $P = 0.049$), a finding that barely reached statistical significance because of the low number of cancers in either group.

The authors conclude that estrogen plus progesterone was associated with a higher breast cancer incidence, as well as cancers that were more commonly node-positive. Breast cancer mortality was also higher in the combined hormone group (*JAMA* 2010;304:1684-1692). An accompanying editorial points out that despite the borderline statistical significance of these findings it is likely that "the increase in breast cancer deaths due to hormone therapy has been underestimated in the current study." However, it is still unclear whether short courses of hormone therapy for relief of postmenopausal symptoms right after menopause may be safe and further research is needed "to determine whether lower doses or shorter durations of hormone therapy could alleviate menopausal symptoms without increasing cancer risk" (*JAMA* 2010;304:1719-1720). ■

FDA actions

The FDA has approved fingolimod, the first oral drug for the treatment of relapsing forms of multiple sclerosis. Fingolimod is a sphingosine 1-phosphate receptor modulator that is believed to reduce migration of lymphocytes into the central nervous system. Compared to interferon beta-1a, the annualized relapse rate was significantly lower with fingolimod. Patients need to be monitored for decreased heart rate and elevation of liver transaminases. Fingolimod is given as a once-daily 0.5 mg tablet. It is marketed by Novartis as Gilenya™.

As anticipated, the **FDA has approved dabigatran to prevent strokes and blood clots in patients with atrial fibrillation.** The drug is a direct thrombin inhibitor and is given orally twice a day. The approval was based on the RE-LY trial, which showed that dabigatran at 150 mg given twice a day was superior to warfarin for this indication. Unlike warfarin, dabigatran requires no monitoring. Dabigatran will be available in 75 mg and 150 mg capsules and will be marketed as Pradaxa® by Boehringer Ingelheim Pharmaceuticals.

The FDA has ordered a labeling change for bisphosphonates, warning of the risk of atypical femoral fractures. In March, the FDA announced an ongoing safety review of bisphosphonates and the occurrence of subtrochanteric and diaphyseal femoral fractures. The new warning is a result of that review and, while not acknowledging a direct link, the warning suggests that these fractures may be related to use of bisphosphonates for longer than 5 years. The agency further suggests that health care professionals consider periodic reevaluation of the need for continued bisphosphonate therapy in patients who have been on the drugs for more than 5 years. The labeling change will only affect bisphosphonates approved for osteoporosis, which include alendronate (Fosamax®), risedronate (Actonel®), ibandronate (Boniva®), and zoledronic acid (Reclast®).

The FDA has approved extended-release naltrexone to treat and prevent relapse of patients with opioid dependence who have undergone detoxification treatment. Extended-release naltrexone is administered by intramuscular injection once a month, and blocks opioid receptors in the brain. It was initially approved in 2006 to treat alcohol dependence. The drug is only approved for patients who have completed rehabilitation, otherwise it may trigger opioid withdrawal. The efficacy of naltrexone was shown in a 6-month placebo-controlled trial in which treated patients were more likely to stay in treatment and refrain from using illicit drugs. Extended-release naltrexone injection is marketed as Vivitrol® by Alkermes Inc. ■

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