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ABSTRACT & COMMENTARY

Combination Treatment with Low-Dose Protracted Temozoloamide and Bevacizumab for Heavily Pretreated Patients with Recurrent Glioblastoma

By Bindu Kanapuru, MD
Institute for Advanced Studies in Aging and Geriatric Medicine, Falls Church, VA
Dr. Kanapuru reports no financial relationships relevant to this field of study.

SYNOPSIS: In this Phase 2 trial, 32 heavily pretreated patients including those who received adjuvant temozolamide, were treated with daily low-dose temozolamide at 50 mg/m^2 and twice-weekly Bevacizumab. The treatment was well tolerated with a median progression-free survival of 15.8 weeks and a median overall survival of 37 weeks. However, this was lower than those reported in studies with single-agent bevacizumab and bevacizumab/irinotecan combination.

SOURCE: Desjardins A, et al. Bevacizumab and daily temozolomide for recurrent glioblastoma. *Cancer* 2012;18:1302-1312.

Very few therapeutic options are currently available for patients with recurrent glioblastoma multiforme (GBM), and median survival continues to be dismal for untreated patients. GBM is characterized by endothelial proliferation and increased expression of vascular endothelial growth factor. Consequently, treatment with single-agent bevacizumab resulted in an objective response rate of 28.2%, 6-month progression-free survival (PFS) rate of 42.6%, and median overall survival time longer than 9 months. When combined with irinotecan, 6-month PFS improved to 50.3%, but no difference in median survival was observed (8.7 months).[1] Concurrent treatment with temozolamide during radiation followed by a 5-day course every month for 6 months has become the standard of care in the first-line setting.[2] However, benefit appears to be confined predominantly to those with a mutated promoter for the (O^6-methylguanine DNA methyltransferase) MGMT gene.[3] Prolonged low-dose therapy with temozolamide has the potential to overcome the resistance of an unmethylated promoter of MGMT,[4] as well as demonstrable

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antiangiogenic activity, and has been associated with clinical responses even in patients who had prior treatment with temozolamide.[5] Consequently combining bevacizumab with low-dose prolonged temozolamide may provide additive angiogenic effect and at the same time sensitize the cells to alkylating chemotherapy.

The authors performed a Phase 2 trial of combined protracted daily temozolomide and biweekly bevacizumab for patients with recurrent glioblastoma who previously had received radiation therapy and temozolomide.

The patients were heavily pretreated with more than three-fourths having received two or more treatment regimens, and there was no limit on the number of prior chemotherapy regimens for trial entry. Thirty-two adult patients were enrolled. Patients received temozolomide 50 mg/m^2 daily and bevacizumab 10 mg/kg intravenously every 14 days. No pneumocystis carinii prophylaxis was given. Patients underwent physical examination and brain magnetic resonance imaging every 8 weeks.

The authors observed a 6-month PFS rate of 18.8% (95% confidence interval [CI], 7.6%-33.7%) and a median PFS of 15.8 weeks. The median overall survival (OS) was 37 weeks, the 6-month OS rate was 62.5% (95% CI, 43.5%-76.7%), and the 12-month OS rate was 31.3% (95% CI, 16.4%-47.3%). PFS and OS did not differ significantly in patients who did or did not receive prior adjuvant therapy with 5-day temozolamide, or in those who had MGMT expression low or increased. However, patients who were on steroids during treatment had PFS of only 7.9 weeks, which was lower than 16.4 weeks seen with patients off steroids. Nine patients (28%) had a radiographic response, and 7 patients (22%) had disease progression within the first 8 weeks of treatment. Patterns of progression were available for 21 patients. The authors observed that 52% of patients (n = 11) progressed locally, 38% (n = 8) progressed with a diffuse pattern, and 10% (n = 2) progressed at a distant site within the brain. Two patients discontinued therapy secondary to toxicity (prolonged thrombocytopenia and grade 4 pancreatitis). One patient experienced grade 5 pneumonia.

The current study demonstrated that a regimen of combined daily temozolomide and biweekly bevacizumab had some activity and was well tolerated. However, the results obtained in this study were inferior to those observed in studies of bevacizumab monotherapy and of combined irinotecan and bevacizumab therapy. The current patient population was more heterogeneous and was more heavily pretreated than patients in previous studies.

COMMENTARY

Effective treatment for recurrent glioblastoma has been elusive until the recent trials with bevacizumab, which have shown promising activity in this setting. As single agent or in combination with irinotecan after failing standard therapy, bevacizumab is associated with objective response rates of nearly 30% and median OS of nearly 9 months. Although the response rates in this trial were less than 20%, it is still encouraging as the population included those who had progression on prior temozolamide regimens as well as bevacizumab. The regimen was well tolerated even in this heavily pretreated population, and no pneumocystis carinii pneumonia was reported, despite lack of prophylaxis. In addition, PFS and OS did not differ based on the MGMT status or prior use of adjuvant temozolamide.

However, despite being well tolerated, there was one treatment-related death among 32 patients. It is also hard to infer that the regimen is active in those who have increased MGMT as the number of patients was too small to make this conclusion. As other studies using similar dosing regimens have shown better response rates, albeit in treating patients at first recurrence,[6] this regimen may be considered as a viable option in that setting, particularly as a way to overcome MGMT resistance.

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ABSTRACT & COMMENTARY

Erlotinib Improves Chemotherapy Response Rates for Patients with Advanced Biliary Tract Cancers

By William B. Ershler, MD

SYNOPSIS: In a Phase 3 trial including 268 patients with advanced biliary tract cancers, response rates were improved in patients receiving erlotinib with chemotherapy (gemcitabine/oxaliplatin) compared to chemotherapy alone. However, progression-free survival was not enhanced except for the subset with cholangiocarcinoma.

SOURCE: Lee J, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary tract cancer: A multicenter, open label, randomized, phase 3 trial. *Lancet Oncology* 2012;13:181-188.

For carcinomas arising in the biliary tract, including gall bladder, ampullary of Vater, or cholangiocarinoma, long-term survival hinges on complete surgical resection.[1] However, the majority of patients present with advanced disease and for these patients treatment has offered only modest success. Combination chemotherapy with gemcitabine and a platinum-based agent is currently regarded as a standard treatment,[1] although a number of other drugs and combinations have been evaluated in this setting.[2] Results of several Phase 2 studies have shown that the combination of gemcitabine and oxaliplatin is equivalent in efficacy and less toxic than gemcitabine/cisplatin and is more tolerable.[2-4] Results of Phase 2 trials of single-agent erlotinib in biliary-tract cancer[5,6] and of gemcitabine plus erlotinib in pancreatic cancer[7] have shown modest benefits. Thus, in an effort to enhance treatment responses for patients with advanced biliary tract cancers, Lee and colleagues throughout South Korea performed an open-label, randomized, Phase 3 trial comparing gemcitabine/oxaliplatin with or without erlotinib. A total of 268 patients were randomly assigned to receive either first-line treatment with chemotherapy alone (gemcitabine 1000 mg/m^2 on day 1 and oxaliplatin 100 mg/m^2 on day 2) or the same drugs plus erlotinib (100 mg daily, orally). Treatment was repeated every 2 weeks until disease progression or unacceptable toxic effects. The primary endpoint was progression-free survival.

Median progression-free survival was 4.2 months (95% confidence interval [CI] 2.7-5.7) in the chemotherapy alone group and 5.8 months (95% CI 4.6-7.0) in the chemotherapy plus erlotinib group (hazard ratio [HR] 0.80, 95% CI 0.61-1.03; P = 0.087). A significantly higher number of patients had an objective response in the chemotherapy plus erlotinib group than in the chemotherapy alone group (40 patients vs 21 patients; P = 0.005), but median overall survival was the same in both groups (9.5 months). The most common grade 3-4 adverse event was febrile neutropenia (eight [6%] patients in the chemotherapy alone group and six [4%] in the chemotherapy plus erlotinib group) and there was treatment-related mortality during the study. Subgroup analyses by primary site of disease showed that for patients with cholangiocarcinoma, the addition of erlotinib to chemotherapy significantly prolonged median progression-free survival (5.9 months [95% CI 4.7-7.1] for chemotherapy plus erlotinib vs 3.0 months [1.1-4.9] for chemotherapy alone; P = 0.049).

COMMENTARY

This is the first Phase 3 trial to add a targeted agent to the combination of gemcitabine and oxaliplatin for the treatment of advanced biliary tract cancer, although Phase 2 studies have been reported using bevacizumab plus erlotinib[5,8] erlotinib alone,[6] or gemcitabine/oxaliplatin with cetuximab.[8] Although the current trial resulted in no significant difference in progression-free survival for the group of advanced biliary tract cancer as a whole, the addition of erlotinib to gemcitabine and oxaliplatin showed antitumor activity as indicated by a higher objective response rate. Furthermore, for the subset with cholangiocarcinoma, prolonged progression-free survival was observed, a finding that warrants confirmatory studies.

A few caveats are worth noting. First, this study was conducted exclusively in South Korea and all patients were Asian. Whether other ethnic groups would have similar responses remains to be established. Furthermore, additional studies are required to determine if responses correlate with EGFR overexpression or KRAS mutation, as might be expected from the larger experience with non-small cell lung cancer. Also, inasmuch as progression-free survival was comparable, it would be important to establish the effect of added erlotinib on quality of life. Despite these concerns, it is encouraging to see even a small step forward in the treatment of advanced biliary tract cancer, a disease with projected survival measured in months.

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ILLUSTRATIVE CASE SERIES

Managing Chemotherapy-induced 'Hot Flashes'

By Jerome W. Yates, MD

Hematology/Immunology Unit, National Institute on Aging, NIH

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

A 48-year-old woman, who is 8 years post-hysterectomy for excessive menstrual bleeding, just completed a four-cycle course of chemotherapy (doxorubicin and cyclophosphamide), for a 2.8 cm, high-grade breast cancer with a negative sentinel node biopsy. She experienced an abrupt menopause with severe vasomotor instability following the second cycle of this therapy. Currently, she complains that she is having up to 40 hot flashes per day, which she documents in a diary, and the most distressing are those that occur at night. She awakens at least 5 to 10 times each night with severe sweats and sleeps less than 2 hours between these episodes. As a result, she feels she is unable to function effectively at home or at work where she is an English teacher. She says the burden of repetitive hot flashes interferes with her family, social relationships, and work effectiveness. She has tried non-hormonal interventions that range from relaxation techniques to nonprescription medications, without achieving relief. Her oncologist is considering placing her on antidepressant medication and has discussed with her the risks of recurrent breast cancer countered by the probable quality-of-life benefits she might experience with hormone replacement therapy.

Discussion

Abrupt chemotherapy-induced menopause results in more severe vasomotor instability (hot flashes) than occur with a more gradual normal menopause.[1] Frequent "night sweats" compromise sleep patterns in 10-20% of chemotherapy-treated premenopausal breast cancer patients, and this can lead to a major clinical depression and chronic fatigue.[2] A variety of pharmacologic interventions — including venlafaxine and gabapentin, alternative dietary supplements, acupuncture, and stress management techniques — all have been generally disappointing in the control of marked vasomotor instability. The most effective available treatment is hormone replacement therapy: estrogen alone and estrogen with progesterone. Multiple cohort studies provide evidence that both new and recurrent breast cancers may be caused by exogenous estrogen exposure. The validity of these conclusions is open to question because they were not randomized, controlled studies. Cohort, case-control, cross-sectional studies all carry the risk of significant selection bias, which is the one type of bias that is difficult to correct by statistical manipulation. Prospective randomized studies have the advantage of eliminating or minimizing selection bias.

The Women's Health Initiative (WHI) was a randomized trial comparing estrogen alone vs placebo in women 50-79 years of age who had undergone a hysterectomy in an effort to assess

estrogen impact on osteoporosis or cardiovascular disease.[3] This is the only large, randomized, long-term, placebo-controlled trial of hormonal therapy in postmenopausal women. After a median follow-up of approximately 12 years, it was noted there was a lower incidence of invasive breast cancer in the estrogen-treated group compared with the placebo group. Similarly, there was a reduction in death attributable to breast cancer in the group that received estrogen. In addition, the all-cause mortality following a breast cancer diagnosis was significantly less in the estrogen-treated group. Analyses of subgroups indicate that individuals with known risk factors for developing breast cancer may not experience a cancer reduction following treatment with estrogen. The WHI results suggest that estrogen treatment alone in women with a history of a hysterectomy may prevent breast cancer for those with normal risk profile, which is in conflict with reports from other studies.[4,5] Information from a parallel WHI randomized trial of estrogen plus medroxyprogesterone acetate increased breast cancer incidence and attributable mortality, which is consistent with other cohort studies.[6]

For 70 years it has been noted that pharmacologic doses of estrogens in metastatic breast cancer have yielded durable remissions, most probably the result of concentrations of estrogen far in excess of normal physiologic doses to which breast cancer cells rapidly develop a resistance.[7] In the WHI report by Anderson, conjugated equine estrogens derived from the urine of pregnant mares consisting of more than 10 different estrogens was used. The WHI study and the observational studies all agree that there is an increased risk of breast cancer with estrogen and progesterone combined hormone replacement therapy. Only the WHI supports estrogen's role in breast cancer prevention with long-term follow-up and an increased risk for new breast cancers with the combination of estrogen and progesterone. Recent newspaper reports have been overzealous in reporting the benefit from estrogen alone while ignoring this as a special case in women with a previous hysterectomy. Such women proved not to be at increased risk for developing endometrial cancer from the estrogen exposure. The North American Menopause Society position suggests "additional research is needed to understand the different effects of ET and EPT and how they apply to individual women."[8]

The data from the WHI are sufficiently compelling to advise the patient presented earlier that she could benefit from estrogen therapy for symptom relief. Clearly this study offers hope to women without a uterus suffering from severe symptoms accompanying chemotherapy-induced abrupt menopause. Whether women at normal risk for breast cancer who have severe menopausal symptoms and an intact uterus could or should be treated with estrogens alone for a finite time (e.g., < 6 months) is a research question. A more gradual menopause causes less vasomotor instability and such an approach, in patients closely followed for signs of endometrial metaplasia, could provide improved supportive care for women with severe menopausal symptoms.

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ABSTRACT & COMMENTARY

Fludarabine/Rituximab for Relapsed Hairy Cell Leukemia: Canadian Experience

By William B. Ershler, MD

SYNOPSIS: Response rates for patients with hairy cell leukemia are high and typically of long duration, yet one-third or more will relapse. The use of oral fludarabine in combination with rituximab in four monthly cycles was shown to be highly effective in reinducing durable remissions.

SOURCE: Gerrie AS, et al. Fludarabine and rituximab for relapsed or refractory hairy cell leukemia. *Blood* 2012;119:1988-1991.

Hairy cell leukemia (HCL) was first described in 1958 and was characterized by its refractoriness to treatment and poor prognosis.[1] It is now known to be a rare adult B-cell lymphoid leukemia characterized by pancytopenia, splenomegaly, and absolute monocytopenia. Morphologically, HCL is characterized by circumferential cytoplasmic projections. Bone marrow biopsy is typically hypercellular, with an infiltration of cells having nuclei widely separated by abundant cytoplasm, giving a "fried-egg" appearance. Early hematopathologists relied on staining with tartrate-resistant acid phosphatase to confirm the diagnosis.[2] More recently, the demonstration of B-cell antigens CD19, CD20, and CD22 coupled with the characteristic appearance serves the same purpose.

Whereas initial clinical experience was typically not effective, outlook was better with the introduction of interferon[3] and improved beyond that with purine analogues (pentostatin and cladribine),[4,5] which have become the existing standard of care for newly diagnosed HCL.[6] Currently, the great majority of patients enjoy long-term remission. Nevertheless, despite the high rate of response and lengthy duration of remission, approximately 30-40% of patients relapse.[7]

The current report deals with treatment of HCL patients with recurrent or refractory disease with a combination of fludarabine and rituximab. The authors identified 15 patients treated in British Columbia with fludarabine and rituximab from 2004 to 2010 for relapsed/refractory HCL after first-line cladribine (n = 3) or after multiple lines of therapy (n = 12). The regimen consisted of fludarabine 40 mg/m^2 per day orally on days 1 to 5 (adjusted in some on the basis of renal function) and rituximab 375 mg/m^2 on day 1 of 28-day cycle. Four cycles of treatment were administered. With median follow-up of 35 months, 14 patients were progression-free, whereas one patient developed progressive leukemia and died. Five-year progression-free and overall survivals were 89% and 83%, respectively.

COMMENTARY

For patients with relapsed HCL, cladribine is known to produce a high rate of second remissions, albeit of shorter duration. For example, Jehn and colleagues in Munich reported their experience with single-agent cladribine in which 44 patients were followed for a median of 8.5 years.[8] All but one achieved a complete remission (CR). Of these, 17 (39%) relapsed with a median duration of remission of 48 months (range, 8-131 months). Nine patients received a second course of cladribine and eight of the nine achieved a second CR for a median duration of second remission of 2.5 years. Thus, this approach is commonly used, particularly for those who have experienced lengthy periods of progression-free survival. In a recent review from the Mayo Clinic, the recommendation was forwarded that cladaribine (or pentostatin) be readministered for those with initial remissions of 18 months or more.[6]

Rituximab has been studied as a single agent for those with relapsed disease. In a Phase 2 trial in 24 patients who relapsed after cladribine initial therapy, three patients achieved a CR and three had a partial remission.[9] In that trial, febrile reactions and one death resulted from ruptured diverticular abscess during treatment. Somewhat more favorable responses were reported by the Swiss Group for Clinical Cancer Research.[10] They evaluated rituximab in 25 patients relapsing after prior cladribine treatment. In that trial, the overall response rate was 80%, with a 32% CR rate. Still, the median remission duration was just less than 3 years.

Fludarabine, another purine analogue, has not been extensively examined in patients with HCL, but has proven efficacious in the initial treatment of chronic lymphocytic leukemia and indolent lymphoma.[11] Its use in combination with rituximab is logical for patients with relapsed HCL and the current data would suggest a high likelihood of durable second remissions, comparable, if not superior to repeating initial cladribine (or pentostatin) and certainly superior to rituximab alone. The dose, schedule (monthly x 4), and route of administration (oral) of the fludarabine was shown to be both safe and effective, and certainly should be considered an effective therapeutic option for relapsed/refractory HCL.

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ABSTRACT & COMMENTARY

Dose Dense Weekly Carboplatin-Paclitaxel Prior to Concurrent Chemoradiotherapy for Locally Advanced Head and Neck Cancer

By William B. Ershler, MD

SYNOPSIS: With more effective local therapy achieved by concurrent chemoradiotherapy for patients with advanced squamous cell carcinoma of the head and neck, the occurrence of distant relapse is becoming increasingly observed. In a Phase 2 study, six weekly doses of carboplatin and paclitaxel prior to concurrent chemoradiotherapy resulted in comparable local control and fewer distant relapses when compared to prior studies from this group. The role for induction chemotherapy and the agents selected remains to be established.

SOURCE: Ready NE, et al. Weekly paclitaxel and carboplatin induction chemotherapy followed by concurrent chemotherapy in locally advanced squamous cell carcinoma of the head and neck. *Am J Clin Oncol* 2012;35:6-12.

Concurrent radiation with platinum-based chemotherapy as initial therapy for locally advanced squamous cell cancer of the head and neck region has resulted in improved local control and overall survival when compared to radiation therapy alone.[1,2] Approximately 20% of patients treated in this manner recur with metastases at distant sites.[3] The current trial was designed to test the hypothesis that a short course of systemic chemotherapy prior to combined chemoradiotherapy (CRT) would result in a lower incidence of distant metastatic disease. The study (HN-79) was conducted at multiple participating centers coordinated by the Brown University Oncology Group (BrUOG).

Thirty-five patients received six weekly doses of carboplatin (area under the curve = 2) and paclitaxel (135mg/m^2) followed 2 weeks thereafter by concurrent weekly paclitaxel (40 mg/m^2) and carboplatin (area under the curve = 1) and daily radiation (66-72 Gy). The initial treatment volume included the gross disease with a margin of 2 cm and potential sites of tumor extension and regional lymph nodes to a dose of 4500 cGy at 180 cGy fractions with parallel opposed lateral fields. The boost volume included tumor plus 2 cm margin or the anatomic compartment (e.g., larynx, nasopharynx, etc.) as necessary. A second cone down or boost was recommended when possible after tumor dose of 5940 cGy to allow normal tissue sparing. A single anterior neck field was used to treat the supraclavicular lymph nodes to a depth of 3 cm. Electron beam was used to treat neck nodes when deemed appropriate. Maximal dose to the spinal cord at any given point was 4500 cGy.

During the initial induction chemotherapy, the most common grade 3 or 4 toxicities were neutropenia without fever (26%), mucositis (17%), dysphagia (17%), dermatologic (9%), and neuropathy (6%). The dysphagia usually was present at diagnosis and tumor related. During combined chemoradiotherapy (CRT), the most common grade 3 or 4 toxicities were mucositis (50%), dysphagia (32%), dermatologic (18%), neutropenia without fever (12%), and dehydration (6%). One patient died from neutropenic sepsis and a second experienced sudden death during CRT without any hematologic or other toxicities > grade 2. This 50-year-old patient had comorbid illnesses that included diabetes, sleep apnea, and significant obesity. The overall response rate with induction was 79%. With more than 40 months of follow-up, the 36-month overall survival was 67% and loss of life for causes directly related to squamous cell carcinoma of the head and neck was 16% (i.e., head/ neck cancer-specific survival was 84%). The locoregional relapse rate was 40% at 36 months and distant relapse rate was 8% at 28 months.

COMMENTARY

With more effective local treatment, it comes as no surprise that distant relapses are increasingly observed. Thus, developing comprehensive treatment strategies not unlike the application of neoadjuvant chemotherapy for patients with breast and colorectal cancer is a worthy consideration. For patients with locally advanced head and neck cancer, there is this sense of urgency about achieving local control and the "dose dense" induction chemotherapy, such as this developed by the BrUOG, seems to be a reasonable and effective approach. Reasonable in that CRT was only delayed 8 weeks and effective in that distant relapses were detected in only 8% at 28 months. This rate of distant recurrence is comparably less than both their own and other trials, in which CRT was initial therapy and distant metastases developed in 20% or more. Of course, to be sure, a randomized, controlled clinical trial would be needed to answer the question. To this end, ongoing Phase 3 trials in which induction chemotherapy (with docetaxel, cipslatin, and 5-fluorouracil [TPF] followed by CRT vs CRT alone) are underway, and others recently have been published in which various induction chemotherapies are being tested.[4,5]

The current study included patients enrolled more than a decade ago and although the chemotherapy used and "dose dense" scheduling remain appropriate, the use of more modern intensity-modulated radiotherapy may influence clinical outcomes in a more favorable way and the role for molecular targeting agents, such as cetuximab, needs to be established in the context of both induction and concurrent therapy.

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CME Questions

1. In the study of bevacizumab and temozolomide for recurrent GBM, which appeared to be associated with improvement in PFS and OS?

a. MGMT expression by immunohistochemistry
b. Disease progression while treated previously with temozolomide
c. Enrolled > 6 months or < 6 months after disease progression on 5-day temozolomide
d. Not being treated with steroids at the time of enrollment on study

2. For newly diagnosed patients with advanced biliary tract cancer, the addition of daily, oral erlotinib to a chemotherapy regimen of gemcitabine and oxaliplatin was shown to:

a. enhance objective tumor response rate.
b. improve progression free survival.
c. improve overall survival.
d. All of the above

3. For women with prior hysterectomy on the WHI study, those treated with estrogen replacement, compared to controls treated with placebo alone, were found to experience:

a. a lower incidence of invasive breast cancer.
b. a reduction in death attributable to breast cancer.
c. a reduction in all-cause mortality among those who developed breast cancer.
d. All of the above
e. None of the above

4. A positive outcome of the study conducted by the Brown University Oncology Group in which weekly carboplatin/ paclitaxel was administered as induction therapy prior to CRT for patients with locally advanced squamous cell cancer of the head and neck region when compared to historical controls treated with CRT without induction therapy was:

a. reduced rates of local recurrence.
b. reduced toxicity.
c. reduced rate of distant failure.
d. None of the above

[IN FUTURE ISSUES]

The Prognostic Significance of Occult Axillary Nodes in Early Stage Breast Cancer

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Statins and the Risk of Diabetes

In this issue: Statins and diabetes risk; new treatment guideline for diabetes; new pertussis vaccine recommendation; antibiotics and rhinosinusitis; fluoroquinolones and cystitis; and FDA actions.

Do statins increase the risk of diabetes?

Studies have suggested that statins may increase the risk of diabetes in the elderly, women, and Asians. A new study reviews data from the 162,000 postmenopausal women enrolled in the Women's Health Initiative to investigate whether the incidence of new onset diabetes mellitus (DM) is associated with statin use among these women. This study reviewed records from women who were enrolled between 1993 and 1998 through 2005. More than 7% of the women in the study reported taking statins. Statin use at baseline was associated with an increased risk of DM (hazard ratio, 1.71; 95% confidence interval, 1.61-1.81). This association remained after adjusting for other potential confounders, including obesity, and was observed for all types of statin medications. The authors conclude that statin medication use in postmenopausal woman is associated with an increased risk for DM and that this may be a medication class effect (*Arch Intern Med* 2012;172:144-152). As pointed out in a brief comment in the same issue, observational data are potentially susceptible to "bias (confounding) by indication." In other words, women who would be prescribed statins may be inherently at risk for DM. This study did a good job of evaluating women with and without a history of cardiovascular disease and found that there was still an increased risk of DM. This finding "may have important implications for the balance of risk and benefit of statins in the setting of primary prevention in which previous meta-analyses show no benefit on all-cause mortality." The FDA has issued a new warning about statins and the risk of diabetes (see FDA actions). ■

Oral medications for diabetes

The American College of Physicians has published a new guideline for the "Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus" in the February 21 issue of the *Annals of Internal Medicine*. The guideline suggests that if diet, exercise, and weight loss fail to improve hyperglycemia, oral drug therapy should be initiated. Most diabetes medicines lower HbA_{1c} levels to a similar degree, and none of the medications have compelling outcomes data to suggest one class is superior to another class with regard to cardiovascular or all-cause mortality. But metformin "was more effective than other medications as monotherapy as well as when used in combination therapy with another agent for reducing HbA_{1c} levels, body weight, and plasma lipid levels (in most cases)." Therefore, the guideline recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy for most patients with type 2 diabetes. Metformin is effective at reducing glycemic levels and is not associated with weight gain. Additionally, the drug helps reduce LDL cholesterol and triglyceride levels. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

failure, and any conditions that might lead to lactic acidosis. For patients with persistent hyperglycemia despite metformin, a second drug should be added. No good evidence supports one combination over another. Sulfonylureas have a higher risk for hypoglycemia and thiazolidinediones are associated with an increased risk for heart failure. There are no specific recommendations for the use of the glinides (nateglinide or repaglinide) or the DPP-4 inhibitors (linagliptin, saxagliptin, or sitgliptin). The guideline does not make a recommendation for combinations of more than two oral agents. Injectables, such as the various insulins and GLP-1 analogs, were not addressed in the guideline. (*Ann Intern Med* 2012; 156:218-231). ■

New recommendation for Tdap vaccine

The Advisory Committee on Immunization Practices, a division of the Centers for Disease Control and Prevention, is recommending that all adults get immunized against pertussis (whooping cough). Previously the committee had recommended that only adults who spend time around infants or young children should be immunized. The goal of the expanded recommendation is to prevent teenagers and adults from spreading the disease to infants. In 2010, California experienced a pertussis outbreak that infected 9000 people and resulted in 10 infant fatalities. The adult vaccine combines tetanus, diphtheria, and acellular pertussis (Tdap). ■

Antibiotics not needed for rhinosinusitis

Physicians now have more ammunition for not treating patients with acute rhinosinusitis with antibiotics, based on the results of a new study that shows amoxicillin is of no benefit in these patients. Researchers at Washington University in St. Louis randomized 166 adults with uncomplicated, acute rhinosinusitis to a 10-day course of amoxicillin 500 mg three times a day or matching placebo. The main outcome (change in the Sinonasal Outcome Test) was not significantly different between the two groups at day 3 or day 10. There was a slight improvement in the antibiotic group at day 7. The authors conclude that "treatment with amoxicillin for 10 days offers little clinical benefit for patients clinically diagnosed with uncomplicated acute rhinosinusitis." Patients with symptoms indicative of serious complications were excluded from the trial (*JAMA* 2012;307:685-692). ■

Fluoroquinolones for cystitis

Cefpodoxime is inferior to ciprofloxacin for short-course treatment of acute uncomplicated cystitis in women, according to new study. In a randomized, double-blind trial, 300 women ages 18-55 with uncomplicated cystitis were randomized to ciprofloxacin 250 mg orally twice daily for 3 days or cefpodoxime 100 mg twice daily for 3 days. The overall clinical cure rate with the intent-to-treat approach in which patients lost to follow-up were considered as having a clinical cure was 93% for ciprofloxacin compared to 82% for cefpodoxime. For the intent-to-treat approach in which patients lost to follow-up were considered as not having responded to treatment, the clinical cure rate was 83% for ciprofloxacin compared to 71% for cefpodoxime. The microbiological cure rate was 96% for ciprofloxacin compared with 81% for cefpodoxime. At follow-up, 16% of women in the ciprofloxacin group had vaginal *Escherichia coli* colonization compared with 40% in the cefpodoxime group. The authors conclude that cefpodoxime did not meet criteria for non-inferiority to ciprofloxacin for treating uncomplicated cystitis in women (*JAMA* 2012;307:583-589). The study is somewhat disappointing given the increasing rates of fluoroquinolone resistance in the community and the need for effective alternatives. ■

FDA actions

The FDA has issued a new warning and is requiring label changes to all statins regarding the risk of elevated blood sugar and reversible cognitive changes. The agency is making these changes after a comprehensive review of multiple studies that show increases in blood sugar associated with the drugs. A separate labeling change warns that cognitive effects have been reported with statin use, including transient memory loss and confusion — symptoms that are reversible with stopping the medication. There is no evidence that statins are associated with long-term cognitive changes or dementia. Statins affected by these warnings include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In a separate warning, lovastatin is now contraindicated with strong CYP3A4 inhibitors, such as itraconazole and erythromycin. This is a similar warning to that issued for simvastatin in 2011.

In one of the strangest stories of the year, the FDA is warning oncologists that a counterfeit version of bevacizumab (Avastin) may have been purchased and used by some medical practices in the United States. The counterfeit version does not contain any active drug and may have resulted in patients not receiving needed therapy. Counterfeit bevacizumab was purchased from a foreign supplier known as Quality Specialty Products or Montana Health Care Solutions. The FDA is recommending that physicians stop using bevacizumab purchased from the suppliers and call the FDA immediately. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Rationale for Zinc Supplementation in Older Adults with Wounds

Source: Sallit J. *Ann Long-Term Care: Clin Care Aging* 2012;20:39-41.

Zinc deficiency is defined as a serum zinc level < 60 mg/dL. Unfortunately, there is some question about the reliability of zinc levels to accurately reflect zinc status, since some persons with prototypic symptoms of zinc deficiency (loss of appetite, diarrhea, hair loss, delayed wound healing, and smell and taste disturbances) have normal zinc levels. Residents of long-term care facilities are at risk for zinc deficiency, both because they may be consuming diets that are lower in zinc and also because they may not absorb zinc from the diet as well as younger persons. For instance, one clinical trial of patients from nursing homes (n = 617) found that almost half had subnormal zinc levels. Some medications can compound the issue — diuretics can deplete zinc.

The roles of zinc in wound healing are diverse, including collagen and protein synthesis, cell proliferation, and immune function. The body's demands for zinc are thought to increase at the time of injury, and continue through the early inflammatory phase; hence, zinc deficiency at this time can delay wound healing.

When a long-term care facility resident sustains a wound, although it is reasonable to ascertain zinc status through serum levels and treat accordingly, it appears equally reasonable based upon a high level of suspicion of zinc deficiency to simply supplement zinc at moderate doses (15-30 mg/d), since such dosing is well tolerated. Indeed, a clinical trial at slightly higher supplementation doses (25-50 mg/d × 3 months) has been documented to have a beneficial effect on wound healing in zinc- deficient individuals. The authors suggest that 40 mg/d be the maximum dose administered to non-deficient persons, due to tolerability issues (diarrhea, nausea, vomiting, vertigo). ■

Occupational Stress and Hypertension

Source: Rosenthal T, Alter A. *J Am Soc Hypertens* 2012;6:2-22.

The consequences of job-related stress (JRS) have been the object of a great deal of research. Of course it is difficult to determine the best measurement tool for JRS, and it is equally difficult to explain how similar levels of JRS are interpreted and managed variably by different individuals. Some of the data on JRS and its relationship to blood pressure suggest that JRS need not necessarily be perceived to be associated with adverse effects. Nonetheless, several lines of evidence lead to the conclusion that identification of JRS is replicable and consequential in some settings.

For instance, a review of data from 34 studies on professional drivers (e.g., bus drivers) found a consistent increased risk of heart disease and hypertension, attributed to the wide range of psychological and physical stressors. To describe the inherent stressful conflict of bus drivers, the authors remind us that the drivers are constantly dealing with the competing agendas of staying on time and optimizing safety.

Despite the large amount of descriptive data that help us identify the negative impact of job stress on health, there is little substantive information that anyone has found highly effective methods to improve outcomes from JRS. It is likely that reducing JRS and its consequences will require interventions on a public health level. ■

Association of Psoriasis with CV Risk Factors

Source: Shapiro J, et al. *J Am Acad Dermatol* 2012;66:252-258.

In the last decade, the recognition that rheumatoid arthritis (RA) is associated with adverse cardiovascular (CV) outcomes has been increasingly highlighted, to the point that some voices suggest including the presence of RA as a formal CV risk factor of similar impact to having a low HDL. Psoriasis (PSR) and RA share some common features, especially including their responsiveness to similar disease-modifying therapies, suggesting common pathophysiology. The mechanism by which RA imparts increased CV risk is unclear, though it is commonly attributed simply to the deleterious effects of chronic inflammation. Might PSR also be associated with CV risk?

To examine this issue, Shapiro et al performed a case-control study that compared PSR inpatients (n = 1079) to age- and gender-matched inpatient controls who had other non-psoriatic dermatitis issues, such as atopic dermatitis and contact dermatitis (n = 1079).

Multivariate logistic regression found that PSR was associated with greater odds

ratio (OR) for diabetes (OR = 1.43) and hypertension (OR = 1.31). Although PSR was associated with CVD, the association was no longer present when correcting for obesity and hypertension. Although the pathogenesis of increased CV risk associated with PSR is uncertain, the fact that PSR produces systemic effects on tumor necrosis factor alpha and other inflammatory markers may be critically linked. ■

Our Patients May Not be Getting the Message About Colon Cancer Screening

Source: Barton MK. *CA Cancer J Clin* 2012;62:1-2.

In its most recent guidance regarding colon cancer screening (CCS), the American Cancer Society iterated a new position on choice of tests, basically stating that "the best test is the test you can get done." This new orientation reflects both the philosophical and logistical realities that of the preventable cancers, CCS is the area in which we see the most missed opportunity. Currently, only about 60% of individuals are receiving any of the age-appropriate CCS available.

Barton reports on an observational study performed in 26 clinics in Michigan in which physicians volunteered to have patient visits audio-recorded, understanding that investigators were evaluating communication in general, but the study physicians were not told about any particular disease-state focus. Prior to the office visit, patients (n = 415) wrote down what information they felt they needed to understand to decide whether to participate in CCS.

Of the patients who indicated that information about test accuracy was very important, such information was imparted by the physician only 7% of the time. Even though most patients (77%-89%) rated information about pros/cons of testing and alternative testing methods as very important, communication about these components was similarly lacking (4% and 29%, respectively).

About half of patients did have questions about CCS, but clinicians invited questions in only about 5% of interviews. These well-demonstrated communication gaps provide an important opportunity for meeting patient needs, which will hopefully translate into better adherence with CCS recommendations. ■

BMD Testing: What's the Appropriate Interval?

Source: Gourlay ML, et al. *N Engl J Med* 2012;366:225-233.

Several national and international guidelines provide advice about when to consider bone mineral density (BMD) screening to identify osteoporosis (OSPS) based upon age, ethnicity, gender, and other risk factors. However, conspicuously lacking from these guidelines is an evidence-based path for when to recheck BMD, once a baseline is established.

The Study of Osteoporotic Fractures enrolled mid-life American women without OSPS at baseline (n = 4957; age ≥ 67) in an observational study. After baseline DEXA, scans were performed again at year 2, year 6, year 8, year 10, and year 16. The primary outcome of the trial was the interval after a baseline DEXA at which point 10% of participants would progress from normal BMD or osteopenia to OSPS.

As might be completely intuitive, the interval for progression to lower BMD levels was proportional to the degree of bone loss at baseline. That is, the interval before progression to OSPS for women with normal BMD or mild osteopenia at baseline was about 17 years; for those with moderate osteopenia, the interval was 4.7 years, and 1.1 years for women with advanced osteopenia (T-score = -2 to -2.49).

Based on these data, the authors suggest that for women with baseline T scores > -1.5, there is little likelihood of progression to osteoporosis (< 10%) over 15 years, and — in the absence of additional new risk factors to dictate otherwise — re-testing BMD might be reasonably put off for that same interval. For women with lower levels of BMD at baseline, however, a shorter interval for re-testing would be appropriate: 5 years for those with moderate osteopenia, and only 1 year for those with advanced osteopenia. ■

How Common is Vitamin B12 Deficiency in Patients on Metformin?

Source: Reinstatler L, et al. *Diabetes Care* 2012;35:327-333.

It has been recognized since the first published metformin clinical trials that B_{12} levels were impacted. For instance, a recent clinical trial found a 19% reduction in B_{12} levels (compared with placebo) after 4 years. Perhaps because common clinical signs of B_{12} deficiency (e.g., anemia, neuropathy, cognitive impairment) related to metformin treatment are rarely seen, clinicians have had low levels of apprehension about the effects of metformin on vitamin B_{12} levels.

How common is B_{12} deficiency in patients on metformin? An answer can be found in the NHANES data. Comparing adults with (n = 1621) and without (n = 6867) type 2 diabetes, Reinstatler et al report that biochemical deficiency of B_{12} (defined as level B_{12} < 148 pmol/L) was seen in 5.8% of diabetics on metformin; this was more than twice as frequent as the prevalence among diabetics not on metformin (2.4%), and about more than 1.5 times as frequent as in non-diabetics (3.3%).

One curious finding from this study was that consumption of B_{12} supplements by diabetics did *not* reduce the frequency of deficiency. It might be that the amount typically found in over-the-counter multivitamin supplements (6 mcg) is insufficient, even though the amount recommended by the Institute of Medicine is only 2.4 mcg/day. ■

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Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
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Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

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