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INSIDE

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Intensive Treatment and Autologous Transplant for Mantle Cell Lymphoma

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

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

Synopsis: *Long-term disease control remains an elusive target for mantle cell lymphoma (MCL), even after aggressive therapy. The Nordic Lymphoma Group treated 160 patients younger than 65 years of age on a phase II protocol using rituximab and CHOP alternating with rituximab and high-dose cytarabine followed by autologous hematopoietic cell transplantation (HCT) for responders. The overall response rate was 96% and 54% achieved CR or CR unconfirmed. The six-year overall survival was 70%, with progression-free survival of 66% and no relapses after five years. Among stem cell products assessed, only 14% were positive for minimal residual disease by molecular methods. Compared to an earlier trial by the same group following the same protocol without rituximab or cytarabine, the recent trial resulted in better response rates, higher overall and progression-free survival, and more molecular negative stem cell products. An intensive program of CHOP, cytarabine, rituximab, and autologous HCT is highly effective, and may lead to prolonged disease control.*

Source: Geisler C, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase II multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112:2687-2693.

MANTLE CELL LYMPHOMA (MCL) IS AN UNCOMMON B-CELL NEOplasm. Despite various attempts using intensive therapeutic approaches, MCL has a continuous pattern of relapse. Efforts to enhance long-term disease control, if not to obtain cures, remain elusive. One major thrust has been autologous hematopoietic cell transplantation (HCT), particularly as consolidation following induction and consolidation chemotherapy. The Nordic lymphoma

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group's initial attempt in the late 1990s at autologous HCT consolidation for mantle cell lymphoma (known as MCL-1 trial) met a similar fate as other studies, in that almost all patients relapsed.[1] Subsequently, newer strategies employing rituximab showed enhanced response rates and preventing tumor cell contamination from the autologous stem cell product.[2] The Nordic group embarked on this follow-up trial (the MCL-2 trial) to optimize long-term outcomes using autologous HCT as consolidation. High-dose cytarabine and rituximab were added to the pre-HCT regimen in an effort to improve tumor control and achieve lymphoma-free stem cell products.

The trial involved 160 patients with newly diagnosed Stage II- IV MCL from 2000 to 2006. Induction included CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone), with alternating cycles of high-dose cytarabine of three cycles each (six cycles total). Stem cells were collected after cycle 6, with the addition of G-CSF. Between four to six doses of rituximab were given, including two doses for the stem cell mobilization cycle 6 for stem cell purging. High-dose chemotherapy with BEAM or BEAC (carmustine, etoposide, cytarabine, and melphalan/cyclophosphamide) was given for HCT conditioning. Molecular monitoring was performed by PCR. Patients who converted from PCR-negative to PCR-positive bone marrow or blood, without signs of clinical relapse after autologous HCT, were offered preemptive therapy with rituximab 375 mg/m^2 weekly for four weeks.

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Induction treatment afforded a response in 96%, with 54% of all patients achieving CR or CR unconfirmed. Another 42% achieved a PR, and 4% did not respond. A total of 145 responders of the original 160 patients went on to high-dose therapy and HCT. The observation time was 3.8 years. Including HCT, non-response or relapse occurred in 30%, and 8% had major protocol-terminating toxicity, including harvest failure (4.4%), graft failure (2.5), and one case of pulmonary embolism. The four-year event-free survival (EFS) rate was 63% on intention-to-treat basis, which was significantly higher than the 18% four-year EFS on the previous MCL-1 trial by this group from 1996-2000, which did not include rituximab or cytarabine ($p < .001$). The four-year overall survival (OS) rate was 81%, significantly higher than the 55% four-year OS of the MCL-1 trial ($p = .002$). No deaths have occurred after 5.2 years among 33 patients. Only one case of myelodysplasia or AML occurred. PCR-negative molecular responses were obtained in 92% of evaluable patients after HCT, compared to only 38% in the MCL-1 trial. On multivariate analysis of survival, only the morphologic variant of MCL and the IPI score demonstrated independent prognostic importance.

■ COMMENTARY

Novel therapeutic strategies for mantle cell lymphoma (MCL) have been explored over the past decade to improve upon the historically poor median survival of 3-4 years after standard chemotherapy approaches such as CHOP. This includes antibody therapy with rituximab,[3] novel chemotherapy combinations, and hematopoietic cell transplantation.[4]

In this report from Geisler et al, combining all three strategies led to very promising long-term outcomes. This trial (MCL-2) was compared to a prior series in a similar population without the addition of rituximab and cytarabine (the MCL-1 trial). The MCL-2 study confirmed higher response rates using rituximab and cytarabine for MCL relative to standard CHOP. The higher response rate is not surprising. However, other studies documenting similarly high response rates of over 90% incorporating cytarabine and rituximab to the chemotherapy regimen suffered from continued late relapses.[5]

The most intriguing finding of this report is the "plateau" five years after HCT where late relapses have not yet occurred. Earlier trials such as the MCL-1, with autologous HCT without the benefit of pre-transplant rituximab and cytarabine, showed many of the stem cell products harbored detectable minimal residual disease (MRD) for lymphoma. In this trial, high-dose therapy and autologous HCT allowed both additional responses and only 14% of stem cell products with molecular

evidence of MRD, further confirming the enhanced activity of the pre-transplant regimen. Another approach in this regimen that may have further led to long-term control was early rituximab at the first sign of MRD after HCT without overt relapse. The incremental benefit of pre-emptive therapy can not be determined.

The standard, but always relevant, caveats of a phase II trial hold. These patients were generally a relatively select group of patients and were younger than 65 years of age. Geisler et al correctly point out that this approach, using patients older than 65 years of age, represent over half of all patients. The low relapse-related mortality for the entire treatment program of induction and autologous HCT certainly contributed to the excellent long-term outcomes. Less select patients and/or treatment outside of a strict protocol may lead to substantially worse outcomes.

Autologous HCT may have late complications, including therapy-related leukemia. Further, historical results reveal considerable variability in prognosis, with 10-year survival of 71% for low-risk to 36% for high-risk MCL applying The Follicular Lymphoma International Prognostic Index (FLIPI).[6,7] Thus, 10-year follow-up is necessary and accountable. Ultimately, randomized trials would most confidently determine the absolute benefit of this intensive approach. The target is always shifting in oncology as newer treatments are introduced such as bortezomib. New treatments pose a challenge in assessing studies requiring long-term follow-up, as highly active novel therapies may increase the number of responders and thus patients eligible for autologous HCT, as well as improving the natural history of the disease without HCT.

These data will not alter treatment guidelines for mantle cell lymphoma, although this offers additional evidence to support a role of autologous HCT for consolidation for MCL. In fact, National Cancer Center Network guidelines indicate consolidation with autologous HCT may improve progression-free survival; an overall survival benefit has not been demonstrated. The option of HCT should be discussed with relatively fit patients diagnosed with MCL. Clinical trials incorporating HCT are ongoing. ■

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Erythropoiesis-stimulating Agents and Myeloma: Bad News or No News?

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a retrospective analysis of 323 patients with multiple myeloma, of which 169 patients received one or another form of ESA for treatment of disease or treatment-associated anemia, multivariate analysis, using a proportional hazard model, indicated worse progression-free and overall survival associated with ESA treatment. This report is quite different from another recently reported analysis, and highlights the problems associated with retrospective studies. Nonetheless, there is a prevailing sensibility that ESA treatment for anemic myeloma patients, as with all cancer patients, must be cautiously applied and carefully monitored.*

Source: Katodritou E, et al. Erythropoiesis-stimulating agents are associated with reduced survival in patients with multiple myeloma. *Am J Hematol*. 2008;83:697-701.

THERE HAS BEEN MUCH CONCERN IN RECENT MONTHS regarding the possibility that the use of erythropoiesis-stimulating agents (ESA) may negatively influence overall survival for patients with cancer. The focus has been on solid tumors, for which such evidence has been mounting.[1-3] Yet, for hematologic malignancies, the issue has been less well studied. In the current retrospective analysis, Katodritou et al from the Greek Myeloma Study Group reviewed their experience with 323 multiple myeloma patients followed between 1988 and 2007 to determine whether ESA treatment influenced progression-free or overall survival. One hundred and sixty-nine patients received ESA and 154 did not. The median duration of ESA administration was six weeks (range 4-10 weeks), and the median baseline hemoglobin (Hb) levels of patients who received ESA were 9.4 g/dL (range 7.3-11.9). Anemia response for the patients who received ESA was 68%.

Established myeloma prognostic factors (age, serum LDH, hemoglobin concentration, platelet number, serum creatinine, International Scoring Scale [ISS] score, and beta-2 microglobulin) and ESA use were each proven to be of prognostic significance in terms of overall survival (OS) by univariate analysis ($p < 0.05$, for all parameters). Using a proportional hazards model for multivariate analysis, including all of the parameters found significant by univariate analysis (as above), only beta-2 microglobulin, age, and ESA use predicted survival ($p < 0.05$ for each). The median OS of patients in the ESA group was 31 months (95% CI: 25- 37 months), whereas in the group without ESA administration, it was 67 months (95% CI: 55-79 months; $p < 0.001$). Deep vein thrombosis (DVT) was observed in 11 patients (6.5%) in the ESA group and in seven patients (4.5%) in the group without ESA ($p = 0.59$). The odds ratio for thrombosis after ESA administration was 1.46 (95% CI: 0.51-4.3).

■ COMMENTARY

This report runs counter to that of Baz et al,[4] who described the Cleveland Clinic experience with regard to outcomes of myeloma patients in the context of ESA use. Their study population consisted of 257 patients treated from 1997-2003, and followed for at least one month. Of these, 127 patients received an ESA for at least one month, whereas the remainder had not. On average, patients who received ESA were older, had more advanced disease, higher serum creatinine, lower serum hemoglobin, higher beta 2-microglobulin, lower platelet counts, and a longer time from diagnosis to enrollment at the myeloma program ($p < 0.001$ for all). They found, however, that after adjusting for age, months from diagnosis to enrollment, serum creatinine, hemoglobin, platelet count, and beta 2-microglobulin, the use of an ESA was associated with improved overall survival (hazard ratio = 0.6; 95% CI = 0.38-0.94) in patients with intermediate or advanced disease but not in patients with early stage disease.

On the surface, it's hard to reconcile the findings from these two studies. Whereas the current report from Greece is somewhat larger and the study population a little more homogenous (care had been taken to exclude those who had been transfused as well as those who were treated beyond a hemoglobin of 13 g/dL), the Cleveland Clinic report reflected patients with more sustained ESA use (median ESA treatment duration was 36 weeks, compared with only six weeks in the Greek study). Thus, inherent differences in the population may explain the different findings.

It is disconcerting that we don't have an answer on this, but it is unlikely that a retrospective review, as large as it might be, will provide the solution. When myeloma patients develop anemia, it usually reflects advancing disease. Physicians rely on a whole host of factors, including the presence or absence of comorbidities, socioeconomic factors, and the ability to afford expensive therapy, that the confounders obviate comparable groupings, even in a well constructed multivariate analysis, such as attempted in the current report. Instead, a prospective, randomized trial would be the most direct way to answer this question, but don't look for this to happen anytime soon. Once again, clinicians will need to rely on their experience and clinical judgment rather than established evidence when confronted with the decision about how best to manage symptomatic anemia in patients with multiple myeloma, or any cancer for that matter. ■

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associated with increased overall survival in patients with multiple myeloma. *Acta Haematol*. 2007;117: 162-167.

XELOX for Second-Line Pancreatic Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Capecitabine and oxaliplatin were used in combination for patients with advanced pancreatic cancer refractory to first-line gemcitabine. The combination was well tolerated and, although only one patient met criteria for partial response, stable disease was seen in approximately 25% and overall survival was 23 weeks. The combination appears active in this setting and may be well suited for those with good performance status, particularly if they initially responded to first-line treatment.*

Source: Xiong HQ, et al. Phase II trial of oxaliplatin plus Capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. *Cancer*. 2008;113: 2046-2052.

For almost a decade, gemcitabine has been considered the standard chemotherapeutic approach to advanced pancreatic cancer.[1] Several combinations have been tested, but none have added clinically significant improvements to this drug used alone. Furthermore, few studies have demonstrated, or even addressed, treatment options for those who have become refractory to gemcitabine. In previous studies, both capecitabine and oxaliplatin have been used as components of front-line therapy for advanced pancreatic cancer. For patients with good performance status, capecitabine added to gemcitabine significantly improved median overall survival as first-line therapy, compared to gemcitabine alone.[2] (This was not true for the entire treatment cohort; just for those with good performance status.) Similarly, oxaliplatin, when used in combination with gemcitabine, was shown to improve progression-free, but not overall survival when compared to gemcitabine alone.[3] Thus, there was rationale to test the combination of capecitabine and oxaliplatin as second-line treatment for gemcitabine-resistant pancreatic cancer. Accordingly, Xiong et al conducted a Phase II trial designed to evaluate the efficacy of oxaliplatin in combination with capecitabine (XELOX) in gemcitabine-pretreated patients with advanced pancreatic cancer.

For this, patients aged 65 years or younger who had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 received oxaliplatin at a dose of 130 mg/m^2 given on Day 1 and capecitabine at a dose of 1000 mg/m^2 twice daily for 14 days. For patients who were over 65 years of age or who had an ECOG PS of 2, the oxaliplatin dose was 110 mg/m^2 on Day 1 and the capecitabine dose was 750 mg/m^2 twice daily for 14 days on 21-day cycles. The primary outcome measure was survival at six months.

The study enrolled 41 patients. Of the 39 evaluable patients, one patient had a partial response and 10 patients demonstrated stable disease. The Kaplan-Meier estimate of the overall median survival was 23 weeks (95% confidence interval [95% CI], 17.0-31.0 weeks). Progression-free survival was 9.9 weeks (95% CI, 9.6-14.5 weeks). The six-month and one-year survival rates were 44% (95% CI, 31%-62%) and 21% (95% CI, 11%-38%), respectively. The most common grade 3-4 non-hematologic toxicity was fatigue (toxicity was graded using the National Cancer Institute Common Toxicity Criteria [version 2.0]).

■ COMMENTARY

Thus, the combination of capecitabine and oxaliplatin is active in gemcitabine-pretreated patients with advanced pancreatic cancer. Typically, survival after patients become refractory to gemcitabine therapy is approximately eight weeks,[4] and thus, the observed overall survival of those second-line XELOX-treated patients of 23 weeks suggests potential for significant improvement in outlook.

Other second-line regimens have also been tested; some with comparable results. Regimens tested included irinotecan plus raltitrexed,[5] irinotecan plus oxaliplatin,[6] 5-fluorouracil and leucovorin plus oxaliplatin,[7] and capecitabine plus erlotinib.[8] In this regard, the value of XELOX may also relate to ease of administration and low toxicity profile.

Advances in imaging technology allow the recognition of patients with smaller volume of tumor, many of whom will have well maintained performance status. Thus, clinicians are likely to encounter patients refractory to gemcitabine but functionally capable, and desiring, second-line treatment, with the goal of maximizing survival. The capecitabine/oxaliplatin regimen seems a reasonable choice in that setting. For those with good performance status, it is probable that such treatment would provide survival advantage compared with supportive care alone. However, whether this doublet is superior to the others that have been reported could only be determined by randomized clinical trial. ■

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Sorafenib and Hypertension: Meta-Analysis

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Sorafenib is a multikinase inhibitor approved for treatment of renal cell and hepatocellular carcinomas. The occurrence of hypertension has been mentioned in a number of clinical reports, but the precise risk has not yet been determined. In the current study, Wu et al have reviewed published experience with this drug, and performed a meta-analysis. The results indicate approximately one in four cancer patients will develop hypertension, and that severe hypertension occurs in just under 6%. Physicians need to monitor blood pressure closely and institute antihypertensive medications promptly to avoid cardiovascular and neurologic complications.*

Source: Wu S, et al. Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2008;9:117-123.

Sorafenib is a multikinase inhibitor that exhibits a broad spectrum of anti-tumor activity, including inhibition of cellular proliferation and angiogenesis.[1] The clinical benefit of sorafenib seems to rest primarily on the basis of its anti-angiogenesis effects,[2] and demonstrable and meaningful benefit was observed in renal cell and hepatocellular carcinoma clinical trials.[3,4] Hypertension is one of the major side-effects of this drug, and frequencies vary substantially between clinical trials. To gain a better understanding of the overall risk of hypertension in patients with cancer who receive sorafenib, Wu et al performed a systematic review and meta-analysis of published clinical trials to establish the incidence of hypertension associated with sorafenib.

For this, databases, including Medline (July, 1966, to July, 2007) and Web of Science, and abstracts presented at the American Society of Clinical Oncology annual meetings from 2004-2007, were searched to identify relevant studies. Eligible studies were prospective clinical trials of cancer patients treated with single-drug agent sorafenib at 400 mg twice daily with data on hypertension available. Phase I studies were excluded because of the dose variability inherent in that type of trial, and studies with hepatocellular carcinoma because of incomplete recording of blood pressures. For the remainder, incidence and relative risk (RR) of hypertension were calculated using a random-effects or fixed-effects model, depending on the heterogeneity of the included studies.

Of 223 screened articles, there were nine studies published between January 2006 and July 2007, including a total of 4,599 patients with RCC, or other solid tumors, that met criteria for this analysis. For patients assigned sorafenib, the overall incidence of all-grade and high-grade (ie, grade 3 or 4) hypertension was 23.4% (95% CI 16.0%-32.9%) and 5.7% (2.5%-12.6%), respectively. No significant difference was noted between patients with RCC or a non-RCC malignancy (all grade: RR 1·03 [95% CI 0.73-1.45], $p = 0·89$; high-grade: RR 1·23 [0.76-1.99], $p = 0·40$) who were assigned sorafenib. Sorafenib was associated with a significantly increased risk of all-grade hypertension in patients with cancer with an RR of 6.11 (2.44-15.32], $p < 0·001$), compared with controls.

Thus, patients with cancer-assigned sorafenib have a significant risk of developing hypertension. Appropriate monitoring and treatment is strongly recommended to prevent cardiovascular complications.

■ COMMENTARY

Although not a described toxicity in phase I trials, larger phase II and III trials, as well as the expanded access program, have indicated that hypertension is a common observation in sorafenib-treated patients, occurring in 16.0%-42.6% of treated subjects. By the current analysis, the occurrence is expected in nearly one in four treated patients. Although the mechanism is not established, it is notable that other angiogenesis inhibitors, including sunitinib and bevacizumab, demonstrate similar rates of hypertension.[5] Possible mechanisms include the effect of impaired angiogenesis leading to a decrease in the density of microvessels (rarefaction), damage to endothelial cells resulting in decreased nitric-oxide production and oxidative stress, and changes in neuro-hormonal factors or rennin/aldosterone. The latter mechanism seems less likely in light of the findings of Veronese et al, in which no significant change in humoral factors, including serum total catcholamines, epinephrine, norepinephrine, endothelin 1, renin and aldosterone were observed among 20 patients after three weeks of sorafenib treatment despite the occurrence of hypertension in 15 (75%).[6]

The optimal management of sorafenib-associated hypertension remains unresolved. What is clear is that blood pressure should be carefully monitored from the beginning of therapy and promptly treated. By this analysis, severe hypertension occurred in 5.7% of treated patients, and adverse outcomes, including myocardial infarction[4] and posterior leukoencephalopathy syndrome,[7] have been noted to occur under such circumstances. Until there is data available to guide in the choice of pharmacological agents to manage sorafenib-associated hypertension, it might be prudent to avoid drugs metabolized by the cytochrome P450 enzyme system (such as non-dihydropyridine calcium channel blockers such as verapamil and diltiazem). In contrast, dihydropyridine calcium channel blockers (amlodipine and nifedipine), ACE inhibitors, and angiotensin-receptor blockers are reasonable choices for initial management.

Thus, sorafenib treatment is associated with a significant risk of developing hypertension. Oncologists must be aware of this, monitor blood pressure carefully, and institute antihypertensive management promptly. ■

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CME Questions

40. What were the results of adding high-dose cytarabine and rituximab to CHOP chemotherapy followed by autologous hematopoietic cell transplant (HCT) for mantle cell lymphoma (MCL)?

a. Response rates were not improved compared to historical patients receiving only CHOP.
b. The toxicity of autologous HCT was prohibitive at greater than 30% mortality.
c. Very few patients ultimately went on to autologous HCT.
d. Initial response rate (CR + PR) was over 90%, and over 50% had not progressed at five years.

41. The incidence of hypertension development in cancer patients treated with sorafenib is estimated to be:

a. 5%.
b. 25%.
c. 50%.
d. 90%.

42. In patients with multiple myeloma and anemia, ESA treatment is definitively associated with:

a. decreased progression-free survival.
b. decreased overall survival.
c. Both of the above
d. Neither of the above

43. Patients most likely to benefit from second-line treatment of advanced pancreatic cancer with XELOX include those with:

a. good performance status.
b. prior demonstrable response to gemcitabine.
c. smaller tumor burden.
d. All of the above

Answers: 40. (d); 41. (b); 42. (d); 43. (d)

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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.

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14. Issue Date for Circulation Data Below: September 2008

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b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	400	386
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c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			451	448
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	7	10
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g. Total Distribution *(Sum of 15c and 15f)*			479	478
h. Copies Not Distributed			285	55
i. Total *(Sum of 15g. and h.*			764	533
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			94%	94%

16. Publication of Statement of Ownership
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In Future Issues:

Hodgkin's Lymphoma and Male Fertility

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*.

Safety of Inhaled Anticholinergics for COPD Scrutinized

In the Issue: Ongoing safety review of tiotropium; raloxifene reduces the risk of endometrial cancer; one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir; new Clinical Practice Guideline from the American College of Physicians regarding pharmacologic treatment for low bone density and osteoporosis; FDA Actions.

THE SAFETY OF INHALED ANTICHOLINERGICS FOR the treatment of chronic obstructive pulmonary disease (COPD) has come under scrutiny in recent months. In July, the FDA issued an "Early Communication" about an ongoing safety review of tiotropium (Spiriva®) the most widely used agent for the treatment of COPD. The review is focused on a possible increased risk of stroke and is based on a pooled analysis of 29 trials which showed the risk of stroke at 8 patients per 1000 treated with tiotropium versus 6 patients per 1000 treated with placebo.

Now two new studies suggest that inhaled anticholinergics (ipratropium [Atrovent®] and tiotropium) increase the risk for all-cause mortality and cardiovascular disease in patients with COPD. In a large meta-analysis (*JAMA* 2008;300: 1439-1450), researchers reviewed 17 trials involving nearly 15,000 patients with COPD who were randomized to an inhaled anticholinergic or control. The primary outcome was a composite of cardiovascular death, MI, or stroke. The secondary outcome was all-cause mortality. The primary outcome occurred in 1.8% of patients receiving inhaled anticholinergics and 1.2% of patients receiving control therapy (RR 1.58, 95% CI, 1.21-2.06; $P < 0.001$). Inhaled anticholinergics significantly increased risk of MI, cardiovascular death, and all-cause mortality (RR 1.26). When the analysis was restricted to long-term trials, the risk was even greater for cardiovascular death, MI, or stroke (RR 1.73). The number needed to harm for MI was 174 per year, while the number needed to harm for cardiovascular death was 40 per year. The authors concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD.

In a second nested, case-control study (*Ann Intern Med* 2008;149:380-390), the National Veterans Affairs databases were used to review all-cause mortality, respiratory and cardiovascular deaths, and exposure to COPD medications including inhaled corticosteroids, ipratropium, long-acting beta agonists, and theophylline in the 6 months preceding death. The adjusted odds ratios for all-cause mortality were 0.80 for inhaled chronic steroids, 1.11 for ipratropium, 0.92 for long-acting beta agonists, and 1.05 for theophylline. Ipratropium was associated with increased cardiovascular deaths (OR 1.34), whereas inhaled corticosteroids were associated

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

with reduced risk for cardiovascular death (OR 0.80). The authors conclude that there is a possible association between ipratropium and elevated risk for all-cause and cardiovascular death and that further studies are needed. They also suggest that the risk of ipratropium may be somewhat mitigated by concomitant use of inhaled corticosteroids, but caution should be exercised if ipratropium is used alone in patients with recently diagnosed COPD.

Raloxifene reduces endometrial cancer risk

It is well known that raloxifene reduces the risk of breast cancer; now there is evidence that the drug reduces the risk of endometrial cancer as well. Raloxifene (Evista®) is a selective estrogen receptor modulator (SERM) that is indicated for treatment and prevention of osteoporosis and for breast cancer prevention. Researchers from the University of Pennsylvania compared endometrial cancer rates in women on raloxifene, tamoxifen, and non-users of SERMs in a case-control study of 547 women with endometrial cancer and 1410 controls. After adjustment for other risk factors the odds of endometrial cancer among raloxifene users was 50% that of non-users (OR = 0.50; 95% CI, 0.29-0.85), whereas tamoxifen users had 3 times the odds of developing endometrial cancer compared to raloxifene users (OR = 3.0; 95% CI, 1.3-6.9). Among raloxifene users who developed endometrial cancer, the tumors had a more favorable histologic profile and were predominantly stage I and low grade. The authors conclude that raloxifene users have significantly lower risk of developing endometrial cancer compared with tamoxifen users and SERM non-users, perhaps even suggesting a role for raloxifene and prevention of endometrial cancer (*J Clin Oncol* 2008; 26:4151-4159).

One-day famciclovir = three-day valacyclovir

For patients with recurrent genital herpes outbreaks, one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir, according to a new study. In a double-blind parallel group study, 1179 adults with a history of recurrent genital herpes were randomized to receive either famciclovir 1000 mg twice daily for one day vs valacyclovir 500 mg twice daily for 3 days. Patients initiated treatment within 6 hours after a recurrence. Approximately one-third of patients in each group aborted genital herpes outbreaks altogether, but for those who went on to develop lesions, median time to healing was 4.25 days for famciclovir vs 4.08 days for valacyclovir. Time to healing was the same in both groups and the incidence of adverse affects was 23.2% for famciclovir vs 22.3% for valacyclovir. The study demonstrates that a single day of famciclovir (1000 mg twice daily) is equivalent to 3 days of valacyclovir (*Clin Infect Dis* 2008;47:651-658). Other regimens for treatment of recurrent HSV episodes include acyclovir 800 mg 3 times daily for two days or 400 mg three times daily for 3-5 days, famciclovir 125 mg twice a day for 3-5 days, or valacyclovir 500 mg twice daily for 3 days. Both acyclovir and famciclovir are available generically, but acyclovir is considerably less expensive; however, the convenience of a one-day treatment with famciclovir may be worth the extra cost for many patients.

New practice guideline for osteoporosis

The American College of Physicians has issued a Clinical Practice Guideline regarding the pharmacologic treatment of patients with low bone density or osteoporosis (*Ann Intern Med* 2008; 149:404-415). The expert committee recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures. They also recommend that pharmacologic treatment should be considered for men and women who are at risk of developing osteoporosis and that the choice of pharmacologic treatment should be based on assessment of risk and benefits in individual patients. The guideline reviews different treatment modalities including bisphosphonates, calcitonin, estrogen, teriparatide, SERMs, testosterone, and calcium plus vitamin D. Left unanswered are the questions of duration of treatment with bisphosphonates and the optimal dose of calcium and vitamin D.

FDA actions

The FDA has issued warning letters to Ranbaxy Laboratories Ltd. of India in an Import Alert for the company's generic drugs produced in two Indian plants. The warning letters identify concerns about deviations from U.S. current Good Manufacturing Practice requirements at Ranbaxy's manufacturing facilities and the Import Alert allows officials to detain at the rest border any active pharmaceutical ingredients manufactured at Ranbaxy facilities. Ranbaxy manufacturers more than 30 generic drugs including commonly used antibiotics, antihypertensives, and antivirals. ■

Clinical Briefs in
Primary Care
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By Louis Kuritzky, MD
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Cognitive Impairment Progression Blunted by Exercise

Source: Lautenschlager NT, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA* 2008; 300:1027-1037.

CLINICAL TRIALS OF PHARMACOTHERAPY to prevent progression of cognitive decline in those with mild cognitive impairment (MCI) have been disappointing; neither cholinesterase inhibitors (donepezil, rivastigmine, galantamine), vitamin E, nor COX-2 inhibitors has demonstrated any clinically meaningful benefit in placebo-controlled MCI trials.

Observational data are consistent that regular physical activity, even if started late in life, is associated with reduced risk of dementia. Whether exercise might prevent progression in persons with MCI was the subject of this first randomized trial to address the issue.

Subjects (n = 170) with MCI between the ages of 50-77 (mean age, 68.6 years) were randomized to receive either 50-min sessions of moderate-intensity exercise (e.g., brisk walking, ballroom dancing, and swimming) three times weekly vs control (general education about health, including physical activity, diet, alcohol, and stress management). All educational materials were also provided to the intervention group. All participants (control and intervention) wore a pedometer and provided diaries of daily total number of steps. Physical activity and cognitive function were assessed at 6, 12, and 18 months after randomization.

At each assessment point, cognitive scores for the intervention group were better than the control group. The intervention group averaged approximately 6000 more steps/week than the control group. Exercise, averaging as little as 21 min/day, reduces cognitive decline in persons with MCI. ■

Incidentalomas in the Knee

Source: Englund M, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008;359:1108-1115.

ONE OF THE PRIMARY THINGS THAT has stood in the way of definitive diagnosis of acute low back pain is the extraordinarily high rate of false-positive findings seen on plain films, CT, or MRI. Indeed some studies suggest that as many as half of healthy, asymptomatic individuals studied by MRI of the lumbar spine have findings consistent with disk pathology.

Little is known about the frequency of incidental findings seen upon MRI of the knee, since studies generally investigate symptomatic individuals; subsequent radiographic findings, if they correlate with symptomatology, have been taken to support a causal relationship.

Englund et al performed an MRI of the right knee in 991 randomly selected adult subjects ages 50-90 in Massachusetts. Excluded subjects included those with rheumatoid arthritis, knee replacement, terminal illness, or non-ambulatory status.

The incidence of meniscal tears seen ranged from 19% in the youngest women (ages 50-59) to 56% in senior men (ages 70-90). Among the group with radiographic changes of osteoarthritis, the frequency of meniscal tears in symptomatic and asymptomatic individuals was similar (63% vs 60%, respectively). Overall, the majority of persons (60%) with meniscus tears confirmed by MRI had no symptoms referable to the knee.

It appears that as with back MRI, incidental findings of pathology are frequent, and call into question an ironclad attribution of knee symptoms to positive findings on MRI. ■

Hormone Replacement and Skin Health in Menopausal Women

Source: Phillips TJ, et al. Does hormone therapy improve age-related skin changes in postmenopausal women? *J Am Acad Dermatol* 2008;59:397-404.

AS LITTLE AS A DECADE AGO, MENOpausal status alone was the ticket of admission to advocate hormone replacement therapy (HRT). The "story line" went that HRT prevented cognitive decline, improved symptoms, enhanced cardiovascular health, and preserved cutaneous health, i.e., reduced age-related wrinkles, dryness, and laxity. Unfortunately, HRT has failed to live up to numerous of its hopeful claims.

To study the effects of HRT on menopausal women's skin, 485 subjects were randomly assigned to placebo or two different HRT doses in double-blind fashion. Dermatologists evaluated skin wrinkling, laxity, and texture (as did the patients) over a 48-week interval. The mean age of the women was 54 years.

At study end, there were no statistically significant differences in any primary endpoint of the trial. When the data were analyzed for impact of baseline levels of estradiol, race, or age, no meaningful differences were found. During the trial, all study groups enjoyed some skin improvements attributable to daily application of moisturizing cream and sunscreen, but HRT added nothing to this. Claims that HRT provides reduced risk of age-related skin changes are not supported by this trial. ■

Reconfirmation of the Death of Homocysteine

Source: Ebbing M, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled trial. *JAMA* 2008;300:795-804.

HOMOCYSTEINE (HCYS) HAS ALL THE trappings of a first-rate cardiovascular risk factor: as strong an association with CVD endpoints as cholesterol, ease of identification, and simplicity of modulation. Trouble is, trials to date have been unable to show that reductions of homocysteine provide meaningful benefits to patients. Indeed, one recent commentary following a large double-blind intervention-

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al trial of HCYS for cardiovascular endpoints began with "The homocysteine hypothesis is dead … ."

Apparently as undaunted as Mark Twain ("The reports of my death are greatly exaggerated …"), Ebbing et al tested HCYS reduction through B vitamins after coronary angiography. The primary endpoint of the study was all-cause mortality, non-fatal stroke and MI, and hospitalization for unstable angina (composite).

The trial (n = 3096) was designed to follow patients for 4 years, but was stopped at 38 months due to information from another trial that had reported a possible negative effect of B vitamin intervention. B vitamins did reduce HCYS by approximately 30%, but failed to have any impact (positive or negative) upon endpoints. The HCYS hypothesis is still dead. ■

Pramlintide as a Weight-Loss Adjunct

Source: Smith SR, et al. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008;3:1816-1823.

SOMETHING THAT NEITHER MOTHER NOR medical school taught us was that more than one hormone is secreted from the beta cells of the pancreas in response to rising glucose. In conjunction with insulin, the hormone amylin is released. Pramlintide is a synthetic form of amylin. The physiologic effects of amylin include slowed gastric emptying (thereby slowing the rate of glucose delivery to the intestine), suppression of glucagon, and centrally mediated satiety. For addressing obesity, there is great conceptual appeal to an agent that improves satiety.

Smith et al performed a double-blind, placebo-controlled trial of various doses of subcutaneous pramlintide (bid to tid) in obese, nondiabetic subjects, who were also receiving intensive lifestyle (diet/exercise) intervention. The initial 4-month double-blind phase was followed by a 4-month single-blind extension (for those who completed the initial phase without protocol violation).

Weight loss was dose-proportional: At 360 µg twice daily the placebo-corrected weight loss was 3.3 kg at month 4 and 7.2 kg at month 12. No safety concerns were seen. Nausea, which is also the most common adverse event seen in diabetic subjects, was mostly mild to moderate, and improved over time. Nausea is not the mechanism of action, since weight reduction was similar in those who did and did not experience nausea. These initial data are encouraging that pramlintide may find a role in enhancing weight loss when used in conjunction with lifestyle intervention. ■

Undiagnosed Diabetes in Obese Americans

Source: Wee CC, et al. Obesity and undiagnosed diabetes in the U.S. *Diabetes Care* 2008;31:1813-1815.

NO CLINICIAN IS SURPRISED TO SEE that diabetes often goes undiagnosed. Patients can persist with modest symptoms, or even asymptomatically, for protracted periods during the early stages of type 2 diabetes. The fact that literally half of type 2 diabetics have one or more of the traditional complications of diabetes (neuropathy, nephropathy, retinopathy, dermopathy) at the time of clinical diagnosis attests to the fact that diagnosis lags substantially behind disease onset.

Most type 2 diabetics are obese, and obesity provides an environment that promotes insulin resistance, a cardinal dysfunction in early diabetes and pre-diabetes. Hence, scrutiny of obese subjects provides a window of observation into a population felt to be at greater risk for developing diabetes. On the one hand, the clinician might think that the presence of obesity would prompt greater vigilance for diabetes; on the other hand, there is evidence that compared to the non-obese, obese individuals experience delays in receiving preventive care.

From the 1999-2004 NHANES data, it was determined that 9.8% of the population had diabetes (defined as FBG > 126 mg/dL). Slightly more than one-fourth (28.1%) of persons with FBG > 126 mg/dL had not been diagnosed with diabetes. When parsed into BMI categories, normal weight individuals were actually less likely to have undiagnosed diabetes than overweight or obese persons (22.2% vs 32.5% vs 27.4%, respectively). Because more than one-half of undiagnosed diabetes is seen in overweight and obese individuals, enhanced vigilance is appropriate. ■