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INSIDE

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Clinical Oncology Alert's Editor, William Ershler, MD, and peer reviewer, V.R. Veerapalli, MD, report no financial relationships to this field of study.

FISH Adequate to Follow CML after Response

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD

Division of Hematology/Oncology, University of Chicago

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

Synopsis: *Chromosome banding analysis (CBA) of marrow metaphase cells is the standard method to assess response in CML. The authors compared CBA to interphase fluorescence in situ hybridization (I-FISH) in 664 samples where both methods were performed. Of the 537 samples showing complete cytogenetic remission (CCyR) by CBA, I-FISH was < 1% in 82.7%. Of 451 cases with less than 1% positive cells by I-FISH, 444 (98.4%) were in CCyR by CBA. PCR for BCR/ABL showed major molecular responses were more likely for I-FISH less than 1% relative to those with I-FISH 1% to 5% (66.8% vs. 51.6%, p < .001). This difference by I-FISH was also found when restricted to samples showing a CCyR by CBA. A cutoff-value of 1% for I-FISH was established. I-FISH is more sensitive than CBA and could be used to monitor once a CCyR is established by conventional cytogenetics.*

Source: Testoni N, et al. Chronic myeloid leukemia: A prospective comparison of interphase fluorescence in situ hybridization and chromosome banding analysis for the definition of complete cytogenetic response: A study of the GIMEMA CML WP. *Blood*. 2009;114:4939-4943.

CHRONIC MYELOID LEUKEMIA (CML) IS CHARACTERIZED BY THE Philadelphia chromosome (i.e., 9;22 translocation) created by the fusion of the ABL gene on chromosome 9 and the BCR gene on chromosome 22. As a consequence, activation of protein tyrosine kinase drives leukemogenesis and also enables accurate diagnosis and disease monitoring. The traditional method for monitoring chromosome abnormalities has been cytogenetic banding. For known translocations, fluorescence in situ hybridization (FISH) can be used. In addition, the BCR-ABL may be detected and quantified by reverse transcriptase polymerase chain reaction (PCR).[1]

Imatinib inhibits the aberrant tyrosine kinase activity of the Bcr-Abl fusion protein and has considerable activity.[2,3] Achieving a

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complete cytogenetic response (CCyR), as measured by chromosome banding analysis (CBA) of marrow cells, defines response to therapy. However, CBA analysis is time consuming and may be hampered by inadequate marrow samples. Increasingly, FISH is being used to determine CCyR, but prospective data on outcomes are lacking based on I-FISH.

Testoni et al pooled data from three CML trials evaluating various doses of imatinib. CBA and FISH studies were prospectively performed on marrow samples at six months and one year to assess response. The studies evaluated 567 patients, and each patient may have had several marrow examinations. Of these, 90% had evaluable cytogenetics. Among the 537 cases of CCyR by CBA, 71 (13.2%) had 1% to 5% positive cells by I-FISH and 22 (4.1%) had more than 5% positive cells. For the 77 cases of partial CyR by CBA, I-FISH revealed seven (9.1%) had less than 1% of positive cells, 32 (41.6%) had 1% to 5%, and 38 (49.3%) had greater than 5% positive cells. Alternatively, of the 451 cases of < 1% of cells by I-FISH, 98.4% had 0% (CCyR) by CBA. For I-FISH with 1% to 5% or more than 5%, CBA showed 68.9% and 36.7%, respectively.

PCR for BCR-ABL showed that molecular responses were similar for CCyR by CBA or < 1% positive cells by I-FISH. Among CBA with no Philadelphia chromosomes detected (CCyR), the molecular response was 66.1% when I-FISH was < 1%, compared to 49.4% for those where I-FISH was greater ($p = 0.004$).

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■ COMMENTARY

Ironically, the advent of highly effective therapy for CML also has introduced a welcome challenge — the need to accurately measure complete responses. Data from the large imatinib versus interferon trial confirmed the essential value of achieving a complete cytogenetic remission (CCyR)[4] as a gold standard, indicating a very low risk of disease progression. The standard assessment requires metaphase cytogenetics analyzed by chromosome banding analysis (CBA). Not infrequently, samples are inadequate. Further, outside of large university centers, most facilities transport samples to reference laboratories, leading to problems and delays which may further reduce yields. FISH allows rapid analysis, fewer inadequate samples, and analyzes a larger number of cells. By using dual-fusion probes with FISH, false positives are drastically reduced, leading to lower thresholds for cutoff values to around 1%. Still, lack of data for FISH has led to uncertainty in interpreting FISH results, especially when discordant with CBA.

In this prospective study, Testoni et al show interphase FISH may be superior to standard CBA of marrow metaphase cells. Most samples (98.4%) showed a CCyR by CBA (i.e., no Philadelphia chromosome-positive cells). Interestingly, for samples showing CCyR by CBA, I-FISH detected 13.2% of samples with 1% to 5% positive cells and 4.1% of samples with more than 5% positive cells. PCR for BCR/ABL confirmed that greater numbers of cells by I-FISH translated into reduced chances of major molecular responses. The added sensitivity of FISH over standard CBA for detecting low-level disease among those with a CCyR by CBA was not surprising. CBA typically analyzes 20 cells and, sometimes, fewer cells are available. The utility of FISH likely would be even greater if one accounted for samples with failed CBA but where FISH could still be performed.

As Testoni et al point out, CBA still retains value. If I-FISH becomes positive, CBA also may be needed. Importantly, only CBA can detect non-Philadelphia chromosome-acquired abnormalities, which is particularly relevant if loss of response occurs. For now, metaphase cytogenetics by CBA should be performed on subjects receiving tyrosine kinase inhibitors for CML. However, once a CCyR is reached, I-FISH may have additional value, or could be substituted. Other techniques of monitoring, such as I-FISH or molecular monitoring from the blood, hold promise, particularly once a cytogenetic remission is confirmed from the marrow.

In conclusion, interphase FISH is more sensitive to detect residual Philadelphia chromosome-positive cells once in complete cytogenetic remission by standard mar-

row CBA. FISH is an option to confirm continued CCyR previously documented by CBA. ■

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Quality of Life in Long-term Survivors of Hodgkin's Lymphoma

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *A long-term longitudinal assessment of quality of life among patients treated for early-stage Hodgkin's lymphoma reveals that, with the exception of fatigue, there is general improvement over time. Factors that influence the rate of improvement include age and sex, but do not include the type of treatment received (radiation vs. chemotherapy).*

Source: Heutte N, et al. Quality of life after successful treatment of early-stage Hodgkin's lymphoma: 10 year follow-up of the EORTC-GELA H8 randomized controlled trial. *Lancet Oncol*. 2009;10:1160-1170.

Currently, more than 80% of newly diagnosed patients with Hodgkin's lymphoma will be long-term survivors.[1] Yet, little is known about the changes over time in health-related quality-of-life (HRQoL) measures for patients during their post-treatment follow-up and re-adaptation to normal life. To address this, Heutte et al from Europe report on the HRQoL of patients treated in the randomized H8 trial of the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group and the Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Their goal was to assess HRQoL and fatigue following treatment, to analyze relations with treatment, and to identify factors that predict persistent fatigue.

Patients received HRQoL questionnaires at the end of primary therapy and several times during follow-up. The EORTC QLQ-C30 was used to assess HRQoL, and the Multidimensional Fatigue Inventory (MFI-20) was used to assess fatigue. Changes of mean HRQoL scores over time were analyzed with mixed models.

In all, there were 2,666 assessments from 935 patients. Mean follow-up was 90 months (range 52-118 months). Age affected all functioning and symptom scores except emotional functioning, with younger age associated with higher functioning and lower severity of symptoms. Furthermore, improvement with time showed similar patterns between age groups. Women reported lower HRQoL and higher symptom scores than did men. Overall, 3.2% (14/439 for role functioning) to 9.7% (43/442 for social functioning) and 5.8% (29/498 for reduced motivation) to 9.9% (49/498 for general fatigue) of patients reported impairments of 10 points or more (on a 0-100 scale) in QLQ-C30 and MFI-20 scores, respectively, independent of age and sex. Emotional domains were more affected than physical ones. There was no relation between HRQoL outcome and type of treatment. Fatigue (MFI-20 scores) at the end of treatment was the only predictive variable for persistent fatigue, with odds ratios varying from 2.58 (95% CI 1.00-6.67) to 41.51 (12.02-143.33; $p \leq 0.0001$). Sensitivity analyses adjusting for missing data were much the same as the main results.

■ COMMENTARY

HRQoL data after treatment for early-stage Hodgkin's lymphoma show that patients experience strain and limitations in all subdomains, apart from cognitive functioning, and also have reduced motivation. However, in most domains, there was gradual improvement and, although there was no survey prior to treatment, overall HRQoL 18 months or so after treatment was comparable to published data of the general European population.[2-4] Curiously, fatigue status at the end of treatment seemed to predict subsequent HRQoL and general fatigue; reduced motivation persisted throughout the follow-up. What it is about Hodgkin's lymphoma and persistent fatigue that remains incompletely understood? Certainly early on, fatigue figures prominently in the symptom complex and often can be related to anemia or other "B" symptoms. However, why fatigue should persist over the long term remains

unclear, but perhaps is somehow related to depression. Unfortunately, this parameter was not assessed in the current report. It is notable that in another study performed within the Southwest Oncology Group on 244 patients with early Hodgkin's disease, persistent fatigue was observed two years after treatment, at a point when other QoL indicators had returned to pre-treatment levels.[5]

In the current study, while differences in HRQoL improvement with time were linked to age and sex, there was no association with type of treatment (i.e., radiation vs. chemotherapy). On the surface, this runs counter to findings from the SWOG study, in which patients receiving combined modality treatment were found at six months after treatment to have significantly more symptom distress than those who had received radiation alone. However, by one year, there was no difference, a finding consistent with the current report.

Thus, the findings from this report can be considered good news. For the most part, those qualities of life that are impaired with the diagnosis and treatment of Hodgkin's lymphoma gradually return to baseline levels. Yet, the persistence of fatigue remains to be explained. ■

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Physical Activity and Prostate Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a large population-based, prospective cohort study, it was found that spending less than 50% of the day in a sedentary position, and increasing amounts of physical activity (e.g., walking or bicycling) appear to be associated with reduced rates of prostate-cancer development.*

Source: Orsini N, et al. A prospective study of lifetime physical activity and prostate cancer incidence and mortality. *Br J Cancer*. 2009;101:1932-1938.

There has been some controversy on the role of physical activity and exercise in preventing cancer.[1-4] With regard to prostate cancer, a review of 24 studies found inconclusive evidence for an association of physical activity and incident prostate cancer and concluded that more focused investigation was warranted.[5] Subsequently, two case-control studies included an assessment of lifetime physical activity.[6,7] One found a non-significant decrease in prostate cancer risk for lifetime recreational activity,[6] whereas the contrary was found in the other study.[7]

To provide a more detailed and extensive evaluation of the relationship between lifetime physical activity and the incidence of prostate cancer, Orsini et al conducted a prospective cohort study of 45,887 men aged 45-79 years who were followed from January 1998 to December 2007 for prostate cancer incidence (n = 2735) and to December 2006 for its subtypes and for fatal (n = 190) prostate cancer. The study capitalized on a population-based cohort of Swedish men that was established in 1997 among men residing in Vastmanland and Orebro counties (central Sweden). Approximately half of the men (aged 45-79 years) residing in these communities agreed to participate, and they completed questionnaires pertaining to physical activity (walking, bicycling), body weight and measurements, education level, and medical conditions. The participants also were asked to provide information about their physical activity level at age 30 and 50 years, in addition to their current physical activity.

There was an inverse association between lifetime (average of age 30 and 50 years, and baseline age) total physical activity levels and prostate-cancer risk. Multivariate-adjusted incidence in the top quartile of lifetime total physical activity decreased by 16% (95% confidence interval [CI] = 2%-27%) compared with that in the bottom quartile. Also observed was an inverse association between average lifetime work or occupational activity and walking or bicycling duration and prostate-cancer risk. Compared with men who are sedentary for the majority of their time at work, men who spend half their time or less sitting experienced a

20% lower risk (95% CI = 7%-31%). The rate ratio linearly decreased by 7% (95% CI = 1%-12%) for total, 8% (95% CI = 0%-16%) for localized and 12% (95% CI = 2%-20%) for advanced prostate cancer for every 30 minutes per day increment of lifetime walking or bicycling in the range of 30 to 120 minutes per day.

■ **COMMENTARY**

Thus, not sitting for most of the time during work or occupational activity and walking or bicycling more than 30 minutes per day during adult life is associated with reduced incidence of prostate cancer. Although it is not immediately obvious why this would be the case, this carefully conducted, large epidemiological study confirms an association that seems quite reasonable. The size of the study and the carefully conducted methodology and analysis lends credence to the results. Nonetheless, it is an observational report and should not be interpreted as demonstrating that a sedentary lifestyle is causally related to prostate cancer development. Nonetheless, biological factors that are influenced by exercise and/or physical activity include certain hormones, including testosterone, insulin resistance, adiponectin levels, and insulin-like growth factors, and each of these is relevant to the pathogenesis of prostate cancer.

These findings have important public health implications but should be confirmed by additional investigation. A long-term randomized trial of a prescribed exercise program vs. activity as usual would go a long way in settling this issue. However, this would be methodologically challenging. Short of that, a large trial of prescribed exercise within a community, such as that provided in Sweden, for which excellent tumor registry data are available, might be considered. If appropriately selected participants maintained on such a long-term exercise program had significantly less prostate cancer than the general population, matched for all the appropriate characteristics, including age, diet, general health, etc., this would provide additional suggestive evidence that the risk of prostate cancer is modifiable by physical activity and exercise. ■

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The Importance of Lymph Node Status After Neoadjuvant Therapy for Rectal Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a retrospective tumor registry (SEER) analysis of outcomes for rectal-cancer patients treated over a 14-year period with either presurgical or post-surgical radiation therapy, the importance of pathological lymph node status was found to be significantly more adverse for patients who had presurgical treatment. These patients define a subgroup for whom aggressive post-surgical treatment would seem warranted.*

Source: Chang GJ, et al. Lymph node status after neoadjuvant radiotherapy for rectal cancer is a biologic predictor of outcome. *Cancer*. 2009;115:5432-5440.

Surgical resection remains the primary treatment for localized rectal cancer. However, the preoperative use of chemoradiotherapy has become increasingly employed, based upon clinical trials that demonstrated improved local control and overall survival compared with postoperative adjuvant therapy.[1, 2] However, lymph node (LN) status after surgery for rectal cancer is affected by preoperative therapy. In fact, preoperative therapy has been associated with a decrease in pathological stage of both tumor (T) and nodal (N) status in about 60% of those treated and a pathologic complete response in 8%-31% of patients.[2-5] The question addressed in the current research is

whether the persistence of pathologically positive lymph nodes after neoadjuvant chemoradiotherapy has significance beyond that observed in lymph node-positive patients who did not have neoadjuvant therapy.

For this, patients undergoing radical resection for rectal adenocarcinoma were identified from the Surveillance Epidemiology and End Results (SEER) registry (1991-2004). SEER, a population-based cancer registry, collects cancer incidence and survival data from 18 regional, population-based registries covering approximately 26% of the U.S. population. Included are data on patient demographics, primary tumor site, tumor morphology, disease stage, first course of treatment (surgery, radiotherapy), patient follow-up, and survival. The authors evaluated patient characteristics, overall survival, and cancer-specific survival (CSS) by pathologically determined N stage after surgery and use of preoperative or postoperative radiotherapy were compared.

Of the 23,809 patients identified, 12,513 received preoperative (n = 5367) or postoperative (n = 7146) radiotherapy and resection. Preoperative patients were more likely to be younger ($p < .001$) and histopathologically free of detectable nodal metastasis (pN0) than postoperative (51.8% vs. 31.7%, $p < .001$). Median total numbers of LNs (6 vs. 10) and positive LNs (2 vs. 3) were lower among preoperative than postoperative ($p < .001$ for both). OS and CSS were similar among pN0 patients. However, on proportional hazards regression, pathologic lymph node stage was associated with an increase in relative risk for death by 21% overall (HR = 1.21; 95% confidence interval [CI] 1.09-1.35, $p < .001$) and by 23% for cancer-specific mortality (HR = 1.23; $p = .001$) for patients receiving preoperative compared with postoperative chemoradiotherapy.

These high-risk patients should be targeted for studies of novel multidisciplinary approaches, including expanded chemo and biologic therapies.

■ COMMENTARY

Pathologic LN status after neoadjuvant radiotherapy for rectal cancer is a biologic marker of prognosis. That is, patients who have demonstrated nodal disease after presurgical chemoradiotherapy form a subgroup of lymph node positive patients with an adverse prognosis. Although not previously demonstrated, this certainly makes sense. Persistent nodal disease after treatment suggests a more resistant disease, and it would be unlikely that responses to post-surgical treatment would be comparable to those with nodal disease for whom there was no prior experience with radiation or chemotherapy.

The question is what to do with this information. For starters, it would make sense that aggressive systemic treatment, perhaps including novel biologic agents, could be undertaken and, hopefully, this would be the subject of future clinical trials. Although local control is clearly superior for those who had received neoadjuvant therapy, the influence on overall survival has been less obvious, implying that systemic therapy is advisable for most patients after surgery. However, these patients with residual nodal disease may benefit from additional localized treatment, as they may be the patients more likely to experience local recurrence. Again, this would seem an excellent question for clinical trial. ■

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Depression and Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *This meta-analysis revealed overall increased mortality of up to 25% in patients experiencing depressive symptoms after cancer diagnosis, and a 39% higher risk in patients diagnosed with major or minor depression after cancer diagnosis, based upon 25 independent studies. Given the low number of studies available to date, the effect of depressive symptoms on cancer recurrence did not reach a level of statistical significance.*

Source: Satin JR, et al. Depression as a predictor of disease progression and mortality in cancer patients: A meta-analysis. *Cancer*. 2009;115:5349-5361.

THERE IS A SENSE HELD BY BOTH PATIENTS AND ONCOLogists that psychological variables influence the course of cancer. In fact, 85% of cancer patients and 71% of oncologists endorse the belief that psychological variables affect cancer progression.[1] Despite this, the evidence for such an association remains inconclusive. Of the psychological variables, depression has been the most commonly studied in the context of cancer progression and mortality. In a striking early study, Shekelle et al demonstrated a two-fold higher mortality rate in depressed cancer patients at 17 years follow-up,[2] although this finding has been difficult to replicate.[3,4] Furthermore, depression is the only psychological variable more commonly found in cancer patients than in the general public.[5] Thus, Satin et al present a meta-analysis of the existing literature to explore the effect of depression on cancer recurrence and mortality.

Using the MEDLINE (National Library of Medicine), PsycINFO (American Psychological Association), CINAHL (EBSCO Electronic Journal Services), and EMBASE (Elsevier) online databases, Satin et al identified prospective studies that examined the association between depressive symptoms or major/minor depression and risk of disease progression or mortality in cancer patients. Two raters independently extracted effect sizes using a random effects model.

Based on three available studies, depressive symptoms were not shown to significantly predict cancer progression (risk ratio [RR] unadjusted = 1.23; 95% confidence interval [CI], 0.85-1.77; $p = 0.28$). Based on data from 25 independent studies, mortality rates were up to 25% higher in patients experiencing depressive symptoms (RR unadjusted = 1.25; 95% CI, 1.12-1.40; $p < 0.001$), and up to 39% higher in patients diagnosed with major or minor depression (RR unadjusted = 1.39; 95% CI, 1.10-1.89; $p = 0.03$). In support of a causal interpretation of results, there was no evidence that adjusting for known clinical prognostic factors diminished the effect of depression on mortality in cancer patients.

■ COMMENTARY

The present meta-analysis represents a much-needed quantitative synthesis of the often under-powered studies examining depression as a predictor of disease progression and mortality in cancer patients. This is of considerable importance in both theory and practice in determining the risks associated with depression, as well as in providing rationale for psychological intervention with the hopeful benefit of enhancing survival.

As such, this meta-analysis presented reasonable evidence that depression predicts mortality, but not progression, in cancer patients. The associated risk was statistically significant but relatively small. The effect of depression remains after adjustment for clinical prognosticators, suggesting that depression may play a causal role, although how it occurs remains unclear.

Possible mechanisms whereby psychological variables might affect host defenses include activation of the hypothalamo-pituitary-adrenal (HPA) axis, producing a chronic stress pattern observed in a number of biological systems.[6-8] Such activation might modulate both innate and acquired immune functions and, thereby, influence tumor progression. These, of course, remain theoretical constructs derived primarily from cellular or experimental animal studies, and their applicability to the human condition remains to be established.

That depression occurs commonly in cancer patients is now well established. It appears also to be true that there is evidence that depression is associated with a significant but small increased risk of mortality. Although treatment of depression in cancer patients is quite successful in reducing subjective distress, it remains to be established whether successful treatment will improve survival. Statin et al argue that in order to demonstrate this, the mediators of depression-associated increased risk need to be identified and a reduction of such demonstrated when appropriate and successful psychological intervention is undertaken. We are quite far from this level of understanding, but it remains an excellent goal for investigators in the rapidly developing field of psycho-oncology. ■

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CME Questions

1. **How does interphase FISH compare to chromosome banding analysis (CBA) of marrow metaphase cells for monitoring the Philadelphia (Ph) chromosome in chronic myeloid leukemia?**
   a. Interphase FISH detects Ph positive cells even when CBA shows a complete cytogenetic response (i.e., no Ph positive cells).
   b. CBA has no advantage over FISH and should be abandoned.
   c. Interphase FISH can detect mutations in BCR/ABL.
   d. A and C

2. **Among patients cured of Hodgkin's lymphoma, which quality of life parameter is least likely to return to baseline levels?**
   a. Social functioning
   b. Physical functioning
   c. Fatigue
   d. Emotional functioning
   e. Global quality of life

3. **In the population-based, prospective cohort study of the effects of physical activity on prostate cancer development, prostate cancer was found to be lower among individuals who:**
   a. have a job at which they are sedentary < 50% of the time.
   b. engage in physical exercise for a minimum of 30 minutes a day.
   c. Both
   d. Neither

4. **The increase in risk of death from rectal cancer in patients with lymph node-positive disease diagnosed from surgical specimen, compared with those who were also lymph node positive but without prior chemoradiation is approximately:**
   a. 8%.
   b. 23%.
   c. 40%.
   d. 73%.

5. **The presence of depression (either major or minor) has been shown to be associated with:**
   a. increased incidence of cancer.
   b. increased cancer recurrence.
   c. increased cancer mortality.
   d. All of the above
   e. None of the above

Answers: 1. (a); 2. (c); 3. (c); 4. (b); 5. (c)

CME Objectives

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

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

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1. present the latest information regarding diagnosis and treatment of various types of cancer;
2. present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
3. describe new advances in the field of oncology.

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers with the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

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Sincerely,

Cynthia Molnar
Director of Continuing Education
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CLINICAL ONCOLOGY ALERT™
A monthly update of developments in cancer treatment and research

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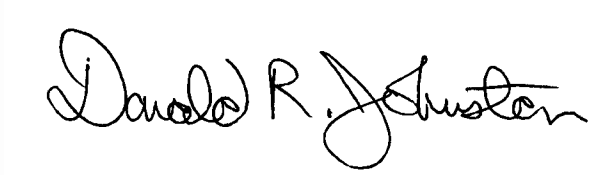

Donald R. Johnston
Senior Vice President/Group Publisher
AHC Media LLC

N #4005

3525 Piedmont Road NE
Building Six, Suite 400
Atlanta, Georgia 30305-1515
Tel (404) 262-7436
Fax (404) 262-7837
www.ahcmedia.com

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The relationship of FPG and A1c to diabetic retinopathy

Source: Cheng YJ, et al. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population. *Diabetes Care* 2009;32:2027-2032.

THE IDEA THAT A1c MIGHT BE A REASONABLE metric to make the diagnosis of diabetes has been kicking around for more than a decade. Only very recently has there been advocacy from the ADA that A1c may be an acceptable method for diagnosis of diabetes (A1c ≥ 6.2%); a primary reason for this shift in perception is the widespread adoption of a nationally standardized A1c testing method. Ultimately, diagnosis is intended to go beyond simply categorizing an individual as diabetic or non-diabetic; rather, it is intended to predict risk for important complications of diabetes like retinopathy.

The NHANES (National Health and Nutrition Examination Survey) is a cross-sectional sampling of non-institutionalized civilian adults. From the NHANES 2005-2006 study population, a group of adults age ≥ 40 years had assessment of retinopathy, A1c, and fasting plasma glucose (FPG).

There was a steep increase in frequency of retinopathy at an A1c ≥ 5.5%. Although a similar increased risk was seen at a FPG of 126 mg/dL, overall, the A1c was a better predictor than FPG. Since A1c may be obtained whether or not the subject has fasted, it may become a more convenient (as well as more sensitive) method than FPG for identifying risk of retinopathy. ■

Getting the most bang for your buck with lipid measurement

Source: The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.

THE EMERGING RISK FACTORS COLLABORATION collected data from prospective observational studies of persons without CV disease at baseline (n = 69 studies, with 302,430 participants). Lipid fractions measured in these studies included LDL, HDL, apo B, and apo A1. Risk for incurring CV endpoints was stratified for each lipid fraction.

Triglycerides have always been the lipid fraction demonstrating the weakest association to CVD endpoints. In this data set, although the unadjusted hazard ratio for triglycerides demonstrated increased hazard, adjusted hazard ratios were not convincing. In contrast, subjects with the lowest HDL levels showed an almost 3-fold greater hazard ratio for CV events than those in the highest third. The ratio of apo B:apo A1 was also an important CV risk predictor.

Interestingly, measurement of total cholesterol, HDL, apo B, and apo A1 in the non-fasting state did not appear to appreciably alter their predictive value. Sufficient information for risk prediction, according to these data, is obtained by simply measuring cholesterol levels (total and HDL). Additionally, the authors were not able to identify any significant additional CV risk prediction by adding triglyceride levels to their calculations.

The simplicity of focusing upon total and HDL cholesterol, and being able to use non-fasting results, may enable clinicians to more readily gather predictive information on a wider population of patients. ■

Nortriptyline, gabapentin, or both for neuropathic pain

Source: Gilron I, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 2009;374:1252-1261.

NEUROPATHIC PAIN (NPN), SUCH AS post-herpetic neuralgia or diabetic peripheral neuropathic pain, often requires what has been described as rational polypharmacy: the combination of multiple agents in an attempt to gain maximum therapeutic advantage while minimizing adverse effects. Both nortriptyline and gabapentin have achieved some success in modulation of NPN as monotherapy. Since the mechanism of action of these agents is complementary, a trial of their combination has intellectual appeal. When choosing among antidepressants for analgesic effects, norepinephrine re-uptake inhibition appears to be a critical component. Hence, SSRIs have minimal effect, but tricyclics (e.g, amitriptyline, nortriptyline), SNRIs (e.g., duloxetine, venlafaxine), and highly selective norepinephrine re-uptake inhibitors (e.g., milnacipran) effectively reduce pain.

Combination nortriptyline and gabapentin provided significantly greater pain reduction than either agent alone. No serious adverse effects were seen in either mono- or combination therapy. Clinicians are already commonly applying combination therapies to neuropathic pain syndromes; it is gratifying to encounter sound evidence supporting this practice. ■

Which insulin regimen for type 2 diabetes

Source: Holman RR, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361:1736-1747.

THE MOST RECENTLY PUBLISHED ADA/EASD consensus algorithm for management of type 2 diabetes (DM2) suggests that when the combination of metformin and lifestyle is insufficient to control diabetes, either sulfonylurea (if close to goal) or insulin is the most well-validated next step. Because there are many different insulins to choose from, the clinician may be uncertain whether basal insulin (i.e., detemir, glargine, NPH), prandial insulin (i.e., regular insulin or rapid-acting insulin analog), or biphasic insulin (a combination containing a basal as well as prandial insulin) should be preferred.

Holman et al performed a 3-year trial in DM2 subjects (n = 708) not at A1c goal with the combination of metformin and a sulfonylurea. Subjects were randomized to biphasic insulin aspart (BIA) bid, prandial insulin aspart (PIA) tid, or insulin detemir (DET) qd (some received detemir bid).

At 3 years, there was no statistically significant between-group difference in A1c attained. Hypoglycemia was least frequent in the DET group, and most common in the PIA cohort. Weight gain was least in the DET group, and greatest in the PIA group.

All regimens were successful in attaining goal A1c. Because hypoglycemia and/or weight gain are often deal breakers for our patients, basal insulin regimens may be preferred. ■

Cardioprotective effects of ACE inhibitors in African American men

Source: Papademetriou V, et al. Protective effects of angiotensin-converting enzyme inhibitors in high-risk African American men with coronary heart disease. *J Clin Hypertens* 2009;11: 621-626.

THE HOPE TRIAL CONVINCED MANY experts that midlife adults (age ≥ 55 years) with existing vasculopathy (history of CAD, CVD, diabetes and CV risk factors) will have improved outcomes on an ACE inhibitor (ramipril, to be specific). There is controversy about whether African Americans achieve similar risk reduction as other ethnicities; for instance, in the SOLVD CHF trial, retrospective analysis suggested less benefit for some endpoints in African Americans.

Papademetriou reviewed electronic records from the Washington, DC, VA Medical Center to study African American study subjects who had CAD documented by catheterization (n = 810). Subjects were parsed into those who had vs had not been treated with an ACE inhibitor.

Over a study period of 3-10 years (mean, 6.8 years), the relative risk reduction for CAD mortality was more than 30% in those treated with ACE inhibitors. All-cause mortality was 80% higher in African American patients who had *not* been treated with ACE inhibitors. Because many African American patients have relatively low renin levels, some clinicians have doubted whether CV benefits would be readily achieved with ACE inhibitors. This data analysis suggests substantial benefit from ACE inhibitor treatment in African Americans with CAD. ■

Missed opportunity: Aldosterone antagonists in heart failure

Source: Albert NM, et al. Use of aldosterone antagonists in heart failure. *JAMA* 2009;302:1658-1665.

THE SEMINAL RALES TRIAL (RANDOMized Aldactone Evaluation Study), in which patients with NYHA Class III-IV systolic heart failure received either aldactone or placebo in addition to standard-of-care treatment (e.g., ACE inhibitors, beta blockers, digoxin) indicated that the utilization of this well tolerated, inexpensive treatment could reduce mortality by as much as 30%.

One might anticipate that such benefits would result in widespread utilization of aldosterone antagonists in heart failure.

Albert et al reviewed data from more than 200 U.S. hospitals, encompassing 43,625 patient admissions for heart failure over the 2005-2007 time period. By this time, the RALES data were more than 5 years old. Contraindications to this life-saving treatment are few, with hyperkalemia being the most common.

According to their analysis, less than 33% of patients with heart failure who were eligible for treatment with an aldosterone antagonist (i.e., without contraindications) received one. With proper monitoring, aldosterone antagonist therapy reduces risk, is safe, and is well tolerated. Although aldosterone antagonist use improved over time (from a baseline rate of 28% to an end-of-study rate of 34%), much opportunity of reduction of mortality was missed. ■

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Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: paula.cousins@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media LLC 3525 Piedmont Road, Building Six, Suite 400 Atlanta, GA 30305.

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PHARMACOLOGY WATCH

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Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

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.

Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■