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

ILLUSTRATIVE CASE SERIES

Newly Diagnosed CML

By Charles Hesdorffer, MD

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

A 64-YEAR-OLD MAN WAS REFERRED BECAUSE OF LEUKOcytosis. He had been in his usual state of health until approximately two months prior to a visit, when he was diagnosed by his primary care provider with pneumonia. At that time, he presented with fever and cough, and chest X-ray revealed a lingular infiltrate. A complete blood count (CBC) revealed leukocytosis with a white blood count of 17x103/cu mm, with 68% neutrophils, 8% band forms, and 8% metamyelocytes, 6% myelocytes, 2% basophils, and 2% eosinophils. Hemoglobin was 12.9 g/dL and platelet count was 480K/cu mm. Sputum and blood cultures were negative, and he was treated with antibiotics. At a follow-up visit two weeks later, he complained of fatigue and diminished appetite. His fever and cough had resolved, but he remained unable to return to work because of general malaise. At a follow-up visit two weeks later, he reported some improvement, but he had noticed abdominal "bloating" and loss of appetite had persisted. Physical examination revealed slight pallor, no palpable lymphadenopathy, and no adventitial breath sounds. His spleen was palpable 4 cm below the left costal margin. A repeat CBC revealed a WBC of $108x10^3$/cu mm, with 52% neutrophils, 14% band forms, 6% metamyelocytes, 10% myelocytes, 5% progranulocytes, 2% blasts, 10% basophils, and 3% eosinophils. Hemoglobin was 12.1 g/dL and platelet count was 480K/cu mm. Bone marrow revealed a hypercellular marrow with prominent myeloid hyperplasia, with 15% blast forms. Cytogenetic studies were sent to a reference laboratory but the results were pending at the time of referral.

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CASE DISCUSSION

This patient most certainly has chronic myelogenous leukemia (CML), but with pending cytogenetic confirmation, other considerations are worthy of mention. Occasionally, patients with acute or chronic inflammatory disease or other myeloproliferative diseases will be found to have white blood counts of greater than 50,000/cu mm. For some patients, the presence of occult infection might present a diagnostic challenge. However, in general, leukemoid reactions associated with inflammation exhibit less of a leftward shift than observed in this case. Also, the presence of a greater percentage of myelocytes than metamyelocytes (so called "leukemic hiatus") is an unlikely occurrence as a result of infection. Furthermore, the increase in basophils is another tip that the diagnosis in this case is more in line with myeloproliferative disease than inflammation-associated leukemoid reaction. The leukocyte alkaline phosphatase (LAP) score may be a useful adjunct to help distinguish CML from leukemoid reaction, as such would be low in CML but normal in those with infection.

Patients with other myeloproliferative disorders, such as polycythemia vera or primary myelofibrosis, may also present with leukocytosis and a large spleen. In these cases, the LAP score would be normal. In the case presented, polycythemia would seem unlikely (in the absence of erythrocytosis), and myelofibrosis would have been evident with the bone marrow aspirate/biopsy.

In this case, the diagnosis of CML is likely to be confirmed by the presence of the Philadelphia (Ph) chromosome (reciprocal translocation between chromosomes 9 and 22) on karyotypic analysis of the bone marrow or molecular analysis for the BCR-ABL fusion product of the CML translocation. Almost all patients with CML have demonstrable Ph chromosome. However, in approximately 2%, there is an insertion of *ABL1* adjacent to *BCR,* resulting in a normal-appearing chromosome 22.[1]

Assuming the clinical suspicion of CML is confirmed by the cytogenetic study, a treatment strategy should be developed promptly, especially in light of the rapid rise in white count in the month prior to referral. For patients with markedly elevated white counts, particularly if clinical symptoms of leukostasis are apparent (stupor, hypoxia, tinnitus, papilledema, priapism, etc.), treatment should be initiated with leukapheresis and hydroxyurea. In the current case, these symptoms were not reported, but I would still favor initial control with hydroxyurea in light of the rapid change in counts over the prior few weeks.

Since the early reports of the IRIS trial were published,[2,3] the standard first-line treatment for chronic phase CML has been with imatinib mesylate. In the trial, imatinib was associated with a superior response rate and improved progression-free survival as compared to interferon alfa plus low-dose cytarabine.

New tyrosine kinase (TK) inhibitors have proven efficacy in patients who have either not achieved cytogenetic response or have progressed while being treated. Thus, both nilotinib (Tasigna®) and dasatinib (Sprycel®) are currently approved for use in this setting.

In a recently published report of a phase 3 multisite, randomized trial of nilotinib vs. imatinib for first-line treatment of chronic-phase CML, nilotinib proved more successful in achieving both complete cytogenetic response (CCR) and major molecular response (MMR) after 12 months of treatment.[4] In the trial, patients were assigned 1:1:1 to nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, or imatinib 300 mg twice daily. At 12 months, patients assigned to nilotinib at either 300 mg or 400 mg had significantly higher rates of CCR (80%, 78%) compared to those treated with imatinib (65%; $p < .001$ for both comparisons). Similarly, nilotinib treatment at either dose resulted in greater rates of MMR than imatinib (44%, 43% vs. 22%; $p < .001$ for both comparisons). On the basis of these data, the FDA recently expanded the indication for dasatinib to include its use in the first-line treatment of chronic-phase CML.

Although there is experience with concurrent use of hydroxyurea and imatinib for the initial treatment of CML for those who present with markedly elevated white counts, the data for nilotinib in this regard is yet to become available. Thus, I would recommend initial treatment with hydroxyurea alone at a dose of 1-2 gm q 12 hours until the white blood count is approximately 20,000/cu mm. At that time, I would taper off the hydroxyurea while adding nilotinib 300 mg twice daily. During the early treatment, it would be important to maintain hydration and keep an eye on uric acid levels and renal function. Once blood counts normalize, it would be useful to determine BCR-ABL transcript level with the hopeful expectation that MMR will be achieved in due time. ■

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RAPID REVIEW

Have We Moved Beyond the Karnofsky Score?

By Jerome W. Yates, MD and William B. Ershler, MD

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Drs. Yates and Ershler report no financial relationships relevant to this field of study.

EXTENSIVE LITERATURE IS DEVELOPING ON THE ROLE OF functional assessment of cancer patients, particularly those who are elderly, in order to provide safer and more effective treatment. The concept of comprehensive assessment, entrenched now in geriatric medicine, finds its roots within medical oncology, as such was the purpose of the performance scale (PS) introduced by Karnofsky and colleagues at Memorial in 1948.[1] Since then, and particularly in the last decade, pretreatment assessment has resurfaced within oncology, primarily because of the rapidly expanding population of cancer patients within the geriatric age group. There is no doubt that age-associated comorbidities and functional impairments influence outcomes, both in terms of treatment tolerance and efficacy. Yet, the optimal method for predicting vulnerability remains to be established.[2-7] In fact, it remains unclear whether any of the new and more extensive instruments will add values commensurate to the costs involved when compared to the simple assessment provided by the Karnofsky scale, something the practicing oncologist can complete in less than a minute.

THE NEED FOR SUCH AN ASSESSMENT

Oncologists are unable to practice evidence-based medicine when it comes to the administration of chemotherapy to "typical" older patients because there is little available data on current drugs and drug regimens when administered to elderly patients, particularly those with functional impairments or comorbidities. This is because clinical trials designed to demonstrate efficacy of a particular drug, regimen, or modality typically enroll patients with good performance status and limited comorbidities. Yet, clinical experience has indicated that most oncology modalities, including surgery, radiation, and chemotherapy can be effective in older functionally impaired patients, but this must be balanced by the increased risks of such treatments, notably in those with functional impairments and comorbidities.[7] For example, we know that cancer patients with impairment in performing activities of daily living (ADL) or instrumental activities of daily living (IADL) are more likely to experience adverse outcomes,[8] and yet approximately half of such patients will present with good or excellent (ECOG) performance status (PS) 0 or 1.[9] To the extent that newly derived assessment instruments can identify those elderly patients who present with good to excellent ECOG PS, but who rapidly decompensate upon challenge with aggressive treatment, patients will be more intelligently treated and age bias reduced.[10]

COMPONENTS OF ASSESSMENT

Investigators in geriatric medicine have developed assessment instruments to operationalize research in the area of frailty. Thus, self report, or observed variables, that capture changes such as weight loss, weakness, slow walking speed, and poor endurance have been linked to outcomes such as hospitalization, nursing-home placement, and death.[11] As the field has evolved, a number of variables have been introduced into the "comprehensive geriatric assessment" (CGA), including an assessment of ADL, IADL, comorbidity, cognitive status, nutrition, depression, social environment, and the presence or absence of geriatric syndromes, such as falls, delirium, pressure ulcers, and incontinence. A full CGA may take several hours or more, and is likely to be in excess of what is needed in oncology practice to meet the needs as outlined above.

Accordingly, abridged versions have been developed for oncology. For example, Balducci and colleagues have introduced a simpler scheme in which, for the purposes of cancer management in the elderly (i.e., increased vulnerability to adverse outcomes), is defined as one or more of the following: age > 85 years, dependence in one or more ADL, presence of three or more comorbid conditions, and/or presence of one or more geriatric syndromes (pressure sores, incontinence, delirium, falls, and functional dependence).[12,13] Using this approach, Tucci and colleagues characterized a series of 84 patients (age 65 years and older) who were treated for diffuse, large B-cell lymphoma at a single institution.[14] The majority of patients (74%) received either CHOP or a CHOP-like regimen. A total of 42 patients were characterized by the geriatric assessment as "fit." Response rates (93% vs. 49%; $p < .0001$) and median survival (not reached vs. 8 months; $p < .0001$) were found to be superior in the patients characterized as fit, compared with those characterized as unfit. Approximately half of the patients deemed "unfit" were treated with palliative therapy, whereas the remainder were treated with curative intent. For this "unfit" group, there did not appear to be a survival difference using either strategy, raising the possibility that patients characterized as unfit or frail may derive similar benefit from palliative approaches.

WHAT'S NEXT?

There is general agreement that we need better tools to define risks of therapy for elderly patients with cancer. Adopting some features of the CGA is a good first step, but for the purposes of prescribing cancer treatment, it would seem such assessment would benefit from inclusion of laboratory parameters that are relevant both to the patient's general condition and the impact on the disease process. For example, a measure of hemoglobin, albumin, and creatinine could easily be incorporated into an overall "fitness" score. However, most importantly, a prospective clinical trial is needed to confirm the value of pre-treatment assessment in terms of response rate, toxicity, and survival. For example, a trial in which elderly patients were randomly allocated to either pre-treatment assessment, with prescribed treatment based upon assessment, or routine management, in which the Karnofsky or ECOG PS was used to guide treatment. It is not clear yet that we have found the right assessment instrument that will better the Karnofsky PS in such a trial. ■

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ABSTRACT & COMMENTARY

Statins and PSA Recurrence Post-radical Prostatectomy

By William Ershler, MD

Synopsis: *Statin use in patients undergoing radical prostatectomy for prostate cancer was associated with a dose-dependent reduced risk of biochemical recurrence.*

Source: Hamilton RJ, et al. Statin medication use and the risk of biochemical recurrence after radical prostatectomy. Results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. *Cancer* 2010;116:3389-3398.

Drugs in the statin class have clearly demonstrated clinical benefit, particularly in lowering cholesterol and reducing cardiovascular mortality.[1] However, statins influence a number of biological responses beyond those observed on lipid metabolism, and many of these are relevant to cancer biology, including a damping down of inflammatory pathways, as well as angiogenesis and cell proliferation, all of which are known to influence cancer development and growth.[2-5] Thus, there has been considerable interest in determining a role for drugs in this class in either prevention or treatment of cancer, and much of this work has been done with regard to prostate cancer (PC). Although there have been conflicting results with regard to disease prevention,[1,2,6] large prospective, cohort studies have found that statins may lower the risk of advanced prostate cancer.[7,8] Furthermore, the authors of the current report had previously demonstrated that for men without prostate cancer, prostate-specific antigen (PSA) levels declined after starting statins, and this decline was independently proportional to the statin dose and the amount by which cholesterol levels lowered.[9]

Thus, to determine the effect of statin use on prostate-cancer risk, a large-scale investigation on as homogeneous a population as possible would be required. Accordingly, Hamilton and colleagues, using the Shared Equal Access Regional Cancer Hospital (SEARCH),[10] examined the association between statin use and outcomes in men undergoing radical prostatectomy.

For this, they examined the time to PSA recurrence in 1,319 men who underwent radical prostatectomy (RP) at one of three Veterans Administration Medical Centers within the United States. The time to PSA recurrence was compared between users and nonusers of statin at surgery using Cox proportional hazards models adjusted for multiple clinical and pathological features.

In total, 236 (18%) men were taking statins at RP. Median follow-up was 24 months for statin users and 38 for nonusers. Statin users were older ($p < .001$) and underwent RP more recently ($p < .001$). Statin users were diagnosed at lower clinical stages ($p = .009$) and with lower PSA levels ($p = .04$). However, statin users tended to have higher biopsy Gleason scores ($p = .002$). After adjusting for multiple clinical and pathological factors, statin use was associated with a 30% lower risk of PSA recurrence (HR, 0.70; 95% CI, 0.50-0.97; $p = .03$), which was dose-dependent.

■ COMMENTARY

Because of the described anti-inflammatory and antiproliferative effects of statins, their effect on cancer development and growth has become an active research question. With regard to prostate cancer, epidemiologic and clinical trials have been conflicting. In observational studies, such as the current report, cautions are raised because patients receiving statins are quite possibly different with regard to other risk factors, some of which are difficult to control. In this study, for example, whereas statin use was associated with a significant reduction in PSA recurrence in patients with low or intermediate BMI, for those with BMI > 35 kg/m^2, statin use was associated with increased recurrence risk (HR, 17.3; 95% CI, 3.39-88.1; $p = .001$). Thus, the authors are to be credited for examining and controlling for as many PC risk variables as possible and for choosing a fairly specific population (those having received radical prostatectomy). In general, statin use was associated with a dose-dependent reduction in the risk of biochemical recurrence.

Put into context, it should be recalled that in healthy men, statin use has been associated with a reduction in PSA.[9] Thus, whether the delay in PSA recurrence translates into a survival advantage remains to be determined. Clearly, a prospective, randomized trial would be best to answer this question; however, with the ubiquitous use of drugs in the statin class these days, such a trial will be difficult to conduct. ■

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ABSTRACT & COMMENTARY

Determining the Importance of Careful Follow-up for Patients with MGUS

By Andrew S. Artz, MD

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

Synopsis: *The benefit of regular follow-up for monoclonal gammopathy of unknown significance (MGUS) to detect progression to multiple myeloma (MM) remains unknown. The authors identified a cohort of 116 patients over 30 years that progressed from MGUS to MM with detailed records available. Optimal follow-up at approximately annual intervals occurred in 69%. For patients having optimal follow-up, only 16% were diagnosed with disease progression based on routine follow-up. In contrast, a diagnosis was rendered after serious symptoms (45%), less serious symptoms (25%), and incidental findings (11%) in most. Of those suboptimally followed, only one of 28 had a diagnosis from routine follow-up. Higher-risk patients defined by an IgG > 1.5 g / dL or non-IgG MGUS were more likely to be optimally followed and more likely to be diagnosed secondary to serial routine laboratory testing (21% vs. 7%). In conclusion, progression from MGUS to multiple myeloma is typically diagnosed by symptoms rather than routine follow-up, especially in low-risk patients.*

Source: Bianchi G, et al. Impact of optimal follow-up of monoclonal gammopathy of undetermined significance on early diagnosis and prevention of myeloma-related complications. *Blood*. 2010:116.2019–2025.

Monoclonal gammopathy of undetermined significance (MGUS) is a common finding that may progress to multiple myeloma.[1] Once a monoclonal protein in the urine or serum has been identified, one must distinguish MGUS from another plasma cell dyscrasia. A serum monoclonal protein concentration < 3 g/dL, fewer than 10% plasma cells in the bone marrow, and absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to a plasma cell disorder defines MGUS, as opposed to myeloma or another plasma cell dyscrasia. The annual incidence of disease progression after an MGUS diagnosis has been estimated at 1% annually.

Recommendations suggest annual follow-up that includes a repeat serum protein electrophoresis in six months and annually thereafter to identify and prevent myeloma-related complications. The authors in this study attempt to assess the value of this empirically recommended strategy.

A portion of patients seen at Mayo Clinic for a diagnosis of MGUS had long-term clinical follow-up information as they resided in one region of the state, presumably where records could be abstracted. Over a 30-year period, the investigators found 116 MGUS patients who eventually progressed to symptomatic multiple myeloma (MM). The median age was 67 years, and 70% showed an IgG isotype. Optimal follow-up, defined as those having repeat serum protein electrophoresis at least every two years, occurred in 69%, whereas suboptimal follow-

up was documented in 24%. As expected, higher-risk MGUS, characterized by an MGUS of 1.5 g/dL or more, or a non-IgG isotype appeared to account for a greater portion of optimal (or close) follow-up (81% vs. 64%, $p = 0$ .07). Seven percent progressed within one year and, thus, optimal follow-up could not be determined. Among optimal follow-up for MGUS, only 16% were diagnosed with MM secondary to routine follow-up. In 45%, serious complications resulted in a diagnosis, most commonly pathologic fractures. Another 25% reached a diagnosis of MM after the evaluation of less serious symptoms (e.g., bone pain), and 11% were diagnosed based on incidental findings. For 3%, the reason leading to the diagnosis could not be ascertained. For suboptimal follow-up, serious complications resulted in a diagnosis of MM at 54%, and incidental evaluation prompted an MM diagnosis in 25%. Only one of 28 (3%) undergoing suboptimal follow-up were diagnosed based on routine follow-up for those undergoing suboptimal monitoring (difference between optimal and suboptimal $p = 0.1$). Taking both optimal and suboptimal follow-up, two-thirds of the MM cases were diagnosed based on serious signs or symptoms.

The subset of MM having smoldering MM was higher in those with optimal follow-up at 30%, compared to 11% in those with suboptimal follow-up. The time from MGUS to MM diagnosis was shorter in optimal follow-up patients compared to suboptimal at 75 months vs. 116 months, respectively ($p = 0.01$). Overall survival, however, did not differ.

■ COMMENTARY

MGUS represents a premalignant disorder associated with around a 1% incidence of progression to MM. Still, most MGUS patients will never develop MM. With increasing availability of routine laboratory testing and serum protein electrophoresis, MGUS may be increasingly recognized. The recommended follow-up after MGUS typically entails annual evaluation and extensive laboratory testing, including a serum protein electrophoresis. The benefit of this approach to detect MM early or avoid MM-related complications remains untested.

The authors identified a fairly substantial number of MGUS patients (n = 116) who eventually progressed to MM, and described presenting features at disease progression by whether follow-up was considered optimal or not. The major finding was that MM was only diagnosed in 16% related to routine laboratory findings in absence of symptoms or complications, despite optimal follow-up. Optimal follow-up did not reduce hospitalization or decrease MM-related complications. For 45% undergoing optimal follow-up, a serious MM-related complication (e.g., pathologic fracture) resulted in an MM diagnosis in between screening visits. At least for this subset, disease progression may be relatively rapid and difficult for intermittent screening to identify. Not surprisingly, optimal follow-up resulted in more cases of smoldering MM at 30%, compared to 11% ($p = 0.05$) for sub-optimal follow-up. Only two of 27 considered low risk had MM diagnosed by routine follow-up.

Several limitations must be noted. This retrospective study occurred over 30 years. Modern diagnostic testing may be more available and more sensitive to detect early progression due to light-chain testing and isoelectric focusing. For example, all nine MGUS patients diagnosed after 1999 underwent optimal follow-up. Although no benefit to optimal follow-up was found, the availability of new agents and bisphosphonates could alter the natural history of MM, once identified. The study did not report race and, considering the area in Minnesota from which the population was derived, one suspects few patients were African-American. Monitoring for optimal follow-up patients included patients who were seen every two years. The actual frequency, or how often patients were seen annually or less, was not reported. That said, in real practice, achieving annual follow-up for a prolonged period may be challenging, and this likely reflects a reasonable benchmark for adherence to annual follow-up. Finally, it is possible that some patients categorized as diagnosed with MM related to symptoms only reported such symptoms because of medical follow-up. Still, almost half of patients with optimal follow-up had a diagnosis of serious related signs or symptoms which likely did not relate to scheduled physician visits.

The authors suggest annual follow-up may not be beneficial, especially for MGUS patients at low-risk of progression to MM, in that many serious complications occur in between screening intervals, and early treatment of MM has not been shown to be beneficial. The authors note that for low-risk patients, the lifetime risk of MM is only 2% and, therefore, annual MM evaluation may not be necessary. Finally, many of the patients identified by screening had smoldering MM, for which treatment would likely be deferred. Others have suggested, at least in low-risk MGUS, that routine follow-up is not necessary.[2] Although this sense is intuitively appealing, the fact that in this study many of the patients harbored so-called low-risk disease, and eventually progressed to MM, shows the limitations of our present tools to predict MM risk from MGUS.

This study highlights the problems with routine follow-up testing and mirror problems with cancer screening strategies. Many cases are missed in the screening interval and these are often more aggressive and cases identified at screening are often more indolent. As a retrospective study the precise risks and benefits of serial clinical and laboratory follow-up for MGUS patients cannot be determined. In short, routine annual follow-up for MGUS patients has a relatively low yield to identify progression to multiple myeloma. ■

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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)	227	223
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f. Total Free Distribution (Sum of 15d and 15e)			24	24
g. Total Distribution (Sum of 15c and 15f)			295	274
h. Copies Not Distributed			92	118
i. Total (Sum of 15g. and h.			387	392
Percent Paid and/or Requested Circulation (15c divided by 15g times 100)			92%	91%

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2010 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/28/10
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PS Form **3526**, September 1999 *(Reverse)*

CME Questions

10. Which of the following cancer-patient groups are likely to benefit most from a pre-treatment assessment of "frailty"?

a. Patients 70-80 years old with ECOG PS 2-3.
b. Patients 70-80 years old with ECOG PS 0-1.
c. Patients 60-70 years old with ECOG PS 2-3.
d. Patients 85 years or older with ECOG PS 1-2.

11. In the current report from the SEARCH database examining statin use and prostate-cancer recurrence in patients after radical prostatectomy, which of the following conclusions can be drawn?

a. Statin use was associated with a dose-dependent decrease in PSA recurrence.
b. Statin use was associated with a dose-dependent decrease in PSA recurrence and improved progression-free survival.
c. Statin use was associated with a dose-dependent decrease in PSA recurrence, progression-free survival, and improved overall survival.
d. None of the above

12. Optimal follow-up of patients found to have monoclonal gammopathy of uncertain significance (MGUS) is associated with which of the following?

a. Identifying multiple myeloma (MM) before symptoms in most patients.
b. Reduced hospitalization and mortality compared to sub-optimal follow-up.
c. A higher percentage of depression compared to sub-optimal follow-up.
d. A higher proportion of diagnosis of smoldering MM compared to sub-optimal follow-up.

Answers: 13. (b); 14. (a); 15. (d)

CME Objectives

Upon completion of this 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.

[IN FUTURE ISSUES]

Alcohol Use and Recurrent Breast Cancer

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

Volume 15, Number 11 Pages 21-22 November 2010

Can vitamins stop photoaging of the skin?

Source: Zussman J, et al. Vitamins and photoaging: Do scientific data support their uses? *J Am Acad Derm* 2010;63: 507-525.

UV light is responsible for some of the skin changes associated with aging, which is known as photoaging (PHA). Expenditures in the United States for so-called "cosmeceuticals" is anticipated to reach more than $6 billion this year, although only a few components of commonly applied topical agents have any clearly demonstrated benefit.

Vitamin A derivatives, particularly the prescription retinoids such as tretinoin cream and tazarotene, are FDA-approved for aging-related fine line wrinkles, skin roughness, and mottled hyperpigmentation. OTC vitamin A derivatives have less convincing evidence, but of these, retinol should be the preferred agent according to Zussman et al.

Amelioration of PHA has been seen in several topical vitamin C trials using L-ascorbic acid; chemically related compounds (e.g., ascorbyl palmitate, ascorbyl tetraiopalmitate) provide greater vitamin C stability, but do not have sufficient clinical trial outcomes data to advocate for them.

Topical formulations of vitamin E, although widely touted for antioxidant potential, do not have data to support their use in management of PHA. Limited data on topical niacin suggest promise.

The best method to address photoaging is overall good nutrition and an appropriate combination of sunscreen and sun avoidance. ■

Once weekly exenatide vs sitagliptin or pioglitazone for type 2 diabetes

Source: Bergenstal RM, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomised trial. *Lancet* 2010;376:431-439.

The incretin class of medications (exenatide, liraglutide, sitagliptin, saxagliptin) all share the favorable quality of not being associated with weight gain. Recently published data support the efficacy, tolerability, and simplicity of once-weekly exenatide. Bergenstal et al compared exenatide once weekly (EXEN-W) with sitagliptin (STG) or pioglitazone (PIO) as add-on therapy for persons with type 2 diabetes (n = 491) who had not attained goal with metformin.

At the end of 26 weeks, several outcomes favored EXEN-W. A1c on EXEN-W was 0.6% lower than STG, and 0.3% lower than PIO. Weight loss was also greatest in the EXEN-W group. Adverse effect profiles with each treatment arm were consistent with prior trials, and the discontinuation rate was similar for each group.

EXEN-W reduced systolic BP more than sitagliptin, but similarly to pioglitazone. Favorable lipid effects were seen with each treatment arm: The greatest increase in HDL was seen with pioglitazone.

As clinicians make their therapeutic choices for diabetes management, the relevance of medication impact upon CV risk factors such as BP, weight, and lipids merits our consideration. ■

Tai chi for fibromyalgia

Source: Wang C, et al. A randomized trial of tai chi for fibromyalgia. *N Engl J Med* 2010;363:743-754.

FDA-approved pharmacologic treatments for fibromyalgia (FIB) include duloxetine, milnacipran, and pregabalin. Although each of these agents has shown both statistically significant and clinically relevant impact, few patients are relieved of all problematic symptoms. Hence, additional treatment paths for FIB are sought.

Exercise has long been recognized as having a favorable impact on FIB, although it has been uncertain which type of exercise should be preferred. For a variety of reasons, some patients will not readily embrace strenuous or aerobic exercise programs, leaving a therapeutic gap in activity programs that can be relied upon to improve FIB symptoms and functionality.

Wang et al enrolled FIB patients (n = 66) into a 12-week program comparing tai chi to a stretching + wellness education component. For the physical activities, both groups participated in two 60-minute sessions per week for 12 weeks. Fibromyalgia patients were diagnosed using the American College of Rheumatology criteria.

At the conclusion of the study, Fibromyalgia Impact Questionnaire and SF-36 physical component scores were superior in the tai chi group as compared to the stretching group. Discontinuation of medications used to treat FIB was seen in both active treatment groups, with a trend favoring tai chi.

Tai chi instruction was provided by a single tai chi master to all of the subjects in that group. Generalizability — whether clinicians can anticipate similar efficacy when tai chi is taught by others — remains to be confirmed. ■

Prevalence of hearing loss in U.S. adolescents

Source: Shargorodsky J, et al. Change in prevalence of hearing loss in U.S. adolescent. *JAMA* 2010;304:772-778.

My grandmother always claimed that listening to loud rock and roll music would be the demise of my hearing … but I still don't know if she was right. In those days we used to listen to something called a record player (younger clinicians interested to see such an archaic device can readily locate one on Google), and I have always wondered whether those cars bouncing up and down at the traffic light next to me, loaded with rap music, would be determined to be similarly ototoxic, or worse. Well, if the NHANES data are correct, we still don't know.

According to this analysis of data from NHANES, the prevalence of hearing loss has increased when one compares the 1988-1994 interval with 2005-2006. Indeed, the relative risk of any hearing loss (induced by any factor) has increased by more than 30%.

Hearing loss was associated with poverty and a history of > 3 ear infections, but not exposure to persistent (> 5 hrs/week) loud noise or firearm use. In support of grandma's point of view, a recent study from Australia noted hearing loss 70% more often in teens who had used personal stereo devices.

Overall, the prevalence of any hearing loss increased from 11.1% to 14.0% over the decade studied; further elucidation of modifiable risk factors would be helpful. ■

When to initiate dialysis? Early vs late GFR threshold

Source: Cooper BA, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;363:609-619.

The number of individuals requiring renal replacement therapy (dialysis) continues to grow. Because dialysis is an expensive, time-intensive, and intrusive intervention, it is wise to try to refine an optimum threshold for initiation of dialysis. Intuition might suggest that earlier is better than later, but few data to support this notion are in evidence.

Cooper et al performed a study of adults (n = 828) who qualified for dialysis. Study subjects were randomized to either early (GFR = 10-15 mL/min/1.73 m^2) or late (GFR = 5-7 mL/min/1.73 m^2) dialysis. The primary outcome of the trial was all-cause mortality.

Over an 8-year interval, 828 diabetic subjects with Stage V CKD (GFR < 15 mL/min/1.73 m^2) were randomized to initiate dialysis at either the early or late GFR threshold. The mean time to dialysis initiation in the early group was 1.8 months vs 7.4 months in the late group, but this difference might be expanded further, since more than 75% of the late start group actually initiated dialysis because of symptoms before reaching a GFR of 7.

Overall mortality during 3.6 years of follow-up was not significantly different between the two groups. There does not appear to be any mortality detriment associated with delaying dialysis until GFR is 7 mL/min/1.73 m^2 or less, although many patients may require earlier dialysis due to symptoms. ■

Postoperative abdominal wall hernias: Best repair methodology

Source: Itani KM, et al. What to advise patients about hernias. *Arch Surg* 2010;145:322-328.

The literature indicates that almost one-fourth of persons who undergo abdominal surgery will subsequently incur an abdominal wall hernia. The optimum method for repairing such hernias has not been established. Itani et al performed a randomized trial of laparoscopic vs open repair of ventral incisional hernias at four Veterans Affairs hospitals (n = 162).

There was a substantial risk reduction for complications in the laparoscopic group vs the open repair group (absolute incidence = 31.5% vs 47.9%). In particular, surgical wound site infection was almost 4-fold less in the laparoscopic group. Pain scores at 1 year were less in the laparoscopic group, and return to work was quicker. The only major advantage of open surgical treatment was the incidence of major complications, primarily bowel injury (4.4% in the laparoscopic group vs 1.4% in the open surgery group). One additional advantage of open surgical repair was a trend toward lower recurrence in this group (8.2% vs 12.5%; *P* = NS).

In general, asymptomatic incisional ventral hernias do not require repair, but once they are symptomatic, laparoscopic surgery shows distinct advantages. The surgeons in this trial had not performed a high volume of laparoscopic procedures; hence, clinicians might anticipate even better outcomes as experience accrues. ■

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Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

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the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■