AHC Media

Vol. 28, Issue 6, June 2012
www.ahcmedia.com

Clinical Oncology

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

ABSTRACT & COMMENTARY

Tanning Beds Revisited

By William B. Ershler, MD

SYNOPSIS: The practice of tanning by artificial means, such as by sunlamps or sunbeds, continues to be popular, particularly in young people despite the acknowledged risk for increased skin cancer. Most data in this regard have been derived from case-control analyses. In the current report from the Nurses Health Study II examining 20-year follow-up of 73,494 nurses, an increased incidence of basal cell, squamous cell, and melanoma was observed in those who reported tanning bed use either during high school/college years or from age 25-35 years.

SOURCE: Zhang M, et al. Use of tanning beds and incidence of skin cancer. *J Clin Oncol* 2012;30:1588-1593.

Artificial exposure to ultraviolet light, such as in a tanning salon, has been associated with increased skin cancers. A meta-analysis of 19 studies revealed that ever-use of sunbeds was associated with 15% increased risk of melanoma compared with never having used a sunbed.[1] This analysis revealed a similar increase in squamous cell carcinoma (SCC), but the risk was found to be insignificant for basal cell carcinoma (BCC). Most prior studies have used case-control methodology with only limited data derived from prospective cohorts. The current research was designed to evaluate skin cancer risk in the context of prior tanning bed use by capitalizing on the rich data available in the Nurses Health Study II (NHSII).

The investigators report on 73,494 female nurses who responded by questionnaire every 2 years over a 20-year span (from 1989 to 2009). Embedded in the questionnaires were questions regarding the frequency of use of tanning beds during high school/college years and at ages 25-35 years. Also extracted from the questionnaire were the development of skin cancer (BCC, SCC, or melanoma). The investigators used Cox proportional hazards models and carefully adjusted for host risk factors, ultraviolet index of residence, and sun exposure behaviors at a young age.

During follow-up, 5,506 nurses were diagnosed with BCC, 403 with SCC, and 349 with melanoma. The multivariable-adjusted hazard ratio (HR) of skin cancer for an incremental increase in use of tanning beds of four times per year during both periods was 1.15 ($P \leq 0.001$) for BCC, 1.15 ($P \leq 0.03$) for SCC, and 1.11 ($P \leq 0.13$) for melanoma.

Financial Disclosure: *Clinical Oncology Alert*'s Editor, William Ershler, MD; peer reviewer, V.R. Veerapalli, MD; executive editor, Leslie Coplin; and managing editor, Neill Kimball report no financial relationships relevant to this field of study.

Clinical Oncology [ALERT]

Clinical Oncology Alert,
ISSN 0886-7186, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to Clinical Oncology Alert, P.O. Box 105109, Atlanta, GA 30348.

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Compared with tanning bed use at ages 25 to 35 years, there was a significantly higher risk of BCC for use during high school/college (multivariable-adjusted HR for use more than six times per year compared with no use was 1.73 during high school/college vs. 1.28 at ages 25-35 years; *P* for heterogeneity ≤ 0.001).

COMMENTARY

There has been concern that the common use of such tanning beds among adolescents and young adults, estimated to be 20-40% in these age groups in the United States,[2,3] will result in the increased occurrence of skin cancers later in life. The current data provide strong evidence that this is the case, as it demonstrates a dose-response relationship between tanning bed use and the risk of skin cancers, especially BCC, and the association is stronger for patients with a younger age at exposure.

Clinical Oncology Alert (COA) readers will recall commentary on an article published last year[4] and reported in the August 2011 COA issue in which an Australian group demonstrated a clear association of adolescent sunbed use and increased risk of early-onset melanoma. Furthermore, there was an apparent dose effect as the risk increased the earlier one started and was most apparent in those with greatest use. In the current prospective observational study, a similar conclusion is drawn, although the greatest risk was for the development of BCC, but was also evident for melanoma and SCC.

There is increasing pressure coming from public and private health agencies, such as the National Institutes of Health and the American Cancer Society, for increased restrictions on indoor tanning, particularly as it is marketed for adolescents and young adults. Inasmuch as BCC is the most common form of cancer in the United States and it is clearly associated with substantial quality of life and economic issues, prevention strategies should be paramount. The Zhang report should be high on the reading list of those who concern themselves with public health policy. ■

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ABSTRACT & COMMENTARY

Responses, Albeit Few, for Ipilimumab-Treated Melanoma Patients with Brain Metastases

By William B. Ershler, MD

SYNOPSIS: Ipilimumab has recently been approved for the treatment of advanced melanoma. The current trial was undertaken to determine its safety and efficacy in patients with brain involvement. Toxicity was manageable and not significantly different than observed in treatment of melanoma patients without brain metastases. There were no complete responses but partial response or stable disease was observed in just under 20% of those with limited (asymptomatic) brain involvement. For those with more extensive brain involvement only 1 of 21 showed partial regression.

SOURCE: Margolin K, et al. Ipilimumab in patients with melanoma and brain metastases: An open label, phase 2 trial. *Lancet Oncol* 2012;13:459-465.

Brain metastases are a common feature of melanoma, occurring in as many as 75% of patients who die with this disease.[1] Although patients with brain involvement are often treated with surgery, stereotactic radiosurgery, or whole brain irradiation, median survival is < 6 months.[2] Systemic therapy,

although commonly attempted, particularly with temozolomide, results in objective responses in only 10% of such patients.[3] Immunological approaches have provided benefit for patients without brain involvement, but not convincingly for patients with brain metastases. Among novel immunological approaches, ipilimumab recently was FDA approved for first-line treatment for patients presenting with advanced disease.

Ipilimumab is a monoclonal antibody that blocks the interaction between cytotoxic T-lymphocytic antigen-4 (CTLA-4) and its ligands CD80/86 and thereby augments T-cell activation and proliferation.[4,5] In Phase 2 and 3 studies, ipilimumab has proven active in the treatment of advanced melanoma.[6-9] The study reported by Hodi et al included 11% (of a total of 540) with brain metastases, and treatment responses in terms of survival were comparable to those without brain metastases.[9]

The current study was designed to determine the safety and activity of this drug specifically for those patients with brain metastases. Between July 31, 2008, and June 3, 2009, the investigators enrolled adult patients at 10 U.S. centers stratified into two parallel cohorts. Patients in cohort A were neurologically asymptomatic and were not receiving corticosteroid treatment at study entry; those in cohort B were symptomatic and on a stable dose of corticosteroids. Patients were treated with four doses of 10 mg/kg intravenous ipilimumab at 3-week intervals. Individuals who were clinically stable at week 24 were eligible to receive additional ipilimumab treatments (10 mg/kg) every 12 weeks. The primary endpoint was the proportion of patients with disease control, defined as complete response, partial response, or stable disease after 12 weeks. Analyses of safety and efficacy included all treated patients.

In all, 72 patients were enrolled. Of these, 51 were in cohort A and 21 were in cohort B. After 12 weeks, nine patients in cohort A exhibited disease control (18%), as did one patient in cohort B (5%). When the brain alone was assessed, 12 patients in cohort A (24%) and two in cohort B (10%) achieved disease control. Disease outside of the brain was controlled in 14 patients (27%) in cohort A and in one individual (5%) in cohort B. Adverse events were somewhat different in cohorts A and B. The most common grade 3 adverse events in cohort A were diarrhea (six patients [12%]) and fatigue (six [12%]), whereas in cohort B, they were dehydration (two individuals [10%]), hyperglycaemia (two [10%]), and increased concentrations of serum aspartate aminotransferase (two [10%]). One patient in each cohort had grade 4 confusion. One patient in cohort A died of drug-related complications of immune-related colitis.

COMMENTARY

Effective treatment for patients with metastatic melanoma has proven elusive, and this is particularly true for those with brain involvement. For years, experimental immunotherapeutic approaches have held the greatest promise, but their application in the community has been limited by the complex technical procedures and expense, let alone paucity of randomized clinical trial data to support such an approach. That stated, ipilimumab, a potent but non-specific stimulant of immune processes, has been shown to improve survival for patients with advanced disease and the current report suggests its benefit may extend to those with brain metastases, particularly if the metastatic involvement in the brain is limited (asymptomatic). No doubt, this is a step forward. But a small one. Toxicity, particularly immune-related adverse events, can be remarkable despite careful clinical monitoring; the drug is very expensive; and much less than a majority exhibited "stable disease" measured at 12 weeks.

Thus, ipilimumab has assumed a role in the treatment of advanced melanoma, and no doubt there will be a larger experience reported as community oncologists become familiar and comfortable with its use. Alone, it has some limited activity for patients with brain metastases, and it is hoped that ongoing trials will demonstrate more substantial success when it is combined with chemotherapy or used as an adjunct to surgery or radiation. ■

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ILLUSTRATIVE CASE SERIES

Recurrent Meningioma: Systemic Therapy

By William B. Ershler, MD

The patient is a 56-year-old woman with known meningioma first resected in 1999 followed by external beam irradiation. In 2005, she developed progressive right leg weakness and had a second operation and course of radiation. The surgical pathology on that occasion revealed a grade II meningioma with significant vascular component. Recurrent disease was diagnosed in 2008 and she was treated with radiosurgery.

She has been recently admitted for progressive weakness and increase in seizure activity. An MRI demonstrated growth predominantly of a lesion located in the left parasagittal area. There was also parasagittal disease on the right that was essentially unchanged (compared to 2008), but other lesions inferior and lateral along the dura on the left showed evidence for growth.

On this occasion she has been seen by both her neurosurgeon and radiotherapist and next-step treatment approaches are under consideration. Accordingly, the role for systemic therapy has been raised and medical oncology opinion was requested.

COMMENTARY

Meningiomas are the most common primary brain tumors of the central nervous system with an annual incidence of approximately 6 cases/100,000 person-years.[1] The great majority are benign, but approximately 20% are atypical, or anaplastic, and demonstrate more rapid growth and a tendency to recur after initial therapy.[2] Initial therapy for symptomatic or growing benign meningiomas is maximum safe resection, whereas radiation therapy is usually added for atypical and anaplastic lesions or for inoperable, progressive grade I lesions.[3,4] Additional radiation or repeat surgery is often considered for recurrent disease, but these options are often limited by the accumulated dose of radiation or the extent of surgery required. Thus, there has been interest in examining the role for systemic therapy under these circumstances.

Unfortunately, most efforts at systemic therapy, including chemotherapy, hormonal, and immunomodulators, have met with unsatisfactory results including both lack of efficacy and toxicity.[4]

Chemotherapeutic approaches have included temozolomide[5] and hydroxyurea[6] but with little objective benefit. However, enthusiasm for treatment with hormonal agents was based on the demonstration of estrogen, progesterone, and androgen receptors in tumor samples from as many as two-thirds of cases.[4] Yet, such treatments did not result in improvement in meaningful outcomes. For example, the Southwest Oncology Group (SWOG) conducted a trial of tamoxifen in 21 patients and observed only one partial response.[7]

With the demonstration that the great majority (approximately 90%) of meningiomas express somatostatin receptors, treatment with the somatostatin analogue octreotide has been undertaken. Indeed, in a pilot study, 5 of 16 (31%) patients who had recurrent meningiomas known to have somatostatin receptors on the basis of radiolabeled octreotide scan experienced partial response to octreotide therapy.[8] The use of agents in this class remains under clinical investigation.

In addition to hormone receptors, meningioma cells, particularly those from high-grade tumors, are also known to express vascular endothelial growth factor receptor,[9,10] thus providing rationale for targeted angiogenesis inhibitors. Indeed, two recent reports have provided retrospective analyses of patients with aggressive meningiomas treated with the VEGF inhibitor bevacizumab.[11,12] These reports both indicate promise for drugs in this class, as toxicity was both minimal and manageable, and evidence for tumor regression or stable disease was observed in some patients. Clearly, it would seem that such targeted approaches provide the best chance for reaching a level of disease control, and hopefully this will be clearly demonstrated in the ongoing Phase 2 trials.

Thus, with regard to the management of the patient presented, if surgical and radiation options have

been exhausted, I would recommend obtaining an octreotide scan. If positive, I would treat with the long-acting formulation of octreotide. If somatostatin receptor is not apparent by scan, or if octreotide proves ineffective, my next step would be a trial of bevacizumab. ■

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ABSTRACT & COMMENTARY

Free Light Chain Levels Offer Predictive Value for Both Myelofibrosis and Myelodysplasia

By William B. Ershler, MD

SYNOPSIS: **Host-related immunoproliferation may contribute to the pathogenesis of certain clonal myeloid disorders such as myelofibrosis and myelodysplasia. In cohorts of such patients, the demonstration of elevated free immunoglobulin light chains (considered a surrogate of polyclonal immunoproliferation) is shown to be associated with poor overall survival in patients with these disorders.**

SOURCE: Pardanani A, et al. Polyclonal immunoglobulin free light chain levels predict survival in myeloid neoplasms. *J Clin Oncol* 2012;30:1087-1094.

Both primary myelofibrosis (PMF) and myelodysplasia (MDS) are clonal hematopoietic stem cell disorders associated with aberrant host responses including immunoproliferation and inflammation. Whereas therapies directed at the involved stem cells have proven only marginally effective, treatments directed at these dysregulated host responses occasionally produce gratifying responses in terms of quality of life. It has been speculated that dysregulated host responses contribute to the pathogenesis of these disorders and to the extent that these host responses can be quantified, it is possible that they would predict meaningful clinical outcomes. In this regard, investigators from the Mayo Clinic had previously demonstrated the prognostic significance of certain pro-inflammatory cytokines for patients with both PMF and MDS.[1,2] In the current report, these same investigators sought to elaborate further the concept of prognostically relevant host-specific biomarkers in PMF and MDS by using a readily accessible B-cell activation marker, plasma immunoglobulin free light chain (FLC) concentration.

They proposed that FLC, as a surrogate marker of host immune response, would predict survival for these non-plasma cell myeloid malignancies (PMF and MDS). Because the FLC assay is readily available (as opposed to the more complex cytokine assays), the findings might have immediate practical applicability.

The study was conducted on two different cohorts of referred patients — those with PMF (n = 240) and those with MDS (n = 74). Kappa (κ) and lambda (λ) FLCs were measured by a quantitative nephelometric assay. For patients with an abnormal κ/λ ratio, monoclonal production was ruled out by immunofixation, but if present, such patients were excluded from analysis.

Values that were above the upper limit of normal for κ or λ FLC were documented in 33% of 240 patients with PMF and 46% of 74 patients with MDS. Increased FLC was significantly associated with increased creatinine, and advanced age in PMF ($P < 0.001$) and hemoglobin < 10 g/dL in MDS ($P < 0.005$). In multivariable analysis, increased FLC predicted shortened survival in both PMF and

MDS, independent of age, creatinine, and other conventional risk factors. Cutoff levels based on receiver operating characteristic analysis for κ plus λ total FLCs delineated risk groups with highly significant differences in overall survival. For PMF, this cutoff value was 3.78 mg/dL and for MDS it was somewhat lower at 3.24 mg/dL.

For patients with PMF, the International Prognostic Scoring System-adjusted hazard ratio was 1.9 (95% confidence interval [CI], 1.3 to 2.7), and for MDS it was 6.3 (95% CI, 2.7 to 16.6). No correlations were seen with leukemia-free survival, karyotype, or *JAK2*, *MPL*, or *IDH* mutations. In patients with PMF who had previously been studied by cytokine profiling, the prognostic value of an increased FLC level was independent of that from circulating interleukin-2 receptor (IL-2R) or IL-8 levels and when the data were taken together, a more precise predictive value was determined. For example, a composite risk model based on total FLC greater than 3.78 mg/dL and two selected cytokines (IL-2R or IL-8; values greater than three SDs): both normal (n = 39; median survival not reached), either abnormal (n = 98; median survival, 70 months), and both abnormal (n = 61; median survival, 32 months; $P < 0.001$).

COMMENTARY

Conventional prognostic variables for inferior survival in PMF and MDS are based on cell-intrinsic properties of the malignant clone, such as unfavorable karyotype, increased tumor burden or proliferative capacity, and ineffective hematopoiesis. A number of reports for both PMF and MDS have indicated various mutations, many of which confer some prognostic information.[3-5] However, these mutations are limited by low mutation frequency and, of course, varying laboratory expertise and technical capabilities, let alone expense. Yet, various host-related factors including age, performance status, dysregulated cytokines,[2,6,7] and now FLC are also relevant to outcomes in patients with these disorders.

The findings from this report indicating the predictive value of plasma FLCs are of interest at a variety of levels. From a biological perspective, the lack of correlation with leukemia-free survival and tumor-specific genetic markers suggests that the increase relates primarily to host response, and the correlation suggests dysregulated immunoproliferation may be causally related to disease progression. Furthermore, for the clinician, this readily available laboratory parameter (FLC) may prove very useful in refining prognosis and determining appropriate interventions. The report capitalized on two relatively large and carefully evaluated cohorts, yet the overall added value remains to be determined in prospective studies. ■

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ABSTRACT & COMMENTARY

Treatment Decisions for Patients with Newly Diagnosed Multiple Myeloma

By Jerome W. Yates, MD

Hematology/Immunology Unit, National Institute on Aging, NIH

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

SYNOPSIS: Two very recent publications address the management of newly diagnosed multiple myeloma. In the first, two bortezomib-containing three-drug regimens proved equally effective as a more complex four-drug regimen in achieving meaningful initial responses. The second demonstrated the value of maintenance lenalidomide for achieving longer progression-free survival.

SOURCES: Kumar S, et al. Randomized, multicenter, phase 2 (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood* 2012;119:4375-4382.
Palumbo A, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med* 2012;366:1759-1769.

Over the past 15 years, new drugs, such as the proteasome inhibitor bortezomib and the IMiDs (thalidomide and lenalidomide), have become available for the treatment of myeloma, and when used in combination either together or with established drugs, such as melphalan, cyclophosphamide, doxorubicin and dexamethasone, there has been striking improvement in response rates, progression-free survival, and overall survival.[1-3] Yet, there remain a number of questions regarding which drug combinations and what schedules will provide optimal outcomes. The EVOLUTION study, funded by Janssen Global Services and Millennium Pharmaceuticals Inc., was designed to examine various bortezomib combinations including the four-drug combination — bortezomib (V), dexamethasone (D), cyclophosphamide (C), lenalidomide (R) [VDCR] — compared with two commonly used three-drug regimens (VDR and VDC) as initial treatment.

The EVOLUTION study design included an initial Phase 1 component in which the maximum tolerated dose of cyclophosphamide as a component of the VDCR regimen was determined, and the results had been previously published.[4] The current report describes the subsequent randomized Phase 2 trial that evaluated VDC, VDR, and VDCR in previously untreated multiple myeloma (MM). Patients received V 1.3 mg/m^2 (days 1, 4, 8, 11) and D 40 mg (days 1, 8, 15), with either C 500 mg/m^2 (days 1, 8) and R 15 mg (days 1-14; VDCR), R 25 mg (days 1-14; VDR), C 500 mg/m^2 (days 1, 8; VDC) or C 500 mg/m^2 (days 1, 8, 15; VDC-mod) in 3-week cycles (maximum eight cycles), followed by maintenance with V 1.3 mg/m^2 (days 1, 8, 15, 22) for four 6-week cycles (all arms).

Using the International Myeloma Working Group uniform response criteria, very good partial response was seen in 58%, 51%, 41%, and 53% (complete response rate of 25%, 24%, 22%, and 47%) of patients (VDCR, VDR, VCD, and VCD-mod, respectively); the corresponding 1-year progression-free survival was 86%, 83%, 93%, and 100%, respectively. Common adverse events included hematologic toxicities, peripheral neuropathy, fatigue, and gastrointestinal disturbances.

Whereas a substantial subset of patients (42%) enrolled in the EVOLUTION study went on to receive autologous stem cell transplant (ASCT) after four cycles of treatment, many newly diagnosed myeloma patients are considered ineligible for such an aggressive approach on the basis of comborbidities, functional impairments, or advanced age. In a separate multicenter trial also published this month, Palumbo and colleagues reported on their Celgene-sponsored study in which newly diagnosed MM patients who were not considered eligible for ASCT (on the basis of comorbidities, functional impairments, or advanced age) were randomly assigned to receive nine 4-week cycles of oral melphalan, prednisone, lenalidomide induction followed by lenalidomide maintenance therapy until a relapse or disease progression occurred (MPR-R; n = 152), or to receive MPR (153 patients) or MP (154 patients) without maintenance therapy. The primary endpoint was progression-free survival and this was found to be significantly longer with MPR-R (31 months) than with MPR (14 months; hazard ratio [HR], 0.49; $P < 0.001$) or MP (13 months; HR, 0.40; $P < 0.001$). Response rates were superior with MPR-R and MPR (77% and 68%, respectively, vs 50% with MP; $P < 0.001$ and $P = 0.002$, respectively, for the comparison with MP). The progression-free survival benefit associated with MPR-R was noted in patients 65-75 years of age but not in those > 75 years of age ($P = 0.001$ for treatment-by-age interaction).

COMMENTARY

The EVOLUTION study demonstrated that bortezomib containing three-drug regimens were highly active and well tolerated in previously untreated MM. Based on their findings, the authors favored VDR or the modified VCD for clinical practice and for further comparative testing. Notably, the four-drug VDCR regimen showed no substantial advantage over the three-drug combinations. For the treatment of patients who might not otherwise be candidates for parenteral therapy, let alone ASCT, the Palumbo report provides direction. As expected, the oral MPR regimen was more effective in terms of response rate when compared to MP, and the addition of maintenance lenalidomide (MPR-R) resulted in remarkably longer progression-free survival. The implications of this important finding were balanced in an accompanying editorial in which concerns were raised about the potential risks of maintenance therapy in terms of second malignancy as well as its impact on quality of life.[5] Also, the editorialist raised the question of the relevance of using progression-free survival as the primary endpoint in maintenance trials.

Thus, community oncologists have two new pieces of data to advise regarding initial management of myeloma. Of course, there remain a number of questions, none the least of which is on what basis do we choose whether a patient will be able to tolerate the more aggressive regimens and will maintenance therapy, now known to extend progression-free survival, translate into improved overall survival? ■

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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.

CME Instructions

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Questions

1. Data from the Nurses Health Study II indicated an increased risk for which type(s) of skin cancer for those who frequented tanning salons at a young age?
a. Squamous cell cancer
b. Basal cell cancer
c. Melanoma
d. All of the above

2. Ipilimumab treatment in patients with asymptomatic brain metastases from primary melanoma resulted in either partial response or stable disease at 12 weeks in approximately what percent?
a. 5%
b. 20%
c. 45%
d. 70%

3. Which of the following agents has proven in clinical trial to prolong survival in patients with recurrent meningioma?
a. Hydroxyurea
b. Tamoxifen
c. Octreotide
d. Bevacizumab
e. None of the above

4. In patients with primary myelofibrosis, which of the following parameters is *not* associated with poor survival?
a. Advanced age
b. Monoclonal elevation of plasma light chains
c. Polyclonal elevation of plasma light chains
d. Poor performance score

5. Myeloma patients treated with the MPR-R regimen, compared to those treated with MPR alone, were shown by Palumbo and colleagues to have:
a. better initial response rate.
b. longer progression-free survival.
c. longer overall survival.
d. All of the above
e. None of the above

[IN FUTURE ISSUES]

More on Aspirin for Cancer Prevention

PHARMACOLOGY WATCH

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

Critical Drug Shortages Are on the Rise

In this issue: Drug shortages; metformin and cancer prevention; migraine prevention guidelines; and FDA actions.

What's causing the shortages?

Drug shortages are happening at an unprecedented rate. Just in the last 2 months, we have seen shortages of diazepam, methotrexate, leucovorin, naltrexone, oxymorphone, mitomycin, fentanyl, metoclopramide, pantoprazole, ondansetron, and dexamethasone among others. What is causing the shortages and is there any end in sight? Although it seems like a new problem, we have seen an increasing number of drug shortages going back to 2005. But while there were about 50 drug shortages in the mid 2000s, last year more than 260 drugs were in short supply, including many commonly used and clinically vital drugs. The cause of these shortages is multifactorial. Some sources in the industry blame price controls, especially for generic drugs. Medicare and Medicaid impose strict controls on most generics, squeezing pharmaceutical companies' ability to make a profit. Some companies have simply decided to drop out of the generic market altogether. Others blame fewer manufacturers. The *Wall Street Journal* reports that there were 26 vaccine makers in the United States in 1967, while currently there are only six. But even these issues do not explain the severe shortages we are seeing. Most experts agree the two major issues causing the current shortages are supply chain disruptions, especially disruptions in raw materials, and problems with manufacturing, especially safety issues, which force the FDA to shut down production of a product line or an entire factory. Safety shutdowns are the most common cause of shortages of sterile injectable drugs. But in other cases, companies limit production themselves when they either have an absolute shortage of raw materials or they decide to divert limited supplies of raw materials from less expensive generics to more expensive brand-name drugs. This is a current issue with some of the attention deficit hyperactivity disorder drugs that have been in short supply for several months. Last month, the FDA initiated a series of steps to increase the supply of critically needed cancer drugs, including allowing the importation of drugs in shortage from Europe and elsewhere. The agency is also fast tracking approval of new manufacturers for short-supply drugs like methotrexate. The FDA, as well as the Obama administration, is also requiring companies to give early warning of potential drug shortages. Finally, the Justice Department will aggressively pursue possible incidences of collusion or price gouging among drug distributors who may be taking advantage of shortages. Despite these steps, there will likely be no short-term easing in drug shortages. ■

Does metformin prevent cancer?

Last month, we reported that low-dose aspirin may be protective against some cancers. Now it looks like metformin may have similar properties. A new study from the American Association for Cancer Research suggests that the diabetes drug may improve the prognosis with pancreatic cancer. In a retrospective study, researchers at the University of Texas studied 302 patients with diabetes and

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pancreatic cancer; 117 of these patients were taking metformin. The 2-year survival rate was 30.1% for the metformin group vs 15.4% for the non-metformin group ($P = 0.004$; x^2 test). The pancreatic cancer patients on metformin lived 4 months longer than non-metformin patients (15.2 months vs 11.1 months). The authors suggest that metformin should be evaluated as a supplemental therapy for patients with pancreatic cancer (*Clin Cancer Res* published online March 31, 2012; doi: 10.1158/1078-0432.CCR-11-2994). Data presented at the AACR meeting in Chicago earlier this year suggest that the drug may also be beneficial for men with prostate cancer, although further research is needed. ■

Migraine prevention in adults

The American Academy of Neurology and the American Headache Society have published their new guideline on pharmacologic treatment for episodic migraine prevention in adults. The highest level (Level A) recommendation for prevention was given to antiepileptic drugs, including divalproex sodium, sodium valproate, and topiramate. Other level A drugs included the beta-blockers metoprolol, propranolol, and timolol as well as the triptan frovatriptan, but this last agent is just for short-term use for menstrually associated migraine (MAM) prevention. Level B drugs included the antidepressants amitriptyline and venlafaxine, the beta-blockers atenolol and nadolol, and the triptans naratriptan and zolmitriptan (also only for short-term MAM prevention). Possibly effective medications included lisinopril, candesartan, some beta-blockers, and carbamazepine. There was little or no evidence to support any other drugs including selective serotonin reuptake inhibitors, calcium channel blockers, or acetazolamide. Drugs that should not be offered include lamotrigine and clomipramine. In a separate section on nonsteroidal anti-inflammatory drugs (NSAIDs) and complementary treatments, Petasites hybridus (butterbur) were given recommended status, while NSAIDs were listed as probably effective (*Neurology* published online April 24, 2012; doi: 10.1212/WNL.0b013e3182535d20, and doi: 10.1212/WNL.0b013e3182535d0). ■

Fibrate use in elderly patients

Fibrate use in elderly patients is associated with worsening renal function and increased risk of hospitalization, according to a new study. Researchers reviewed data from a large Canadian database of patients over the age of 65 who were started on a fibrate or ezetimibe (comparator). Many patients in both groups were also on statins. Fibrate users were more likely to be hospitalized for an increase in serum creatinine (odds ratio [OR] 2.4 [95% confidence interval (CI), 1.7 to 3.3]). Fibrate patients were also more likely to consult a nephrologist, but there was no difference in all-cause mortality or need for dialysis. In a subgroup of 1110 patients in which serum creatinines were available at baseline and within 90 days, 9.1% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine of 50% or more (OR 29.6 [CI, 8.7 to 100.5]). The risk was higher if patients had chronic kidney disease. The authors conclude that new fibrate use in the elderly is associated with an increase in serum creatinine and a small increase in hospitalization and nephrology consultation (*Ann Intern Med* 2012;156:560-569). ■

FDA actions

The FDA has approved the first PDE5 inhibitor in a decade for the treatment of erectile dysfunction (ED). Avanafil (Stendra) joins sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) as the fourth drug approved for this indication. Avanafil will be marketed as having a shorter onset and a shorter half-life than the other drugs in this class. Men should take avanafil as needed 30 minutes before sexual activity with onset of action as quickly as 15 minutes. The approval was based on three randomized, placebo-controlled clinical trials of 1267 patients with ED in which 57% of men achieved erections sufficient for intercourse, up from a baseline of 15% (compared to 27% with placebo). Like other PDE5 inhibitors, avanafil should not be taken with nitrates. Commonly reported side effects include headache, flushing, nasal congestion, nasopharyngitis, and back pain. Avanafil will be marketed by VIVUS of Mountain View, California, as Stendra.

The FDA is requiring new labeling on finasteride — Merck's testosterone blocker used for the treatment of benign prostatic hypertrophy (5 mg as Proscar) and male pattern baldness (1 mg as Propecia). The new labeling addresses sexual adverse events such as libido disorders, ejaculation disorders, orgasm disorders, and even male infertility and poor semen quality. Some of these issues, such as libido disorders and ejaculation disorders, may continue after stopping the drug, while infertility and poor semen quality improve or normalize after discontinuation. The labeling change is based on event reports filed with the FDA, although a clear causal relationship has not been made. Still, the agency is recommending that a discussion of the risks and benefits of finasteride include the possibility of sexual side effects. ■

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 17, NUMBER 6 PAGES 11-12 JUNE 2012

Statins and Dyslipidemia: Should we be Looking Beyond LDL?

Source: Boekholdt SM, et al. *JAMA* 2012;307:1302-1309.

TREATMENT OF DYSLIPIDEMIA WITH STATINS produces consistent, durable lowering of low-density lipoprotein cholesterol (LDL-C), which is associated with substantial reductions in myocardial infarction and stroke. Other lipoprotein markers — in particular apolipoprotein B (apoB) and non-high-density lipoprotein cholesterol (non-HDL-C) — are also associated with vasculopathy. Indeed, the putative pathogenetic role of apoB has garnered some enthusiasm from lipidologists who encourage more routine measurement and modulation of apoB as a primary goal.

Risk reduction with statins is imperfect. That is, substantial risk for vascular events and death exists even with excellent LDL-C reduction. Might levels of apoB or non-HDL-C in patients already on a statin help us to discern which ones remain at high risk?

Boekholdt et al performed a meta-analyis of statin trials (n = 62,154) that included data on apoB and non-HDL-C, examining the relationship between on-treatment levels of LDL-C, apoB, non-HDL-C, and cardiovascular outcomes. For each increase of one standard deviation in the level of any of these three markers, the risk for a cardiovascular event increased, and to a very similar degree (13%-16% increase per standard deviation). However, when comparing the three markers with one another, non-HDL-C showed a statistically significantly greater association with increased risk than the other two markers. The authors suggest that based on this and other data, stronger consideration should be given to promoting non-HDL-C as an important target for reduction in subjects with dyslipidemia. ■

When Thiazides are Associated with Hyponatremia

Source: Rastogi D, et al. *J Clin Hypertens* 2012;14:158-164.

CONTROL OF HYPERTENSION IS REWARDED with important reductions in myocardial infarction, stroke, and cardiovascular death. Yet, the job of hypertension control is daunting, since on a worldwide basis it is estimated that more than one-fourth of all adults have hypertension! It has been known for more than 5 decades that thiazides can produce electrolyte disarray, including hypokalemia, hyponatremia, and hypomagnesemia, any of which can result in serious adverse effects and/or hospitalization. Rastogi et al performed a retrospective case-control study to elucidate risk factors for hyponatremic hospital admission while on a thiazide diuretic. They compared 1802 cases of hospitalized thiazide-associated hyponatremia with controls (n = 9003).

Risk for hyponatremic hospitalization doubled with each 10-year increase in age. The only other statistically significant associations were coadministration of an ACE inhibitor and concomitant hypokalemia. The coadministration of an ARB had a strong trend toward increased risk, but was marginally non-significant. Patients with comorbid diabetes, dyslipidemia, and gastroesophageal reflux disease were also more likely to be admitted for hyponatremia. Hopefully, recognition of these associations will assist clinicians to prevent hyponatremia, or at least detect its presence earlier. ■

Broadening Perspectives on Maintaining Healthy Erectile Function

Source: Meldrum DR, et al. *Int J Impot Res* 2012;24:61-68.

FOR MORE THAN A DECADE, IT HAS BEEN recognized that nitric oxide (NO) is critical in the attainment and maintenance of an erection. Accordingly, pathology that induces endothelial dysfunction, and hence impaired generation of NO, is consistently associated with erectile dysfunction (ED). Traditional cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and cigarette smoking are each associated with increased prevalence and incidence of ED. Increases in oxidative stress appear to be a common denominator for many of the paths that lead to endothelial dysfunction.

Additional lifestyle factors that have been associated with endothelial dysfunction include insufficient exercise, obesity, and specific dietary components (e.g., high carbohydrate diet).

Many of the risk factors associated with endothelial dysfunction are modifiable. For instance, obesity is associated with insulin resistance, which lowers vascular NO. Exercise improves NO levels systemically. A high-fat intake may in-

crease oxidative vascular wall stress.

There is some literature support for multifactorial intervention in men with ED to help restore sexual function. Meldrum et al suggest a list of factors that might favorably impact endothelial health (and hence, sexual functionality), including: 1) maintenance of healthy weight; 2) regular aerobic exercise; 3) low-fat, low glycemic-index diet; 4) smoking cessation; 5) alcohol moderation; 6) folate and omega-3 fatty acid supplementation; and 7) ARB rather than ACE treatment of hypertension. ■

Cancer Risks Associated with Diagnostic X-rays

Source: Linet MS, et al. *CA Cancer J Clin* 2012;62:75-100.

Within a few years after the initiation of diagnostic X-rays, toxic effects were noted, including increased risk for skin cancer, leukemia, dermatitis, and cataracts. In this early period, doses of X-ray, especially from fluoroscopy, were high. Protective devices for patients as well as persons occupationally exposed to diagnostic radiation demonstrably reduced such adverse consequences.

The dose of radiation that is required to induce cancer is not clearly known. However, populations who have been exposed to calculable levels of radiation through wartime exposure (i.e., Japanese atomic bomb survivors) and subjects receiving radiation therapy help us to predict a dose-response relationship. It is not yet clear to what extent the high-dose radiation exposure and subsequent development of cancer reflects cumulative lower dose exposures. Nonetheless, because radiation toxicity may be related to total exposure, peak exposure, or both, radiation from commonly used diagnostic procedures has stimulated concern.

For instance, a CT of the abdomen, commonly used investigationally for persons with acute or chronic abdominal pain, incurs the same amount of radiation exposure as 750 chest X-rays. Linet et al quote recent estimates suggesting that the 70 million CT scans performed each year in the United States could lead to 29,000 additional cancers.

The authors recommend a number of steps to reduce unnecessary radiation exposure, including 1) learning about radiation doses associated with various imaging techniques, 2) consideration of imaging without radiation (i.e., ultrasound, MRI), and 3) avoidance of elective X-rays in pregnant women. ■

The REDEEM Trial: Dutasteride for Management of Localized Prostate Cancer

Source: Fleshner NE, et al. *Lancet* 2012; 379:1103-1111.

Prostate cancer (PCA) comprises 25% of all newly diagnosed cancers in men in the United States. PCA chemoprevention trials with 5-alpha-reductase inhibitors have had mixed results. The first major PCA prevention trial with finasteride showed a 25% decrease in total PCA vs placebo, but an increase in more aggressive (high Gleason score) cancers. A similarly designed large prevention trial with dutasteride again found a 25% decrease in total PCA, but there was an increase in more aggressive cancers (albeit not statistically significant in this trial). Based on these mixed results, clinicians have been reluctant to use 5-alpha-reductase inhibition for PCA prevention.

Might 5-alpha-reductase inhibitors prove more useful for treatment of PCA rather than prevention? The REDEEM trial randomized men with localized PCA (n = 300) who had elected active surveillance for their disease to dutasteride 0.5 mg/d or placebo. At 3 years time, the risk of PCA progression was reduced by 38% in men on dutasteride.

Because dutasteride is generally well tolerated, men with non-aggressive Gleason scores (six or less) who might otherwise select active surveillance for localized disease may have reduced risk of disease progression with the addition of dutasteride. ■

Amantadine for Traumatic Brain Injury

Source: Giacino JT, et al. *N Engl J Med* 2012;366:819-826.

In young adults (age 15-30), traumatic brain injury (TBI) is the most common cause of death and disability. As many as one in seven TBI hospital admissions leaves the hospital in a vegetative state. Amantadine (AMT) has achieved some popularity for inclusion in pharmacotherapy regimens for disorders of consciousness, although the mechanism by which AMT effects positive change is uncertain. Certainly it has been shown that AMT blocks N-methyl-D-aspartate, and is an indirect agonist of dopamine, but what these pharmacologic effects do to enhance outcomes is unclear. In any case, initial trials have supported its use, and a major observational trial indicated better outcomes in TBI for persons who had received AMT.

Patients who had sustained TBI (n = 184) and who were either vegetative or minimally conscious for at least 1 month (and no longer than 16 weeks) after injury were randomized to AMT or placebo. AMT was administered initially at 100 mg b.i.d., and titrated to 200 mg b.i.d. if the Disability Rating Scale had not shown improvement. The course of treatment was 4 weeks in duration, and patients were monitored for 2 weeks after continuation of treatment.

AMT treatment was associated with statistically significantly better functional recovery outcomes than placebo. AMT is not a new medication, so its adverse effects profile, characterized by mild, transient adversities, is well known. These data support the inclusion of AMT in the pharmacologic regimen of serious TBI. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
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