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INSIDE

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Sunitinib and Cardiovascular Toxicity

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a retrospective review of 175 sunitinib-treated renal cell carcinoma patients, grade 3 hypertension was observed in approximately 10% and grade 3 left ventricular dysfunction and/or congestive heart failure in 7%. Preexisting hypertension and coronary artery disease were significant independent predictors of cardiovascular toxicity.*

Source: Di Lorenzo G, et al. Cardiovascular toxicity following sunitinib therapy in metastatic renal carcinoma: a multicenter analysis. *Ann Oncology*. 2009;20:1535-1542.

THE TREATMENT OF METASTATIC RENAL CELL CARCINOMA (RCC) has changed dramatically during the past few years. Sunitinib malate is one of several new agents (including sorafenib tosylate, bevacizumab, temsirolimus, and everolimus) that have improved clinical outcomes in randomized phase III trials by inhibiting the vascular endothelial growth factor and related pathways.[1,2] Sunitinib is a tyrosine kinase inhibitor, and recent data have shown that cardiotoxicity represents a potentially important side effect in patients treated with this class of agents.[3,4] In the current report, Lorenzo et al reviewed cardiac adverse events in patients with metastatic renal cell carcinoma (RCC) who underwent treatment with this sunitinib.

For this, the medical records of 175 patients with metastatic RCC treated with sunitinib at eight Italian institutions were retrospectively reviewed. Alterations in left ventricular ejection fraction (LVEF) and blood pressure were evaluated. Patients with preexisting cardiac risk factors were specifically scrutinized for increased expression of cardiac changes.

Grade 3 hypertension was seen in 17 patients (9.7%); in 12 of these 17, hypertension developed after receiving the third sunitinib cycle. Among these 17 patients, 12 (70.6%) also experienced left ventricular systolic (LVEF) dysfunction. In all, 33 of the 175 patients (18.9%) developed some degree of cardiac abnormality, of which 12 were classified as grade 3 LVEF dysfunction and/or congestive heart

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failure (CHF) (6.9%). Significant univariate associations for predictors of CHF were history of hypertension (p = 0.008), history of coronary heart disease (p = 0.0005), and prior treatment with an angiotensin-converting enzyme inhibitor (p = 0.04). Multivariate analysis suggested that a history of coronary artery disease [odds ratio (OR) 18, 95% confidence interval (CI) 4-160, p = 0.005] and hypertension (OR 3, 95% CI 1.5-80, p = 0.04) were the only significant independent predictors of CHF.

■ COMMENTARY

Thus, patients undergoing sunitinib, especially those with a previous history of hypertension and coronary heart disease, are at increased risk for cardiovascular events and should be monitored for exacerbations of their hypertension and for evidence of LVEF dysfunction during treatment. This report is more or less a confirmation of other earlier reports, yet it represents a fairly large cohort of sunitinib-treated patients with a single tumor type, and it is the first such series where all patients were treated outside of a clinical trial; thus, it more likely represents current clinical practice. Yet, when compared with other reports, the findings are quite consistent and the message for clinicians is coming through quite clearly. For example, Chu et al assessed cardiac risk in sunitinib-treated patients with metastatic gastrointestinal stromal tumors (GIST),[5] and found that 8% developed New York Heart Association class III-IV heart failure and 47% developed hypertension, with grade 3 hypertension occurring in 17% of the patients by cycle 3. In another retrospective review of 48 patients treated with sunitinib for either RCC or GIST, Telli et al found that 15% developed symptomatic grade 3/4 heart failure.[6] The patient characteristics in these three reports were quite different with regard to prior cardiovascular history, exposure to prior tyrosine kinase therapy, and even the type of tumor treated, yet the appearance of both CHF and hypertension was relatively comparable. Symptomatic heart failure and significant hypertension occur in approximately 10%-20% of patients, with hypertension commonly recognized during or after the third cycle.

The mechanism of tyrosine kinase-associated cardiovascular toxicity remains unresolved. It is notable that, like that observed with trastuzumab treatment in breast cancer patients and distinct from anthracycline-associated cardiovascular toxicity, sunitinib cardiovascular toxicity does not appear to be dose-related. Thus, careful cardiac monitoring is warranted in all patients, but particularly those with a prior history of coronary artery disease or hypertension. For patients with preexisting hypertension, consideration should be given to increasing dose of their current hypertensive, or even adding an additional anti-hypertensive, while being treated with sunitinib. If hypertension persists, sunitinib should be held until blood pressure comes under control and reintroduction of sunitinib, perhaps at a lower dose, could be considered; however, alternative approaches at this point might offer a better risk/benefit ratio. ■

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XP For Metastatic HCC

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *Successful treatment for patients with metastatic HCC remains elusive. In this Phase II study, a combination of capecitabine and cisplatin was administered safely to a cohort of 32 HCC patients with measurable extrahepatic disease. Objective response was seen in only 6.3 patients, and the median time to progression was just 2 months. Nonetheless, stable disease was observed in 33.4% and overall survival was 12.2 months.*

Source: Lee JO, et al. Combination chemotherapy with capecitabine and cisplatin for patients with metastatic hepatocellular carcinoma. *Ann Oncology*. 2009;20:1402-1407.

Hepatocellular carcinoma (HCC) commonly presents at an advanced stage and, often, extrahepatic disease precludes local surgical or ablative approaches. Historically, systemic chemotherapy has been of marginal value in HCC patients[1] but, recently, the multikinase inhibitor sorafenib has been shown to extend overall survival in patients who present with advanced disease.[2,3] However, a subgroup analysis of the large phase III studies revealed a relatively low benefit for sorafenib over placebo in patients with extrahepatic spread.[2] Thus, there persists a need for the development of effective treatment for patients with metastatic HCC.

In this context, Lee et al evaluated the efficacy and toxicity of combination chemotherapy with capecitabine and cisplatin (XP) in patients with metastatic HCC. This approach was based upon earlier studies indicating some activity of each drug used as single agents.[4,5] Over a four-year period, they enrolled patients with HCC who had more than one measurable extrahepatic metastatic lesion. Patients received oral capecitabine (2,000 mg/m^2/day) with a schedule of two weeks on and one week off and cisplatin (60 mg/m^2) on the first day of each three-week cycle.

The study cohort consisted of 32 patients with a median age of 53 years. Overall response rate was 6.3% and disease control rate was 34.4%. The median time to progression (TTP) was two months (95% confidence interval [CI] 1.5-2.4) and the median overall survival (OS) time was 12.2 months (95% CI 6.5-17.8). The grade 3/4 hematologic toxic effects included thrombocytopenia (7.6%), neutropenia (4.3%), and anemia (2.1%). The grade 3/4 nonhematologic toxic effects included elevated hepatic aminotransferase (12.9%), jaundice (3.2%), mucositis (3.2%), and nausea (3.2%). There was no treatment-related mortality.

■ COMMENTARY

There are a number of strategies approved, or under development, for the treatment of localized HCC. These include surgical resection, liver transplantation, percutaneous ethanol injection (PEI), and radiofrequency ablation.[1] However, the great majority of patients present with more advanced disease, precluding curative intent approach. Transarterial chemoembolization (TACE) is the recommended first-line, non-curative therapy for inoperable cases,[6,7] but this procedure is indicated for patients who have good liver function, good performance status, no portal hypertension, and no portal vein thrombosis.[8] Sorafenib represents a major advance for the management of this disease, but there remain some for which demonstrable benefit has been only slight. Included are those with extrahepatic metastatic disease.

Based on the observations reported by Lee et al, we remain without a standard systemic approach for patients with metastatic disease. The response rate and TTP in XP-treated patients was only modest. However, the combination showed tolerable toxicity and was associated with a favorable overall survival. Although there remains no standard approach for HCC patients with metastatic disease, XP might be a reasonable approach for some, and might also be explored as an adjunct to primary local approaches in the setting of a clinical trial. ■

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Severe Leukocytosis in Solid Tumor Patients

ABSTRACT & COMMENTARY

By Andrew S. Artz, MD
Division of Hematology/Oncology, University of Chicago
Dr. Artz reports no financial relationships relevant to this field of study.

Synopsis: *Very limited data exist regarding causes and prognosis for extreme leukocytosis among non-hematologic malignancy patients. The authors identified 758 solid-tumor patients with a white blood-cell count exceeding 40,000/uL. The causes included hematopoietic growth factors (69%), infection (15%), corticosteroids (5%), and newly diagnosed leukemia (1%). Thus, 77 (10%) had no cause and were considered to be a paraneoplastic leukemoid reaction (PLR). Among PLR patients, the leukocytosis was primarily a neutrophilia, most had metastatic disease, and 78% died or were enrolled in hospice within 12 weeks. Extreme leukocytosis in solid tumor patients is often related to hematopoietic growth factors. Patients with PLR generally have advanced disease and a poor prognosis.*

Source: Granger J, Kontoyiannis D. Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients: A retrospective, single institution study. *Cancer*. 2009;115:3919- 3923.

EXTREME LEUKOCYTOSIS AMONG PATIENTS WITH NON-hematologic malignancies is an infrequent but troublesome issue.[1,2] The prevalence, causes, and prognostic relevance remain poorly described. Etiologies may include infection, corticosteroids, growth factors, a concurrent hematologic malignancy, an acute inflammatory reaction, or a paraneoplastic leukemoid reaction (PLR).

PLR appears to occur among many tumor types, and is likely driven by colony-stimulating factors such as G-CSF, GM-CSF, interleukin-6 or other growth factors.[2-5] Without specific assays, PLR is a diagnosis of exclusion.

The authors reviewed the electronic medical records of cancer patients with a leukocyte count > 40,000/uL over a three-year period. All patients with hematologic malignancy were excluded. Among 3,770 consecutive patients with extreme leukocytosis, 758 had solid tumors and formed the study cohort. Among these, leukocytosis was related to hematopoietic growth factors in 522 (69%), infection in 112 (15%), steroids or vasopressors in 38 (5%), and leukemia in 9 (1%). The remaining 77 patients (10%) without an obvious cause were categorized as related to PLR.

Among those with infections, half were related to pneumonia and 27% had bacteremia. A broad range of infectious agents were identified. For the 77 patients having extreme leukocytosis related to PLR, the mean WBC was 53,000/uL. Leukocytosis was generally neutrophilic. Almost all (99%) were afebrile, and many had documented white blood cell counts > 20,000/uL at least one month before the white blood-cell count exceeded 40,000/uL indicated a subacute process. Most (78%) had metastatic disease and an unspecified number had large primary tumors. Among PLR patients, 54 patients (76%) died within 12 weeks or were enrolled in hospice and 89% died within one year of the initially documented extreme leukocytosis. The 10% who survived for > one year had leukocytosis that resolved after chemotherapy and/or surgical resection of the tumor.

■ COMMENTARY

The occurrence of leukocytosis in the setting of a non-hematologic malignancy (i.e., a "solid tumor") is not uncommon clinically, but precise estimates are lacking. While many cases will be clearly associated with infection, steroids, or growth factors, a significant and troublesome proportion may have no obvious cause. PLR may be defined as leukocytosis without another cause and related to the underlying malignancy. As with other paraneoplastic syndromes, factors secreted by the tumor appear to drive the leukocytosis. G-CSF and GM-CSF secretion are best described, but other factors may be involved.[2-5] Since no clinical assay is readily available to test the serum or a tumor block, the diagnosis remains a clinical diagnosis of exclusion.

This retrospective review by Granger and Kontoyiannis represents the largest series to date on severe leukocytosis in non-hematologic malignancy patients. They defined extreme leukocytosis as greater than 40,000/uL. They found 758 solid tumor patients with extreme leukocytosis. Hematopoietic growth factors

accounted for 69% of cases of severe leukocytosis, with only 11% a documented infection. Concurrent, newly diagnosed leukemia was uncommon (1%). Seventy-seven (10%) patients without infection, leukemia, or exposure to steroids or growth factors were classified as related to PLR. As expected, most of these patients had metastatic disease. The authors state these related to a variety of tumor types but did not specify the exact range. The majority of PLR patients (76%) died within 12 weeks of finding extreme leukocytosis. Interestingly, a subset of 10% survived for > 1 year, all of whom received effective chemotherapy or radiation therapy.

Unfortunately, the authors do not provide the denominator of the number of solid tumor patients evaluable to estimate the prevalence of extreme leukocytosis. Further, we do not know if the review was restricted to inpatients, outpatients, or both. One would expect quite different findings, at least for causes of extreme leukocytosis between inpatients and outpatients. Finally, the survey of a tertiary cancer center may not reflect the typical population an oncologist sees.

In addition, as a retrospective review, diagnostic classification is limited. Confidently excluding infection as a cause is difficult without prospective evaluation. However, the authors appear to have performed a thorough review to exclude alternative causes for leukocytosis so that diagnosing as PLR appears valid. For example, among those with PLR, only one had a fever and most had less severe leukocytosis more than one month before extreme leukocytosis was detected, providing confidence in excluding underlying infection or other reversible causes. Using an extremely high WBC probably enhanced accuracy for PLR, as clinicians would generally perform an infectious evaluation for severe leukocytosis. The results may represent the "tip of the iceberg," in that less severe leukocytosis is certainly more common. Prospective studies of less severe leukocytosis are clearly warranted to confirm the various causes, to determine the prevalence of PLR, and to determine the prognostic value. More importantly, oncologists could use data to support the extent to which other factors must be excluded before diagnosing PLR among a solid tumor patient with leukocytosis.

In conclusion, extreme leukocytosis (> 40,000/uL) among patients with non-hematologic malignancies is often related to hematopoietic growth factors and less often to infection or steroids. However, in around 10% of the cases, leukocytosis is a paraneoplastic reaction and generally is associated with advanced cancer and a poor prognosis. ■

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Dasatinib for Imatinib-resistant CML: Two Years Later

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a two-year follow-up of an initial report of a multisite, randomized trial comparing dasatinib 70 mg twice daily with imatinib 400 mg twice daily for patients who had proven resistant to lower doses of imatinib (400 mg or 600 mg daily), the improved cytogenetic responses initially reported appear durable, and the estimated progression-free survival was better for the dasatinib-treated patients.*

Source: Kantarjian H, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily. Two-year follow-up of a randomized phase 2 study (START-R). *Cancer*. 2009;115:4136-4147.

PRIOR TO THE APPROVAL OF DASATINIB, AND THEN LATER nilotinib, the treatment options for imatinib-resistant patients with chronic myelogenous leukemia (CML) included dose escalation of imatinib to 800 mg/m^2; there was also some indication that this was

effective in some patients.[1,2] As dasatinib was developed, it was apparent that its potency in vitro was 325-fold greater than imatinib at inhibiting unmutated BCR-ABL,[3] and this, coupled with its activity against imatinib-resistant mutations in vitro,[4] provided rationale for its investigation in patients with imatinib resistance. Indeed, there are now several published reports of the effectiveness of dasatinib in this situation,[5-7] including an earlier report of the current clinical trial.[8] This was a an international multisite, randomized study in which 150 adult patients with chronic phase CML (CP-CML), who were resistant to imatinib at doses of 400-600 mg daily, were enrolled within one calendar year (2005) and treated with either dasatinib 70 mg twice daily (n = 101) or imatinib 400 mg twice daily (n = 49). The primary endpoint of this study was the estimated major cytogenetic response rate (MCyR) at 12 weeks, and it was found that dasatinib treatment resulted in higher MCyR (52%) than high-dose imatinib (33%) (p = 0.023). The study was designed so that patients could cross over to the alternate treatment arm for disease progression or intolerable toxicity. The current report details responses after two years of follow-up. Dasatinib-treated patients continued to demonstrate higher rates of complete hematologic response (93% vs. 82%; p = 0.034), major cytogenetic response (MCyR) (53% vs. 33%; p = 0.017), and complete cytogenetic response (44% vs. 18%; p = 0.0025). At 18 months, the MCyR was maintained in 90% of patients on the dasatinib arm and in 74% of patients on the high-dose imatinib arm. Major molecular response rates also were more frequent with dasatinib than with high-dose imatinib (29% vs. 12%; p = .028). The estimated progression-free survival also favored dasatinib (unstratified log-rank test; p = .0012).

■ COMMENTARY

Thus, the two-year follow-up data demonstrate the efficacy and safety of dasatinib administration for imatinib-resistant CP-CML patients. Dasatinib also demonstrated a positive effect regardless of the prior imatinib dose received by patients. Furthermore, it is notable that dasatinib resulted in complete cytogenetic response (CCyR) in 44% of patients because the experience with imatinib treatment suggests that such a milestone is associated with a low risk of disease progression and improved survival.[9]

The dose of dasatinib (70 mg, twice daily) might be more than is needed. Recently, a phase III, dose-optimization study, with a median treatment duration of eight months in similar patients (i.e., chronic phase CML with imatinib intolerance or resistance),[10] demonstrated that 100 mg once daily and 70 mg twice daily produced similar levels of efficacy, but the single 100 mg dose was associated with a lower incidence of cytopenias and a significantly lower incidence of grade 3/4 thrombocytopenia and pleural effusion. In fact, reading the details of the current report, because of the planned dose modifications, the average median dose of dasatinib for those initially prescribed at 70 mg twice daily (140 mg) was approximately 100 mg. Thus, it is apparent that the 100 mg, once-daily dose has a better risk/benefit ratio and should be considered the optimal choice when using this drug in this situation. ■

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Bisphosphonates and Overall Survival for Prostate Cancer Patients

ABSTRACT & COMMENTARY

By William B. Ershler, MD

Synopsis: *In a late analysis of two trials conducted to test whether an oral bisphosphonate would influence outcomes in patients with prostate cancer, it is apparent that for those with metastatic disease, treatment resulted in improved overall survival. However, for those patients who did not have metastatic disease, bisphosphonate treatment had no effect on overall survival. The study supports the role of drugs in this class for patients with metastatic prostate cancer, but it remains to be determined whether oral agents, such as clodronate, will be as effective as the newer agents that have become available since the initiation of this trial, over 15 years ago.*

Source: Dearnaley DP, et al. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: Long-term overall survival results from the MRC PRO4 and PRO5 randomized controlled trials. *Lancet Oncol*. 2009;10:872-876.

In the mid 1990s, the Medical Research Council (MRC) sponsored two trials to determine the effectiveness of an oral, first-generation bisphosphonate (clodronate) for patients with prostate cancer. The first trial, PR04, evaluated patients with non-metastatic disease, whereas the second, PR05, evaluated those with metastatic disease. The primary reports for both trials have been published,[1,2] and the purpose of the current report was to present the long-term data, particularly with regard to overall survival.

Men with metastatic disease (n = 311) were recruited to PR05 between 1994 and 1998 and those with non-metastatic disease (n = 508) to PR04 from 1994 to 1997. All men were treated according to the recruiting site's standard practice at the time: for metastatic disease, all men were either starting or responding to long-term hormone therapy; for non-metastatic disease, most men had radiotherapy, hormone therapy, or both. Men were randomly assigned to take four tablets per day of sodium clodronate (total daily dose, 2080 mg) or matching placebo for up to three years (metastatic disease) or five years (non-metastatic disease). Long-term overall survival was assessed on an intention-to-treat basis in all men at sites in England and Wales using data from the National Health Service Information Center, which held data for 278 of the 311 men in the PR05 trial and 471 of the 508 men in the PR04 trial. PR04- and PR05-enrolled subjects who lived in Scotland or New Zealand were not included in this final analysis because their records were not accessible through the National Health Service Information Center.

Of the 278 men with metastatic disease, 258 (93%) died. Evidence of a benefit for those with metastatic disease from use of sodium clodronate compared with placebo was seen in overall survival (hazard ratio [HR] 0.77, 95% CI 0.60-0.98; $p = 0.032$). Of the 471 men with non-metastatic disease, 281 (60%) were reported to have died and, in this cohort, there was no evidence of improvement in overall survival with clodronate compared with placebo (HR 1.12, 0.89-1.42; $p = 0.94$).

COMMENTARY

These trials, first launched about 15 years ago, were among the first to look at the role of bisphosphonates in the management of prostate cancer. Since then, a number of studies have demonstrated the value of drugs in this class, particularly for patients with myeloma or breast cancer. For patients with multiple myeloma, it has long been known that intravenous pamidronate was a useful treatment for disease-associated hypercalcemia. However, reduced bone pain, improved quality of life, and possibly even slower tumor growth and improved survival have been reported, and the more general use of bisphosphonates in this disease is reflected by the recent American Society of Clinical Oncology guidelines.[3] Similarly, for patients with breast cancer, the routine use of IV bisphosphonates has lessened the impact of skeletal complications and skeletal metastases, thereby decreasing the frequency of pathologic fractures, surgery for fracture or impending fracture, need for RT, spinal cord compression, and hypercalcemia. They have not been shown to have any survival impact in this disease, and the role of oral bisphosphonates remains unclear.[4]

The rationale for use in prostate cancer is less empiric, since metastatic disease is usually "blastic" and not "lytic." Nonetheless, fractures do occur and, as evidenced by the current report, bisphosphonates have been studied in men with prostate cancer for the purpose of delaying skeletal progression, protecting the bone from loss in density that can accompany treatment with androgen ablation therapy, and for palliation of bone pain. Furthermore, from the current report, it appears that overall survival is improved for patients with metastatic disease (but not for those treated for non-metastatic disease). It is also notable that an oral bisphosphonate was shown to be effective.

In more recent trials, zoledronic acid administered intravenously to patients with metastatic disease was shown to reduce skeletal fractures in patients with hormone-resistant prostate cancer[5] but, once again, when used in those with early disease, there is not a clear indication of efficacy.[6]

In this context, the late analysis provided by this current report supports a role for bisphosphonate therapy in the management of patients with prostate cancer and bone metastases. Whether oral agents, such as clodronate (not available in the United States), will be comparable to the more powerful drugs in this class, such as zoledronate, remains to be determined. Furthermore, it remains an appealing concept that the early introduction of such drugs may be associated with reduced or delayed skeletal metastases when administered to patients with a high likelihood of developing metastases, but this has yet to be established by appropriate clinical trial. ■

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CME Question

13. The analysis of the data from the MRC-sponsored trials investigating the use of clodronate in patients with prostate cancer indicated improved overall survival for those with:
a. no evidence for metastatic disease at the time of initial treatment.
b. metastatic disease at the time of initial treatment.
c. all of the patients (non-metastatic or metastatic) at the time of initial treatment.
d. None of the patients.

14. For patients with chronic phase CML and demonstrated resistance or intolerance to imatinib, switching to dasatinib (70 mg, twice daily) when compared to increasing the imatinib dose to 400 mg twice daily, was associated with:
a. improved rate of complete hematological response.
b. improved rate of major cytogenetic response.
c. improved rate of complete cytogenetic response.
d. improved progression-free survival.
e. All of the above

15. What did the authors show regarding extreme leukocytosis > 40,000/uL among patients with non-hematologic malignancies?
a. Around 10% had a paraneoplastic leukemoid reaction (PLR), defined as no other clear cause.
b. An extensive evaluation revealed occult infections in all patients.
c. A high incidence of newly diagnosed chronic leukemia was found.
d. The leukocytosis often leads to leukostasis complications such as cerebrovascular accidents and myocardial infarction.

16. In the Phase II trial by Lee et al in which patients with measureable metastatic HCC, the objective response rate and overall survival were:
a. 5%-10% and 6 months, respectively.
b. 5%-10% and 12 months, respectively.
c. 30%-40% and 12 months, respectively.
d. 30%-40% and 24 months, respectively.

17. Sunatinib treatment is associated with hypertension in approximately what percent of renal carcinoma patients?
a. 5%
b. 15%
c. 50%
d. 80%

Answers: 13. (b); 14. (e); 15. (a); 16. (b); 17. (b)

CME Objectives

The objectives of *Clinical Oncology Alert* are:
- to present the latest information regarding diagnosis and treatment of various types of cancer;
- to present prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- to describe new advances in the field of oncology.

In Future Issues:

IMiDs and Colon 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, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
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The short-term risks of bariatric surgery

Source: The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium; et al. *N Engl J Med* 2009;361:445-454.

Long-term benefits from bariatric surgery have been definitely established. Nonetheless, perioperative risks associated with bariatric surgery are not insignificant, especially since persons undergoing bariatric surgery often suffer comorbidities of diabetes, hypertension, and dyslipidemia.

The LABS Consortium performed an observational study of short-term outcomes subsequent to bariatric surgery in the United States. From 2005 to 2007, data supplied by 10 different clinical sites (combined total n = 4776 first-time bariatric surgical procedures) provided information on the composite endpoint of 30-day major adverse outcomes (death, DVT, postoperative intervention, and extended hospital stay). Roux-en-Y bypass was performed on approximately 70% of subjects; the majority of the other patients underwent gastric banding.

Death occurred in 0.3% of subjects within 30 days; an additional 4% of subjects experienced at least one adverse event included in the composite primary endpoint. A previous history of DVT was associated with greater likelihood to incur a postoperative adverse event; additionally, the higher the BMI (mean BMI in this report = 46.5 kg/m^2), the greater the frequency of adverse events.

Bariatric surgery has significant associated risks. For most appropriately selected patients, the long-term benefits far outweigh these risks, but patients need to be informed of the potential for serious adverse outcomes. ■

Parsing the death toll of COPD

Source: Zvezdin B, et al. *Chest* 2009; 136:376-380.

Worldwide, COPD is the fourth leading cause of death; unless current trends reverse, the toll will rise. Mortality rates associated with hospitalized acute exacerbations of COPD have been as high as 30%; the mortality in the 1 year after hospitalization is as high as 43%. Some of this mortality is directly attributable to COPD; however, other prominent comorbidities (e.g., CVD, pulmonary embolism) are also responsible. Often, because post-mortem examination is limited, the cause of death can only be opined. To provide greater clarity, Zvezdin et al report on autopsies of 43 patients who died within 24 hours of COPD hospital admission.

The mean age of the study subjects was 70. According to autopsy results, more than half of the deaths were attributed to diagnoses other than COPD: heart failure (in 37%) and pulmonary embolism (in 21%). The authors also separate pneumonia as a "non-COPD" cause of death (occurring in 28%), defining COPD death as those individuals who die of respiratory failure due to COPD progression (14%).

If these results (from a Serbian tertiary care university hospital specializing in pulmonary diseases) are generalizable to U.S. populations, clinicians will need to exercise greater vigilance, enhanced preventive techniques, and intensified intervention for potentially fatal comorbidities when patients are admitted for acute COPD exacerbation. ■

Vardenafil and premature ejaculation

Source: Aversa A, et al. *Int J Impot Res* 2009;21:221-227.

Although clinicians are much more familiar with erectile dysfunction, over the lifespan premature ejaculation (PEJ) is more common. A much smaller percentage of men with PEJ seek help, attributable to factors such as embarrassment, absence of available FDA-approved medications, and lack of public awareness of PEJ as an important sexual health dysfunction.

The technical definition of PEJ is a matter of controversy, although most experts agree that consistent unintended/unwanted ejaculation within 1 min that causes distress is satisfactory for the diagnosis.

The most commonly used metric for measuring PEJ is intravaginal ejaculatory latency time (IELT), or the time after vaginal intromission at which ejaculation occurs. Population studies have suggested that in established heterosexual couples, typical IELT is 6-10 min. Subjects enrolling in PEJ trials typically have an IELT of 30-90 sec, or even ejaculation ante portis (prior to intromission). The above definition would, by construction, seem to exclude gay men or ejaculation involving other orifices/body parts, but the similarities of diagnosis and management of PEJ in gay couples suggest that IELT, while at times anatomically inconsistent, incorporates the broader concepts

of early ejaculation in a variety of sexual settings.

SSRIs have an established role in management of PEJ. Success with SSRIs is greatest when taken on a maintenance schedule; however, patients would generally prefer as-needed administration, all things being equal.

Aversa et al studied men with PEJ (n = 42), all of whom consistently experienced IELT < 1 min. Patients were randomized (double-blind) to placebo or vardenafil 10 mg administered 15-30 min before sexual activity. The primary outcome was change in IELT.

Use of vardenafil provided a significant improvement in IELT (from 36 sec to 4.5 min) compared with placebo (IELT went from 42 sec to 54 sec). The tolerability of vardenafil is well established. Vardenafil appears to be a viable option for PRN treatment of PEJ. ■

Testosterone, depression, and hypogonadal men

Source: Shores MM, et al. *J Clin Psychiatry* 2009;70:1009-1016.

SUBTHRESHOLD DEPRESSION (sDEP), also known as minor depression, occurs in as many as 1 of 4 elderly patients. Although by definition the symptom burden of sDEP is less than major depressive disorder (MDD), it is more common than MDD and is still associated with diverse negative outcomes including decreased quality of life and function, and increased morbidity, mortality, and health care utilization.

Symptoms of hypogonadism include fatigue, decreased libido, and dysphoria, any of which may also be manifestations of depression. Shores et al studied the impact of testosterone replacement in hypogonadal men (total testosterone < 280 ng/dL) meeting DSM-IV criteria for sDEP.

This double-blind trial randomized adult men (n = 33) to testosterone gel 7.5 g/d or placebo for 12 weeks. The primary outcome was change in the HAM-D depression score.

At the end of the trial, testosterone-treated men had a significantly improved HAM-D score compared to placebo, and the percent with remitted sDEP was dramatically different (52.9% vs 18%) favoring testosterone.

No serious testosterone-attributable adverse effects were seen. Testosterone replacement shows benefit for improving sDEP in hypogonadal men. ■

Aspirin after colon cancer diagnosis

Source: Chan AT, et al. *JAMA* 2009; 302:649-658.

MOST COLORECTAL CANCERS OVEREXPRESS cyclo-oxygenase 2 (COX-2). Primary prevention with aspirin (ASA) is associated with reduced risk for colon cancer and colonic adenoma. Secondary prevention with ASA (and celecoxib) is effective in reducing risk of new adenomas in persons who have been previously diagnosed with colonic neoplasia. Because ASA has recognized toxicities, including cerebral hemorrhage and GI bleeding, it is important to determine whether use of ASA in high-risk subjects (persons previously diagnosed with colon cancer) provides net benefit for overall and/or colon cancer-specific mortality.

The Physicians' Health Study and the Nurses' Health Study are observational studies, providing a window of observation for the role of ASA in both primary and secondary prevention. A cohort within both populations took maintenance ASA prior to any diagnosis of colon cancer, and further information about effects of ASA in persons who developed colon cancer and continued with ASA subsequent to the cancer diagnosis (vs subjects who did not take ASA after a diagnosis of colon cancer) is presented here.

Of subjects who developed colon cancer (n = 1279) in these two study populations (combined), there were statistically significant differences in total mortality (35% vs 39%) and colon cancer-related mortality (15% vs 19%) favoring use of ASA. Concordant with current thinking on the putative mechanism of ASA benefit, the risk reduction was greatest in persons whose colon cancer overexpressed COX-2. Despite these favorable results, the authors caution that routine utilization of ASA post colon cancer might be considered premature since these data are observational; placebo-controlled randomized trials are needed for confirmation. ■

The Emperor's new vertebroplasty?

Source: Buchbinder R, et al. *N Engl J Med* 2009;361:557-568.

VERTEBROPLASTY (VERT) HAS RECENTLY enjoyed increased popularity as treatment for painful osteoporotic vertebral fractures. Observational or open-label studies have provided most of the supportive information. Enthusiasm for other previously popular surgical procedures has been dampened when double-blind randomized trials have failed to confirm positive outcomes: Two randomized trials in the last 7 years comparing arthroscopy for knee osteoarthritis found no outcomes difference when compared to placebo.

Buchbinder et al performed a randomized, double-blind, sham procedure-controlled trial of VERT for painful osteoporotic fracture in 78 participants. The primary outcome was pain reduction, which did not differ at weeks 1, 3, or 24 after treatment between intervention and sham intervention.

The Buchbinder study was published immediately preceding another VERT trial in the *New England Journal of Medicine* examining pain and disability at 1 month post intervention, which similarly did not find positive outcomes. These trials call for closer evaluation of the (potential) value of VERT. ■

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WHO Issues Global Alert on Antiviral Use

In this issue: WHO recommendations for antiviral use for H1N1 flu; antibiotic use trends for acute respiratory tract infection; denosumab clears FDA Expert Panel; FDA Actions.

Antiviral Recommendations for H1N1

The World Health Organization (WHO) has issued a global alert and response regarding the use of antivirals for pandemic H1N1 flu, reiterating that antivirals should be used to prevent severe illness and death in children and adults. The neuraminidase inhibitor oseltamivir (Tamiflu®) is recommended for patients who initially present with severe illness or whose condition begins to deteriorate. H1N1 remains sensitive to the neuraminidase inhibitors such as oseltamivir despite isolated reports of resistance earlier this year. The WHO recommends that clinicians in communities where the virus is circulating widely assume that patients with flu-like symptoms have H1N1 and not wait for laboratory confirmation. Most patients with pandemic flu experience typical flu symptoms and recover within a week. These patients do not need antivirals. But in patients with severe illness, studies have shown that early treatment, within the first 48 hours, is associated with better clinical outcomes. WHO also states that if oseltamivir is unavailable zanamivir (Relenza®) may be used in its place. This recommendation applies to all patient groups including children and pregnant women. The WHO statement comes in response to an article in the *British Medical Journal* suggesting neuraminidase inhibitors provide minimal benefit for children with seasonal influenza and have little effect on asthmatic exacerbations or use of antibiotics (Shun-Shin M, et al. *BMJ* 2009;339:b3172). ■

Antibiotic Use Declines Overall, While Use of Broad-Spectrum Increases

Physicians are prescribing fewer antibiotics for acute respiratory tract infections (ARTIs), but if an antibiotic is used, it is more likely to be a broad-spectrum drug. Using data from 1995 to 2006, antibiotic trends were reviewed from a national database for ARTIs, which included otitis media (OM). Children younger than age 5 were seen less frequently for ARTI than in the past, and they were less likely to be prescribed an antibiotic (36% reduction; 95% confidence interval [CI], 26%-45%). Among children age 5 or older, ARTI visit rates remained stable but antibiotic prescription rates decreased by 18% (95% CI, 6%-29%). Excluding otitis media, antibiotic prescription rates decreased by 41% among all age groups. Prescription rates for a penicillin, cephalosporins, and sulfonamide/tetracycline decreased while the rate of prescriptions for azithromycin increased, making it the most commonly prescribed macrolide for ARTI and OM. Among adults, quinolone prescriptions also increased. The authors conclude that overall antibiotic prescription rates for ARTI decreased in the last 10 years; however, prescription rates for

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broad-spectrum antibiotics increased significantly (Grijalva CG, et al. *JAMA* 2009;302:758-766). This study points out the success of multiple campaigns to decrease antibiotic use for ARTIs, which are primarily caused by viruses. However the increasing use of broad-spectrum antibiotics is concerning. ■

Denosumab Receives Conditional Approval from FDA Expert Panel

Denosumab is a new human monoclonal antibody that suppresses osteoclast function and thus inhibits bone resorption. It is being evaluated by the FDA for treatment of osteoporosis in men and women, and although it has not yet been approved, a recent FDA Expert Panel has given conditional approval paving the way for full FDA approval this fall. Two recently published, industry-sponsored studies suggest the drug is effective in 2 different populations. In the first study, more than 1400 men receiving androgen-deprivation therapy for nonmetastatic prostate cancer were randomly assigned to receive denosumab 60 mg SQ every 6 months or placebo for 2 years. The primary endpoint was change in bone mineral density (BMD) at the lumbar spine, with secondary endpoints of change in BMD in the hip as well as fracture incidence. At 24 months, BMD increased in the lumbar spine with denosumab (5.6% increase vs 1% decrease for placebo; $P < 0.001$). BMD was also increased in the total hip, femoral neck, and distal radius, and the effect was maintained for 36 months. New fracture rate was also decreased with treatment (1.5% vs 3.9% with placebo; $P = 0.006$). Rates of adverse events were similar in both groups (Smith MR, et al. *N Engl J Med* 2009;361:745-755).

In the second study, 7868 postmenopausal women with low BMD were randomized to denosumab 60 mg SQ every 6 months or placebo for 36 months. The primary endpoint was new vertebral fractures. Denosumab was associated with a reduction in vertebral fractures (2.3% vs 7.2% placebo; $P < 0.001$), a reduction in hip fractures (0.7% vs 1.2% placebo; $P = 0.04$), and a smaller reduction in nonvertebral fractures. There was no increase in risk of cancer, infection, cardiovascular disease, delayed fracture healing, hypocalcemia, or osteonecrosis of the jaw in this study (Cummings SR, et al. *N Engl J Med* 2009; 361:756-765).

These last findings are important because the FDA's Expert Panel expressed concerns about infection and cancer data in giving a recommendation to approve denosumab when the FDA votes on the drug in October. If approved, which seem likely, denosumab will be marketed by Amgen under the trade name Prolia™. ■

FDA Actions

The FDA is requiring new boxed warnings on TNF-blockers regarding the risk of lymphoma and other malignancies in children and adolescents who have received the drugs. The new labeling will include warnings regarding cases of leukemia in adults, adolescents, and children, as well as new onset psoriasis. The labeling will also include a revised Medication Guide to reflect the safety information. Products subject to the new boxed warning are infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), and the recently approved agents certolizumab pegol (Cimzia®) and golimumab (Simponi™). These TNF-blockers are used to treat rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis. The warning is based on reports of nearly 50 cases of various cancers associated with the drugs, of which half were lymphomas.

The FDA has approved a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. Bristol-Myers Squibb and AstraZeneca's saxagliptin (Onglyza™) is the second DPP inhibitor approved after sitagliptin (Januvia®). It is the first drug approved since the FDA changed its standards for diabetes drug approvals, requiring evidence of cardiovascular safety. While saxigliptin has not shown evidence of higher rates of cardiovascular disease, the FDA is requiring post-marketing studies to specifically look at cardiovascular safety in high-risk populations. Saxigliptin is dosed once daily and is approved as monotherapy or in combination with metformin, sulfonylureas, or thiazolidinediones.

The FDA has announced that it is reviewing adverse event reports of liver injury in patients taking the weight-loss drug orlistat, marketed as the prescription drug Xenical® and over the counter as Alli®. The agency has received 32 reports of serious liver injury in patients taking the drug in the last 10 years. Of these, 6 resulted in liver failure. Almost all of the reports are from outside the United States. The FDA is not recommending patients discontinue the drug, but is suggesting that those who have used orlistat should consult a health care professional if they develop jaundice, fever, fatigue, brown urine, or other symptoms of liver injury. ■