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

ILLUSTRATIVE CASE SERIES

Renal Cancer

By Bindu Kanapuru, MD
University of Maryland; National Institute on Aging
Dr. Kanapuru reports no financial relationships relevant to this field of study.

A 61-YEAR-OLD MAN PRESENTED TO THE EMERGENCY room with back pain of approximately one month duration. His medical history was significant for hypertension, for which he received diltiazem 180 mg daily. His weight had been stable at 175 lbs and, other than back pain, he suffered no constitutional symptoms. He has worked as an auto mechanic for 40 years. He smokes approximately 20 cigarettes a day and has done so for all of his adult years. He has no family history of cancer.

In the emergency room, he appeared robust, with good color, normal vital signs, and no palpable lymphadenopathy. His pain was described as constant, not related to exertion and was to the right of midline at the level of the lower ribs.

Laboratory studies of note were a slightly reduced hemoglobin concentration (11.8 g/dL) and a white blood count of 9.5 K/cu mm. Platelet count was normal. Serum chemistries revealed an alkaline phosphatase of 206 IU/mL, with normal levels of LDH, AST, ALT, and amylase. Serum creatinine was 1.2 mg/dL and serum calcium was 9.4mg/dL.

Chest X-ray revealed two nodules, one in each lung, each approximately 2 cm in diameter. Computerized tomography (with contrast) revealed a solid right-renal mass 4 cm in diameter, enhanced by contrast. CT-guid-

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ed biopsy of lung nodule revealed pathology consistent with clear cell-renal carcinoma. Bone scan revealed no evidence for osseous metastaes. Patient underwent nephrectomy and was referred for further management.

CASE DISCUSSION

Incidence of renal-cell carcinoma has been increasing by gradually over the past several decades, possibly related to increased incidental diagnosis on imaging studies for atypical symptoms, such as with our current patient. The classical triad of flank pain, hematuria, and renal mass is seen in less than 10% of patients. Most patients remain asymptomatic until the disease is advanced, or may present with symptoms related to the metastatic disease. Approximately one-third of patients with renal cell carcinoma will have metastatic disease at presentation. The most frequent sites are the lung, followed by lymph nodes, bone, brain, and liver. The finding of pulmonary nodules in a patient with a contrast-enhancing solid renal mass is highly suggestive of renal cell cancer. The incidence of malignancy increases with the size of the lesion (93% in tumors ≥ 7 cm),[1] but a smaller size does not preclude metastatic disease, and even patients with tumors ≤ 4 cm have a 5.2% prevalence of metastasis at presentation.[2] In patients with possible metastatic disease, biopsy of the metastatic disease is appropriate to confirm the diagnosis and identify the histology. CT is the preferred modality for staging, and a bone scan in patients with symptoms suggestive of possible metastasis.

Before I discuss further management, it is worth mentioning the role of nephrectomy and metastasectomy in patients with metastatic disease. Two identical randomized trials, SWOG 8949/EORTC 30947, addressed the role of nephrectomy for those with metastatic disease. Patients with advanced renal cell cancer (T4NOMO OR any T, N with M1 disease) were randomized to nephrectomy followed by interferon alpha-2b vs. interferon alpha-2b alone. In combined analysis of both trials, there was a 31% decrease in risk of death with nephrectomy. Median survival was 7.8 months for IFN only vs. 13.6 months in the nephrectomy plus IFN arm ($p \leq .01$). Patients with lung as the only site of metastasis had better median survival with nephrectomy than those with metastatic disease at other sites. Response rates with interferon alpha-2b also were better in patients who underwent nephrectomy. The role of nephrectomy in patients being treated with targeted therapy is less clear.[3] Resection of lung metastasis also is a reasonable option in this patient, since this is the only site of metastatic disease and long-term remission is possible, although he is likely to relapse at the original site.[4]

Cytokine treatment should be considered in appropriate patients (adequate organ function and good performance status) as it is the only therapy proven to produce durable remissions in these patients. In addition, certain clinical factors, like presence of clear cell histology, a single metastatic site, prior nephrectomy, and other features are associated with favorable response to cytokine treatment and may be used to select patients. Although no survival benefit has been seen in RCTs with interferon alpha alone or other schedules and routes of IL-2 administration, high-dose intravenous IL-2 has demonstrated consistently superior response rates and prolonged remissions in those achieving complete response and is, therefore, the cytokine treatment of choice.[5] High-dose IL-2 can cause significant hemodynamic changes, as well as toxicities related to multiple organs, and close monitoring is essential for early detection and management, according to current recommendations.[6]

Despite the experience with high-dose IL-2, most patients nowadays are treated with anti-angiogenic agents or multikinase inhibitors, which affect VEGF (vascular endothelial growth factor) directly or its downstream pathways. Sunitinib, bevacizumab in combination with interferon alpha, and pazopanib have category 1 recommendation for first-line treatment of advanced renal cell cancer with clear-cell histology. Treatment is associated with significant improvement in progression-free survival (8.5-11 months vs. 5 months with placebo), but objective response rates are only about 30%.[7] In patients with more than three of six poor prognostic factors, low Karnofsky performance status (60%-70%), high lactate dehydrogenase level (> 1.5 x normal), low hemoglobin level,

high serum calcium, more than one metastatic site, and < 1 year between diagnosis and start of therapy temsirolimus, an mTOR inhibitor significantly improved overall survival compared to interferon alpha.[8]

So in our patient with clear cell histology, prior nephrectomy, excellent performance status, and lung metastasis, high-dose IL-2 is a reasonable option under close monitoring. It also is reasonable to consider starting treatment with molecularly targeted therapy. Close monitoring of blood pressure will be required since hypertension is a common side effect of antiangiogenic agents and can be life threatening in 10% of cases. In addition, as diltiazem and verapamil are contraindicated due to their effects on sutent through the cyp3A4 pathway, an alternate antihypertensive drug must be initiated. ■

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RAPID REVIEW

Breast Cancer in Men

William B. Ershler, MD

Breast cancer occurs in approximately 1 in 100,000 men each year,[1] a rate that is slightly less than 1% of that in women. Although the rate might be rising somewhat,[1-3] the absolute number of cases remains low (less than 2000 new cases per year in the United States).[1] Although the majority of patients will have no discernible risk factor, breast cancer is more common in men who have a family history of breast cancer, who have sustained a bone fracture after the age of 45 years old, and who are obese.[4] In a meta-analysis,[5] men with the following characteristics also were found to be at increased risk: never married, Jewish ancestry, gynecomastia, history of testicular or liver disease, or prior chest wall irradiation. Much of those with a family history of breast cancer can be attributed to inherited mutations in BRCA (both 1 and 2) and, as with women, those who carry these mutations are likely to be diagnosed in their 30s and 40s.[6,7]

Male breast cancer has certain histologic and biochemical features that are different from breast cancer in females. An overwhelming majority exhibit invasive ductal histology (approximately 90%), whereas lobular histology is rare.[8-10] Almost 90% will express estrogen receptor and 80% progesterone receptor,[2,8] whereas Her2 overexpression occurs about half as frequently as in females (approximately 10%).[11,12]

Typically, male breast cancer will present as a small subareolar painless mass with nipple involvement in 40%-50% of cases.[13,14] In contrast, gynecomastia is more often bilateral, less well defined, and tender. Mammography also is helpful in distinguishing gynecomastia from tumor, but any suspicious mass should be biopsied. As with breast cancer in women, staging involves assessment of tumor size, axillary node involvement, and presence of distant metastases. Surgical approach also is similar, with the modified radical mastectomy and axillary node dissection the most commonly undertaken procedure. A negative sentinel lymph node biopsy precludes the necessity for axillary node dissection unless there is clinical suspicion of involvement based on either physical exam or imaging studies.

Evidence on which to balance therapeutic options is not available for male breast cancer and, thus, decisions are most often extrapolated from data derived from clinical trials that define management stage-matched

female breast cancer. Because the majority of cases are hormone-receptor positive, adjuvant tamoxifen is widely prescribed, and retrospective analyses would suggest this provides survival advantage.[2,15] Similarly, there is very little data on which to base the use of adjuvant chemotherapy for breast cancer in men. Thus, under circumstances in which chemotherapy would be recommended for female breast cancer, similar recommendations are typically offered to men.

The SEER database was recently examined by Harlan and colleagues to define clinical features and survival in 512 male breast cancer patients diagnosed in 2003 and 2004.[14] They found that among men who had invasive disease, 86% underwent mastectomy, 37% received chemotherapy, and 58% received hormone therapy. In multivariate analysis, tumor size ($p = .01$) and positive lymph node status ($p < .0001$) were associated positively with the use of chemotherapy, whereas age group ($p < .0001$) and current unmarried status ($p = .01$) had negative associations. As would be expected, factors associated with poor prognosis were associated with the selection of chemotherapy.

Thus, there remain numerous questions regarding male breast cancer. These include a finer definition of risk factors and a more thorough understanding of the biological differences that exist when cancer develops in the male breast. It is unlikely that we will see randomized clinical trials to distinguish an optimal therapeutic approach, but hopefully, with a better understanding of the genetic and molecular antecedents, specific targeted therapy will become available. In the meantime, male breast cancer treatment decisions will require abstraction from the experiences in women with the disease. ■

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ABSTRACT & COMMENTARY

Erlotinib Maintenance for Patients with Advanced NSCLC

William Ershler, MD

Synopsis: *In a multinational trial of erlotinib (Tarceva®) for patients with advanced NSCLC following conventional chemotherapy, improved progression-free and overall survival were demonstrated. The improvement was approximately one week for PFS and one month for OS. However, for the subset with demonstrable activating mutations in the EGFR gene, the benefit of erlotinib treatment was more substantial.*

Source: Cappuzzo F, et al. Elotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomized, placebo-controlled phase 3 trial. *Lancet Oncol.* 2010;**11**:521-529.

First-line chemotherapy for advanced non-small cell lung cancer (NSCLC) is usually limited to four to six cycles, and results in responses or stable disease in about 80% of cases. Nonetheless, additional therapy (beyond four to six cycles) is associated with higher levels of toxicity without improving results, and overall survival remains approximately 11-12 months.[1,2] When disease recurs, it is often very aggressive and associated with a decline in performance status, such that nearly half of those affected are not considered suitable for second-line chemotherapy.[3,4] Accordingly, maintenance therapy, administered immediately after first-line treatment for those who responded (including those with stable disease) has been the focus of recent investigative interest.[5]

The oral epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib has proven efficacy and tolerability in second-line NSCLC.[6,7] In a multinational phase 3, placebo-controlled trial conducted at 110 sites in 26 countries, and sponsored by Hoffmann-LaRoche, the use of erlotinib as maintenance therapy in patients with non-progressive disease following first-line platinum doublet chemotherapy was tested. Between December 2005 and May 2008, 1,949 patients were included in the run-in phase. For this, participating physicians chose one of seven platinum-based combinations for four cycles of initial chemotherapy. Upon completion of this initial therapy phase, 889 patients who did not have progressive disease were entered into the main study and were randomly allocated (1:1) to receive erlotinib (150 mg/day; n = 438) or placebo (n = 451) until progression or unacceptable toxicity. Patients were stratified by EGFR immunohistochemistry status, stage, Eastern Cooperative Oncology Group performance status, chemotherapy regimen, smoking history, and region. Co-primary endpoints were progression-free survival (PFS) in all analyzable patients irrespective of EGFR status and PFS in patients whose tumors had EGFR protein over expression, as determined by immunohistochemistry.

Of these patients, 884 patients were analyzable for PFS; 437 in the erlotinib group and 447 in the placebo group. After a median follow-up of 11.4 months for the erlotinib group and 11.5 months for the placebo group, median PFS was significantly longer with erlotinib than with placebo: 12·3 weeks for patients in the erlotinib group vs. 11·1 weeks for those in the placebo group (HR 0.71, 95% CI 0.62–0.82; $p < 0{\cdot}0001$). PFS also was significantly longer in patients with EGFR-positive immunohistochemistry who were treated with erlotinib (n = 307), compared with EGFR-positive patients given placebo (n = 311; median PFS 12·3 weeks in the erlotinib group vs. 11·1 weeks in the placebo group; HR 0.69, 0.58–0.82; $p < 0{\cdot}0001$). As expected among the small subset (n = 40), in which tumor DNA had demonstrable EGFR mutations, erlotinib maintenance provided the greatest benefit (HR 0.10, (0.04-0.25).

The most common grade 3 or higher adverse events were rash (37 [9%] of 443 patients in the erlotinib group vs. none of 445 in the placebo group) and diarrhea (seven [2%] of 443 patients vs. none of 445). Serious adverse events were reported in 47 patients (11%) on erlotinib compared with 34 patients (8%) on placebo. The most common serious adverse event was pneumonia (seven cases [2%] with erlotinib and four [< 1%] with placebo).

■ COMMENTARY

The question of maintenance therapy for patients

achieving benefit from initial platinum-based chemotherapy for advanced NSCLC has been raised before. Fidias and colleagues recently reported their experience with docetaxel given either immediately after initial platinum-based therapy compared with delayed (i.e., at the time of clinically apparent progressive disease). They found that overall survival was not different between the two groups, but 37% in the delayed group never received the planned therapy.[3] In a similar trial in which pemetrexed was compared with placebo, approximately one-third of those randomized to placebo received only the induction therapy, whereas over half of the patients who received pemetrexed were treated with a third line of chemotherapy upon clinically recognized progression.[8]

In the current report, erlotinib was shown to be both well tolerated and successful in prolonging PFS and overall survival (OS), albeit by only small margin (PS, 12.3 weeks vs. 11.1 weeks for those receiving placebo; OS 12 months vs. 11 months for those receiving placebo). These improvements were apparent in the overall population, irrespective of EGFR status, and also irrespective of sex, ethnic origin, histology, or smoking status.

Should all NSCLC patients who have responded or achieve stable disease after initial chemotherapy receive erlotinib? On the positive side, it appears the drug is well tolerated and briefly prolongs PFS and OS. However, enthusiasm for such an approach must be balanced by fiscal reality; this is an expensive drug and the benefits, although statistically significant, are small. In the United States, three months of erlotinib retails at just short of $15,000. With the number of close to 200,000 new lung cancer patients each year, only a substantial fraction would be eligible. Conservatively, assuming this as a standard approach, it would cost over one billion dollars annually.

Erlotinib is an effective drug, with its greatest benefit for those patients who harbor discernible EGFR mutations. Its use in such patients is clearly justified. Its benefit for patients without EGFR mutation is present, but marginal, and there remains a need for developing more effective maintenance treatment for NSCLC. ■

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ABSTRACT & COMMENTARY

PET Scan Predicts Survival After Transplant for Relapsed Diffuse Large B-Cell Lymphoma

Andrew Artz, MD

Division of Hematology/Oncology, University of Chicago

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

Synopsis: *High-dose chemotherapy and autologous hematopoietic stem cell transplant (ASCT) is standard therapy for relapsed or refractory diffuse large B-cell lymphoma after salvage chemotherapy. In this retrospective study of 39 patients with diffuse large B-cell lymphoma (DLCL) who had undergone ASCT, the authors assessed outcomes based on post-salvage pre-ASCT PET imaging. PET scans were positive in 17 (44%) and negative in 22 (56%) after salvage. A negative PET scan predicted for less relapse and better three-year OS at 81%, compared to 39% for PET-positive patients. Results are excellent for patients achieving PET negativity prior to ASCT; the optimal approach for PET-positive patients remains undefined.*

Source: Dickinson M, et al. Improved survival for relapsed diffuse large B-cell lymphoma is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy. *Br. J. Haematol.* 2010;150:39-45.

High-dose chemotherapy, followed by reinfusion of autologous hematopoietic stem cells (ASCT), represents the standard of care for patients relapsing from diffuse large B-cell lymphoma (DLCL) with chemosensistive disease.[1] Chemosensitivity to treatment after relapse remains a critical determinant to outcome.[2] More precise determination of disease responsiveness may be obtained employing ^{18}fluoro-2-deoxy-D-glucose positron-emission tomography (FDG-PET). Lack of PET response early after CHOP chemotherapy predicts for poor outcome.[3] The authors evaluated the utility of PET scanning for relapsed DLCL prior to ASCT.

In this retrospective review from two institutions, they identified 39 patients who received an ASCT between 2002 and 2007 for relapsed or refractory DLCL, and a PET scan was performed prior to ASCT. Salvage chemotherapy consisted of numerous regimens, most commonly ifosfamide, carboplatin, and etoposide (ICE) with rituximab (RICE). ASCT used peripheral blood stem cells and a variety of conditioning regimens, including BCNU, etoposide, ara-c and melphalan (BEAM) (n = 15), cyclophosphamide, BCNU, etoposide (CBV), busulphan/melphalan (bu/mel) (n = 7), and TBI based regimens (n =4).

PET scans were positive prior to ASCT in 17 (44%), whereas 22 (56%) had negative PET scans. There were no deaths documented related to transplant complications. Overall survival (OS) and progression-free survival (PFS) was 67% and 64% at three years, respectively. Relapse occurred in 11/17 with positive PET scans, compared to 4/22 with negative PET scans (HR = 5.3, 95% CI 1.8-15.5), despite greater use of post-ASCT radiation in the PET positive cohort. OS was 39% for PET-positive patients, compared to 81% for PET-negative patients ($p = 0{\cdot}01$). For patients with primary refractory DLCL (n = 13), irrespective of PET results, three-year OS was 46%. Of these, relapse occurred in five of seven with positive PET scans and three of six with negative PET scans. Thus, for PET-negative patients, relapse primarily occurred in those entering salvage with primary refractory disease.

In a multivariate model including relapsed vs. refractory disease and PET result, a negative PET scan was associated with longer OS ($p = 0{\cdot}04$), whereas relapsed compared to refractory did not reach statistical significance ($p = 0{\cdot}06$). Age-adjusted IPI was missing in many patients and, thus, not included in these models. Twenty-eight patients underwent CT scanning in addition to PET or PET/CT scanning for restaging. All six patients with a confirmed CR by CT scanning showed a negative PET scan, and none of these patients relapsed. For those who did not achieve CR (i.e., residual mass by CT), PET results were 75% specific for (95% CI: 53%-90%) and 73% sensitive (95% CI: 45%-91%) for relapse.

■ COMMENTARY

Autologous hematopoietic stem cell transplantation (ASCT) remains the standard of care for relapsed or refractory DLCL. Disease sensitivity to salvage chemotherapy strongly predicts for outcome, and most transplant centers require chemosensitive disease (PR or CR) to salvage. With the advent of routine PET imaging, incorporation of the results should inform prognostication for potential ASCT recipients.

As expected and suggested by other publications,[4,5] patients with a negative PET scan at the completion of salvage chemotherapy, but prior to ASCT, fared quite well. Only 4/22 (18%) with negative PET scans relapsed. In contrast, 65% of those with positive PET scans suffered relapse, even though many received additional therapy, such as post-ASCT radiation. OS at three years was achieved by 81% of those having negative PET scans vs. 39% in those with positive imaging ($p = 0.01$). Although a negative PET scan resulted in inferior results after ASCT, OS at three years of 39% in such a poor prognosis group suggests ASCT may still provide a benefit for select patients in this cohort. The largest limitation of this retrospective study design relates to this study being derived from patients who

underwent ASCT. It is quite possible, if not likely, that patients having positive PET and/or CT scans after salvage chemotherapy did not proceed to ASCT. As a result, OS and relapse, particularly for PET-positive DLCL after salvage chemotherapy, may be considerably worse than described. Criteria for PET positivity also remain controversial and may be subject to greater variation in community practice.

These results confirm the value of PET negativity after salvage chemotherapy for relapsed or refractory DLCL prior to ASCT. Whether PET or PET/CT can substitute for standard CT imaging in this setting requires further evaluation. For PET positive patients, in addition to ASCT, consideration should be given to clinical trials, novel therapies, or allogeneic SCT. ■

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CME Questions

10. Which of the following features of male breast cancer, in comparison to female breast cancer, is correct?

a. A lower likelihood of ER/PR expression.
b. A greater likelihood of Her2 overexpression.
c. A larger tumor mass at time of presentation.
d. All of the above
e. None of the above

11. Maintenance treatment with erlotinib for patients with NSCLC was shown to:

a. improve progression free survival by approximately one month.
b. improve progression-free survival by approximately one week.
c. have no effect on progression-free survival, except for patients with demonstrable activating mutations of the EGFR gene.
d. improve progression-free survival for all treated patients but improve overall survival only for those with increased EGFR activity as demonstrated by immunohistochemistry.

12. For relapsed or refractory diffuse large B-cell lymphoma, which of the following is NOT true for patients achieving a negative PET scan prior to high-dose chemotherapy and autologous hematopoietic stem cell transplantation?

a. Relapse only occurred in 4/22 (18%).
b. Three-year OS was significantly better for patients than having a positive PET scan after salvage.
c. Transplant-related mortality was the most common cause of death by three years.
d. PET scans were negative in all six patients achieving CR. by CT scanning after salvage chemotherapy.

Answers: 10. (e); 11. (b); 12. (c)

CME Objectives

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

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

[IN FUTURE ISSUES]

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VOLUME 14, NUMBER 10 PAGES 19-20 OCTOBER 2009

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

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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

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

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. ■