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

ABSTRACT & COMMENTARY

Reduced CNS Metastases in TKI-Treated Renal Cell Carcinoma: Data from a Retrospective Analysis

By William B. Ershler, MD

SYNOPSIS: In an analysis of outcomes for patients treated at M.D. Anderson for metastatic renal cell carcinoma before and since the advent of treatment with tyrosine kinase inhibitors (TKI), the development of brain metastases was shown to be significantly reduced. The authors speculate that TKI treatment is altering the natural history of renal carcinoma.

SOURCE: Verma J, et al. Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma. *Cancer* 2011;117:4958-4965.

Prior to the introduction of tyrosine kinase inhibitors (TKI), there were few treatment options for patients with metastatic renal cell carcinoma (mRCC), and progression-free and overall survival were limited. Over the last decade, three TKIs have been approved for treatment and the outlook for patients with mRCC has improved substantially. The approval of sunitinib (2006) came after demonstration of superiority in terms of progression-free survival (PFS) to the previously established standard interferon when used as first-line treatment for patients with RCC.[1] Sorafenib (approved in 2005) was shown to improve PFS when compared to placebo for patients with recurrent or refractory disease,[2] and pazopanib (2009) for demonstration of superiority (compared with placebo) for both previously untreated and cytokine-refractory disease.[3]

Approximately 30% of RCC patients present with metastatic disease, most commonly to lung, bone, and lymph nodes, and a substantial portion of these ultimately will develop CNS metastases. There was a clue derived from the TARGET (Treatment Approaches in Renal Cancer Global Evaluation) trial that the incidence or rate of development of brain metastasis was reduced with sorafenib treatment.[4] Inasmuch as the development of brain involvement has catastrophic consequences, this observation led to an expanded effort to determine if TKI treatment influences the incidence or duration to appearance of CNS metastases.

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This current retrospective analysis from a single institution (University of Texas M.D. Anderson Cancer Center) was designed to evaluate the impact of TKIs on incidence of brain metastasis and overall survival (OS) in patients with mRCC. For this, all patients who presented with mRCC but no brain metastasis in the intervals 2002-2003 and 2006-2007 were identified using the institutional tumor registry. The following data were collected: age, sex, Fuhrman grade, disease sites, nephrectomy, systemic therapy including TKIs (sorafenib or sunitinib), Memorial Sloan-Kettering Cancer Center risk category, brain metastasis treatment, and vital status. Statistical analysis was performed using the Cox proportional hazards model and the Kaplan-Meier method.

Of the 338 patients with mRCC, 154 (46%) were treated with a TKI and 184 (54%) were not. There were no significant differences with regard to age, histology, prior nephrectomy, involved sites of disease other than lung, or Memorial Sloan-Kettering Cancer Center risk category between the groups. The latter is a risk stratification system calculated using serum LDH, hemoglobin, corrected serum calcium, performance status, and time from diagnosis to treatment, treatment with TKI or other systemic agent, and occurrence of CNS involvement (described in reference 5).

Median OS was longer in the TKI-treated group (25 months vs 12.1 months, $P < 0.0001$). In multivariate analysis, TKI treatment (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.38-0.74; $P < 0.001$) was associated with improved OS. Of the total analysis cohort, 44 (13%) developed a brain metastasis, including 29 (15.8%) of the non-TKI group and 15 (9.7%) of the TKI group. The 5-year actuarial rate of brain metastasis was 40% vs 17%, respectively ($P < 0.001$). TKI treatment was associated with lower incidence of brain metastasis in Cox multivariate analysis (HR, 0.39; 95% CI, 0.21-0.73; $P = 0.003$).

When stratified by the Memorial Sloan-Kettering Cancer Center score, patients with low risk (score of 0) had a median survival of 79.6 months, those with intermediate risk (score 1-2) 23.5 months, and those with high-risk (score 3-5) 11.6 months. For the most part, when this score as well as a number of other clinical variables were included in multivariate analysis, receipt of TKIs remained an independent predictor of better survival. Of particular note, the presence of lung metastasis increased the risk of brain metastasis (HR, 9.61; 95% CI, 2.97-31.1; $P < 0.001$).

COMMENTARY

This report provides additional impetus for the use of TKI as initial treatment for patients with metastatic RCC, as it appears such treatment reduces the incidence of brain metastases. Of course, clinicians already are aware of the value of these drugs for mRCC, as outcomes such as progression-free and overall survival far exceed those resulting from prior therapies.

The study needs to considered with the same reservations we hold for single institutional retrospective analyses, particularly when the study cohorts came from two distinct time periods. Nonetheless, the findings are consistent with expectations and the conclusions are clearly not overstated. Furthermore, it is unlikely we will see another randomized prospective study in the near future that will address this as drugs in this class have moved quickly to the front line. Perhaps, TKI administered in the adjuvant setting will be the next frontier for early management of RCC.

A clinically useful observation demonstrated high risk for the development of brain metastases among RCC patients with lung involvement (HR > 9 in both univariate and multivariate analysis). Of the 44 patients who developed brain metastasis, 90% had previously recognized lung metastases, whereas only 2.5% of patients without lung metastases ultimately developed brain metastases. Thus, for patients with lung metastases at the time of presentation, the data would support close surveillance for early recognition and treatment of CNS disease. This is particularly relevant, in light of the observation that brain metastases were asymptomatic in 50% of the cases.

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ABSTRACT & COMMENTARY

Occurrence of Second Malignancies after Treatment for Hodgkin's Lymphoma: Who's at Fault?

By William B. Ershler, MD

SYNOPSIS: Capitalizing on a large cohort of British patients followed after treatment for Hodgkin's lymphoma, the risk of occurrence of second malignancy was assessed in the context of treatment with chemotherapy alone vs treatment with combined chemotherapy and radiation. Chemotherapy treatment alone was found to be associated with an increased risk of leukemia, non-Hodgkin's lymphoma, and lung cancer, whereas treatment with combined modality was associated with an even greater risk of these three malignancies as well as cancers arising at a number of other anatomic sites. Furthermore, whereas the risk of malignancy after chemotherapy alone peaked at 5-9 years and was minimal at 15 years, the risk of malignancy after combined modality remained elevated at 25 years after treatment.

SOURCE: Swerdlow AJ, et al. Second cancer risk after chemotherapy for Hodgkin's lymphoma: A collaborative British cohort study. *J Clin Oncol* 2011;29:4096-4104.

Long-term survival is now the expected outcome for patients with Hodgkin's lymphoma (HL), but the occurrence of second malignancies is becoming a well-recognized late effect.[1] The risks associated with radiation therapy are clearly established,[2] as well as those associated with certain chemotherapeutic agents.[3] However, for patients with HL, the absolute risk for those treated with chemotherapy alone has been difficult to establish, primarily because most patients in published large cohorts had been treated with radiation, either alone or in combination with chemotherapy. In the United Kingdom, chemotherapy alone has been undertaken more often as initial HL treatment, and the current investigation examining a large cohort of patients aimed to determine the absolute excess risk (AER) of second malignancy with an emphasis on patients treated with chemotherapy alone.

For this, Swerdlow and colleagues reported on 5798 HL patients (of whom 3432 also received radiotherapy treated from 1963 to 2001). Second primary malignancy risk was determined and compared with general population-based expectations.

Second malignancies occurred in 459 cohort members. Relative risk (RR) of second cancer was raised after chemotherapy alone (RR, 2.0; 95% confidence interval [CI], 1.7 to 2.4) but was significantly lower than after combined modalities (RR, 3.9; 95% CI, 3.5 to 4.4). For those receiving chemotherapy alone, the analysis revealed significantly raised risks of lung cancer, non-HL, and leukemia — each contributing approximately equally to the absolute excess risk. For those receiving combined chemotherapy/radiation, there were raised risks of these and several other cancers. Second cancer risk peaked 5-9 years after chemotherapy alone, but it remained raised for 25 years and longer after combined modalities. It appeared that the risk was raised after each common chemotherapy regimen except ABVD, although the numbers and follow-up of patients receiving ABVD alone was limited.

The RR for the development of acute leukemia after either chemotherapy alone or combined chemotherapy/radiation therapy was greater in women than men, was not related to age at first treatment, reached a peak at 5-9 years after treatment, and was virtually non-existent after 14 years.

Other than leukemia and lung cancer, the risk of all other solid tumors combined was raised significantly only for those receiving radiation therapy combined with MOPP, MVPP, or ChlVPP.

The 20-year cumulative risk of second malignancy was 13% for chemotherapy only compared with 18% for combined chemotherapy/radiation patients. Among the chemotherapy-only patients, the risk for second malignancy when initially treated at age 25 years or younger was 3%, but it rose to 46% in those treated at age 55 years or older.

COMMENTARY

The study expands our knowledge by providing data on a large cohort of patients treated for HL with chemotherapy alone. The data show that unlike radiotherapy, which affects cancer risk at almost all sites, chemotherapy is followed by substantial risks for only three malignancies: leukemia, non-Hodgkin lymphoma, and lung cancer. Furthermore, for those treated with ABVD alone, the data did not demonstrate any raised cancer risk, although, as the authors suggest, the period of follow-up was significantly less for this subgroup. This is notable because other studies suggested ABVD/radiation when compared to MOPP/radiation, although associated with lower risk for leukemia, resulted in a greater risk for solid tumors.[4] This does not appear to be the case observed in this large British cohort, although a longer follow-up will be needed to establish this with confidence.

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ABSTRACT & COMMENTARY

Allergy and Brain Tumors: Something to Sneeze At!

By William B. Ershler, MD

SYNOPSIS: There have been reports over the past decade of an interesting inverse association between allergy and glioma. In the current report pooling data from four large cohorts, investigators examined (prediagnostic) immunoglobulin E levels in 169 individuals who were to develop glioma and compared these with levels in 520 matched controls. Mildly elevated prediagnosis plasma IgE levels were associated with reduced risk, although this was not apparent for those with higher levels. The data strengthen a causal association of allergy and reduced glioma risk, but the mechanism remains speculative at present.

SOURCES: Calboli FC, et al. Prediagnostic plasma IgE levels and risk of adult glioma in four prospective cohort studies. *J Natl Cancer Inst* 2011;103:1588-1595. Davis FG, Al-Alem U. Allergies and adult gliomas: Cohort results strengthen evidence for a causal association. (Editorial). *J Natl Cancer Inst* 2011;103:1562-1563.

Several observational studies have demonstrated a reciprocal relationship between allergy history and glioma, and two separate meta-analyses revealed a significant risk reduction of almost 40% for people with a history of allergies compared to that for those with no allergy history.[1,2] It has been speculated that immunoglobulin E (IgE) plays a critical role in regulating inflammatory responses within the central nervous system[3] and this may account for the association of lower risk for glioma in atopic patients. Indeed, an inverse association between serum IgE and risk of glioma was reported recently in a large case-control study,[4] but reverse causality and treatment effects remain potential explanations for those findings.

To address this, Calboli and colleagues combined data from four prospective cohort studies and used a nested case-control design to examine more deeply the association between allergy and glioma. Patients were included who had confirmed glioma and prediagnosis blood available for analysis. Also included were three matched control subjects per case subject, and the final numbers for analyses were 169 case subjects and 520 control subjects. Total IgE, food allergen-specific IgE, and respiratory allergen-specific IgE levels were measured. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression analysis. Stratified analyses were conducted by age and birth cohorts.

For those with mildly elevated total IgE levels (25-100 kU/L), there was a statistically significant inverse association with glioma (OR, 0.63: 95% CI, 0.42 to 0.93), compared with clinically normal IgE levels (< 25 kU/L). This inverse association was not present for those with very high levels of IgE (> 100 kU/L) (OR, 0.98; 95% CI, 0.61 to 1.56). The association between glioma and total IgE was consistent for both men and women. Non-statistically significant inverse associations were noted for elevated IgE levels among individuals born before 1930 (OR, 0.67; 95% CI, 0.34 to 1.34), and when restricting analyses to highly fatal (deceased within 2 years of diagnosis), glioma case subjects (OR, 0.64; 95% CI, 0.34 to 1.19) compared to individuals with clinically normal IgE levels. No associations were observed for either food allergen-specific or respiratory allergen-specific IgE levels.

COMMENTARY

The findings from this report support the curious inverse association between allergy and glioma, yet the biological explanation remains to be established. Individuals with borderline elevations in IgE had a modestly lower risk for glioma, but individuals with clearly elevated levels (i.e., >100 kU/L) did not experience reduced risk. A very similar conclusion was also reported in another recent analysis of a separate large prospective cohort.[5] In fact, the evidence from the number of observational studies and now two large prospective cohort studies are sufficiently compelling to warrant more in-depth investigation aimed at defining the mechanism(s) involved. Although it is tempting to speculate that heightened levels of IgE are somehow associated with enhanced immune surveillance within the CNS, the role of immunoglobulins in this or any class in tumor surveillance has yet to be established. Also, there seems to be a bell-shaped curve, with a failure to achieve risk reduction at the highest levels of IgE.

Like many epidemiological studies, the findings of greatest interest, especially those that are unexpected, serve to engender hypotheses requiring translation back to the laboratory for explanation. It would seem for glioma, for which treatment and survival remain by all accounts unsatisfactory, investigations that relate to disease occurrence may lead to remarkable advances in both prevention and treatment.

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ILLUSTRATIVE CASE SERIES

Incidental Splenic Mass

By Bindu Kanapuru, MD

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

A 61-year-old female was evaluated for intermittent upper abdominal discomfort. A non-contrast enhanced CT revealed 5x3x4 cm lesion in the spleen that appeared to be cystic. Another lesion that appeared to be contiguous with the previous lesion but was solid and hypo-echoic was reported, and a recommendation was made to rule out lymphoma or other primary tumors of the spleen. The imaging studies were negative for abdominal or thoracic lymphadenopathy. No other lesions were identified. The patient was referred for further evaluation to an oncologist. Past history included severe osteoporosis, multiple spinal surgeries, and a prior fracture of the right leg with repair. Her medications included iron, vitamin B12 supplementation, and pain medications. She denied any smoking history, alcohol use, or intravenous drug abuse. There was no personal history of prior cancer. How should this patient be evaluated to rule out a neoplastic process?

CASE DISCUSSION

Although tumors of the spleen are uncommon, they occasionally are discovered during evaluation of other medical problems or in asymptomatic patients. The splenic tissue consisting of red pulp

and white pulp can give rise to primary vascular tumors as well as lymphoid tumors. In addition, although uncommon, the spleen also can be involved with metastasis from other primary cancers. Evaluation of an abnormal splenic mass presents a significant diagnostic challenge, as specific diagnostic features on imaging that would distinguish malignant from benign processes are most frequently lacking.

Hemangiomas are the most common benign vascular neoplasms with prevalence ranging from less than 0.5% to 15% in the general population.[1] These typically are found incidentally and only occasionally involve the spleen, but can present as a large non-tender palpable mass in the left upper quadrant. Laboratory evaluation is usually normal but anemia, thrombocytopenia, and coagulopathy may be seen in Kasabach-Meritt syndrome, typically in very young patients. On CT they appear as hypo- or iso-attenuating solid or complex cystic masses that enhance homogenously after intravenous contrast administration. Hamartomas are extremely rare tumors that can present as an asymptomatic splenic mass. Splenic hamartomas can be associated with tuberous sclerosis and Wiskott-Aldrich syndrome. Ultrasound is the most sensitive imaging test for hamartoma on which they appear as a homogeneous mass. On CT they appear as solid hypo-dense lesions with prolonged enhancement after contrast administration.[2]

Littoral cell angioma is another primary vascular tumor of the spleen of uncertain malignant potential. Such angiomas occasionally are encountered during the workup of cytopenias thought to occur as a consequence of "hypersplenism." Clinical features may mimic a malignant lymphomatous process with the presence of fever, fatigue, and weakness. In addition, confirmation of littoral cell angioma by splenectomy does not rule out absence of primary malignant disease, as association between littoral cell angiomas and gastrointestinal and renal malignancies have been described. They are more likely to present with splenomegaly with multiple hypo-attenuating lesions on CT imaging.[3]

Peliosis is yet another consideration in evaluating splenic mass, although it almost always is associated with peliosis hepatitis and may occur in patients with aplastic anemia and cancer. This lesion can occur on the splenic surface and result in splenic hemorrhage. On CT, peliosis appears as multiple well-defined hypo-attenuating lesions with significant contrast enhancement.

Malignant vascular tumors of the spleen include hemangiopericytomas and angiosarcomas. Although the spleen is not the most common location for hemangiopericytomas, when they originate in the spleen they can be asymptomatic or associated with splenomegaly. Abdominal hemangiopericytomas are aggressive tumors with high rates of local recurrence after wide excision. Lung and bone are the usual sites of distant metastasis. Hemangiopericytoma appears as a large splenic mass with smaller lesions distributed throughout the parenchyma. Angiosarcoma is the most common primary non-lymphoid malignant lesion of the spleen; however, its annual incidence is only about 0.25 cases per million persons. It too is a very aggressive tumor that spreads to liver, lung, bone, and brain. Symptoms range from constitutional (weight loss and malaise) to those associated with splenic expansion (pain) or rupture. Ultrasound reveals splenomegaly with masses containing both solid and cystic components. CT also shows splenomegaly with solitary or multiple nodular masses with irregular margins with heterogeneous low attenuation and occasional peripheral enhancement.[4] For each of these conditions, splenectomy is both diagnostic and therapeutic.

Non-Hodgkin's lymphoma is the most common lymphoid malignancy involving the spleen. For non-Hodgkin's lymphoma patients with splenic involvement, splenomegaly is frequently present, although isolated splenic masses without splenic enlargement may also be seen in up to 30% of cases.[5] In 50%-80% of cases, the spleen is involved as part of a disseminated process and the diagnosis is made by lymph node biopsy, not splenectomy. Splenic lymphomas involving only the spleen or splenic hilar nodes are very rare, occurring in only 0.6% of lymphoma cases. Bone marrow involvement has been reported in 97.3% of low-grade splenic lymphomas and in 85% of high-grade lymphomas.[6] Another study of low-grade lymphomas of the spleen identified bone marrow involvement at diagnosis in 102 (99.0%) and leukemic conversion (LC) in 85 (83.3%) patients, respectively.[7]

In a series of 122 patients who underwent diagnostic splenectomy, diffuse large B cell lymphoma was diagnosed in 29% of patients with splenic mass and in about 10% of cases with splenomegaly. A diagnosis of marginal zone lymphoma was identified in 17% of cases with splenomegaly.[8] Hairy cell leukemia, T cell large granular lymphocytic leukemia, lympho-plasmocytic lymphomas, mantle cell lymphomas, and follicular lymphoma also can present with

primary splenic involvement. Although Hodgkin's lymphoma commonly involves the spleen, it is uncommon to have isolated splenic involvement without supradiaphgramatic lymphadenopathy. Clinical features of splenic lymphomas are usually indistinguishable from other splenic tumors and include left upper quadrant discomfort and fatigue.

Weight loss, fever, and night sweats are more typical for high-grade lymphomas such as diffuse large B cell lymphoma. A comprehensive history may identify specific risk factors, such as infection with hepatitis C or treatment with TNF alpha, both of which favor development of specific lymphoma subtypes.[9] Physical examination may not be very helpful as palpable peripheral lymphadenopathy may be absent. Laboratory evaluation should include complete blood count LDH and beta-2 microglobulin levels, which help estimate the burden of disease. Serum protein electrophoresis may identify an M spike often seen with indolent splenic lymphomas. Whole body CT is the best imaging study to identify additional lymphomatous involvement elsewhere. On CT presentation, splenic lymphomas can range from diffuse splenic infiltration and splenomegaly to focal low attenuation lesions which rarely enhance. PET/CT is very accurate for identifying splenic involvement in diffuse large B cell lymphomas. However, low-grade lymphomas and mantle cell lymphomas may show low to intermediate SUV activity on PET, thus limiting the universal value of PET as a diagnostic tool in splenic lymphomas. MRI has no role in evaluating splenic lymphomas.

Since a high rate of peripheral blood involvement is seen in splenic lymphomas, peripheral blood smear examination and flow cytometry is the next appropriate step in evaluating splenic mass. Peripheral blood examination may reveal hairy cells, prolymphocytes, villous lymphocytes, or large and granular lymphocytes, and flow cytometry may be further helpful by identifying specific immunophenotypic features diagnostic of lymphomas. Bone marrow aspirate and biopsy can establish the diagnosis in splenic marginal zone lymphomas, mantle cell lymphomas, and hepato-splenic T cell lymphomas.[9]

However, despite these investigations, splenectomy ultimately may be needed to definitively rule out a lymphoma when the suspicion is high. Laparoscopic splenectomy can be performed safely even in patients with massive splenomegaly with complication rate around 10%, but with less than 1% mortality.

Fine needle aspiration or biopsy have been used successfully in evaluation of focal splenic lesions,[8] but with major complications occurring in 10% of the cases and minor complications in 6%. Although in some hands adequate tissue for diagnosis is available in more than 90% of cases, the procedure is rarely used.

Splenic metastases are very uncommon, but when they do occur they usually are detected coincident with the primary tumor or shortly after. The most common primary malignancies spreading to the spleen are lung, melanoma, breast, and ovarian cancers. Isolated splenic metastasis from a primary cancer is very rare but has been reported, particularly in ovarian cancers and gastric cancers. Splenic metastases are usually asymptomatic. However, abdominal pain and spontaneous rupture of the spleen also have been reported. On CT, splenic metastases appear as solid or cystic lesions that are hypo-dense with inhomogeneous enhancement on contrast. MRI may be more accurate in detecting splenic metastasis as the majority have evidence of necrosis and/or hemorrhage.

CURRENT CASE DISCUSSION

The patient referenced above had evidence of anemia with Hb of 11.0 g/dL and thrombocytopenia with platelets of 90,000/cu mm. LDH level was normal and beta 2 microglobulin was elevated at 3.0 mg/L. No evidence for hemolysis was detected on further evaluation. The remainder of her labs were within normal limits. Whole body CT did not reveal any other lesions or lymphadenopathy. Peripheral blood smear examination also did not identify any atypical cells. A bone marrow biopsy also showed no evidence for lymphoma. The patient underwent splenectomy and was diagnosed with splenic follicular lymphoma. The patient is currently scheduled for chemotherapy with bendamustine-rituxan based on recent reports demonstrating superior activity of this combination in indolent lymphomas.

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CME Questions

1. For patients with metastatic renal cell carcinoma, the retrospective review of MD Anderson data indicates that:

a. patients with lung metastases had a high risk for subsequent development of brain metastases.
b. approximately 50% of patients with brain metastases were asymptomatic.
c. patients treated with TKIs had fewer brain metastases.
d. patients treated with TKIs had better overall survival.
e. All of the above

2. Compared with the development of acute leukemia after treatment for Hodgkin's lymphoma, the development of solid tumors:

a. occurs later.
b. is more often associated with the use of ABVD chemotherapy either alone or in combination with radiation.
c. occur more frequently in males.
d. All of the above

3. According to recently reported data, which individuals with a history of allergic disease have a significantly reduced risk for glioma?

a. Those with IgE level of < 25 kU/L (normal IgE levels)
b. Those with IgE level of > 25 but < 100 kU/L (borderline elevated)
c. Those with IgE levels of > 100 kU/L (elevated)
d. Those with any IgE level (but a documented history of allergic disease)

4. Primary splenic lymphoma is the presenting feature in what percent of non-Hodgkin's lymphoma?

a. < 1%
b. 6%
c. 15%
d. 20%

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.

[IN FUTURE ISSUES]

Comorbidity and breast cancer mortality

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.*

HPV Vaccine Now Recommended for Males

In this issue: New recommendations for HPV vaccine; guidelines for treatment of essential tremor; updates on smoking cessation drugs; and FDA actions.

HPV vaccine and anal cancer risk

The human papillomavirus (HPV) vaccine is routinely administered to adolescent girls; now the CDC's Advisory Committee on Immunization Practices is recommending the vaccine for 11- and 12-year-old boys as well. The vaccine has been approved for use in both adolescent girls and boys to protect them against HPV but has been somewhat underutilized in girls and rarely used in boys. HPV causes genital warts and cervical cancer in women and the vaccine effectively reduces the rate of both. The vaccine is generally recommended for 11 and 12 year olds when they get other routine vaccines, and before they become sexually active. Although the vaccine is approved for boys, the CDC had not made a recommendation on routine use until now. After evaluating data on efficacy in males, the committee felt that the vaccine could protect boys against genital warts, as well as throat and anal cancer caused by HPV, and could help prevent spread of the virus to girls.

In related news, a new study shows the HPV vaccine is effective in preventing anal intraepithelial neoplasia in men who have sex with men. In a double-blind study of 602 men (ages 16-26) who have sex with men, half were randomized to the quadravalent HPV vaccine and half to placebo. The vaccine reduced the risk of anal intraepithelial neoplasia caused by the four subgroups of HPV covered by the vaccine (HPV-6, 11, 16, and 18) by half in the intention-to-treat population and by 77% in the per-protocol population. Anal intraepithelial neoplasia caused by HPV of any type was reduced by 25.7% and 54.9%, respectively. Rates of anal intraepithelial neoplasia per 100 person years were 17.5 in the placebo group and 13 in the vaccine group in the intention-to-treat, and 8.9% placebo vs 4.0% vaccine in the per-protocol population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to HPV subtypes covered by the vaccine was reduced by 54.2% (intention-to-treat) and 74.9% (per-protocol). The vaccine was well tolerated. The authors conclude that the HPV vaccine reduced the rate of anal intraepithelial neoplasia in men who have sex with men and may help reduce the risk of anal cancer (*N Engl J Med* 2011;365:1576-1585). ■

Treatment of essential tremor

The American Academy of Neurology has published its updated guideline for the treatment of essential tremor. Propranolol and primidone remain first options with a Level A recommendation (established as effective). Alprazolam, atenolol, gabapentin as monotherapy, sotalol, and topiramate are graded as Level B (probably effective), while nadolol, nimodipine, clonazepam, botulinum toxin a, deep brain stimulation, and thalamotomy remain as level C (possibly effective). There is not enough evidence to make a recommendation for gamma knife therapy. The new guideline also states that there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozipine. Levetiracetam and 3,4 diaminopyridine are ineffective and flunari-

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zine is probably ineffective. The guideline was published online in *Neurology* October 19, 2011 (doi: 10.1212/WNL.0b013e318236f0fd). ■

Chantix and neuropsychiatric side effects

There is good news for the smoking cessation drug varenicline (Chantix). Following concern about neuropsychiatric side effects, the FDA sponsored two epidemiologic studies that evaluated the risk of neuropsychiatric hospitalizations associated with the drug. Neither study found a difference in risk of neuropsychiatric hospitalization between varenicline and nicotine replacement therapy, although hospitalization was the only endpoint evaluated and they did not rule out an increased risk of other neuropsychiatric events. While reassuring, the FDA is recommending that health care professionals and patients continue to follow the recommendations previously established and monitor for neuropsychiatric symptoms when prescribing or using varenicline. The manufacturer is conducting a large safety study of the drug to assess neuropsychiatric adverse effects but the results will not be available until 2017 (www.fda.gov/Drugs/DrugSafety/). In related news, the inexpensive partial nicotine agonist cytisine is an effective adjunct to smoking cessation, according to a new study in the *New England Journal of Medicine*. Cytisine is extracted from the seeds of *Cysisus laborinum L.* (Golden Rain acacia) and has been available worldwide for years, particularly in Eastern Europe, where it can be purchased for $6-$15 per course. Researchers randomized 740 smokers to cytisine or matching placebo for 25 days along with counseling. The rate of sustained 12 months abstinence was 8.4% in the cytisine group compared with 2.4% in the placebo group ($P = 0.01$). GI side effects were slightly more prevalent in the treatment group. The authors conclude that cytisine was more effective than placebo for smoking cessation and may be "an affordable treatment to advance smoking cessation globally" (*N Engl J Med* 2011;365:1193-1200). ■

FDA Actions

The FDA is continuing to review the association of oral contraceptives and thrombotic risk, particularly oral contraceptives containing drospirenone. On October 27, the FDA issued a preliminary Drug Safety Communication, with the full report due out in early December. Reviewing the records of Kaiser Permanente members in California and state Medicaid programs in Tennessee and Washington, which included 835,826 women receiving contraceptive prescriptions from 2001-2007, an increased risk of venous thromboembolism (VTE), deep venous thrombosis, and pulmonary embolism was noted with several contraceptives, with low estrogen hormonal contraceptives as a reference. Products containing drospirenone had relative risk of VTE of 1.74 (95% confidence interval [CI] 1.42-2.14). The norelgestromin/ethinyl estradiol transdermal patch was associated with relative risk of 1.55 (95% CI 1.17-2.07) and etonogestrel/estradiol vaginal ring was associated with a relative risk of 1.56 (95% CI 1.02-2.37). The risk was higher in younger users then older women (www.FDA.gov./DRUGS/DrugSafety/ucm277346.htm).

The FDA has approved the first generic olanzapine (Zyprexa) to treat schizophrenia and bipolar disorder. The generic carries the same warnings as the brand regarding increased risk of death in elderly people with psychosis or dementia. Generic olanzapine will be available from several manufacturers as tablets and orally disintegrating tabs.

The FDA has announced that drotrecogin alfa (Xigris) is being withdrawn from the market by Eli Lilly & Co. The withdrawal is based on the results of the recently completed PROWESS-SHOCK trial in which drotrecogin alfa failed to show a survival benefit in patients with severe sepsis and septic shock. The FDA is recommending that the drug should be stopped in any patients currently being treated and should not be initiated in new patients. All remaining product should be returned to the supplier.

The FDA has approved tadalafil (Cialis) for the treatment of benign prostatic hyperplasia (BPH) either alone or when it occurs along with erectile dysfunction (ED). The drug was approved in 2003 for treatment of ED. The approval was based on two trials in which men taking tadalafil 5 mg daily experienced significant improvements in BPH symptoms compared with those taking placebo. A third study in which men had both BPH and ED, tadalafil 5 mg daily improved both symptoms of BPH and ED compared to placebo. Tadalafil should not be used in patients taking nitrates or in combination with alpha blockers for the treatment of BPH.

The FDA has approved a combination of sitagliptin and simvastatin for the treatment of adults with type 2 diabetes and hypercholesterolemia. This represents the first combination drug for treating these two conditions. The fixed dose combination is available in three strengths: 100 mg sitagliptin/10 mg simvastatin, 100 mg/20 mg, and 100 mg/40 mg. The approval was based on "substantial experience with both sitagliptin and simvastatin" and is a "convenience combination," according to the FDA. Sitagliptin/simvastatin will be marketed as Juvisync by MSD International GmbH Clonmel in Tipperary, Ireland. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Lifetime Risk of Developing COPD: A Longitudinal Population Study

Source: Gershon AS, et al. Lifetime risk of developing chronic obstructive pulmonary disease: A longitudinal population study. *Lancet* 2011;378:991-996.

WORLDWIDE, CHRONIC OBSTRUCTIVE pulmonary disease (COPD) is the fourth most common cause of death, and is predicted to become the third most common cause in the near future, especially if smoking habits in populous nations like China — where more than half of adult men are currently smokers — continue on their same trajectory. According to Gershon et al, no prior publications have provided adequate insight into the lifetime risk of developing COPD. Hence, using health administrative data from the entire population of Ontario, Canada (n = approximately 13 million), they reported on a 14-year follow-up of persons who did *not* have COPD at baseline.

Based on the window of observation from 1996-2010, the population was divided categorically into: a) physician-diagnosed COPD, b) reached age 80 without a COPD diagnosis, or c) death. By age 80, more than one-fourth (28%) of persons free of COPD at baseline had been diagnosed with COPD by a physician. To put this into perspective, a new diagnosis of COPD was more likely than congestive heart failure, acute myocardial infarction, or even diabetes.

The authors mention that they have observed less public awareness of COPD than might be merited based on its epidemiological presence, and they encourage greater energies be invested in smoking cessation and public education about COPD. ■

The Burden of Painful Diabetic Peripheral Neuropathy

Source: Abbott CA, et al. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 2011;34:2220-2224.

RECENTLY PUBLISHED TELEPHONE SURVEYS of large populations of diabetics indicate a low level of recognition of the diagnostic terminology "Diabetic Neuropathy," despite commonplace problematic symptoms consistent with this disorder. Diabetic peripheral neuropathy (DPN) and diabetic peripheral neuropathic pain (DPNP) are associated with major morbidities. For instance, the leading cause of amputation in diabetics is foot ulcer subsequent to impaired sensation in the feet from diabetic neuropathy. Similarly, DPNP is often worsened by activity, which tends to compromise exercise capacity and may also interrupt sleep.

The North-West Diabetes Foot Care Study screened 15,692 adult diabetics in northwest England. The presence of neuropathy was established using scoring systems as well as specific nerve function testing (vibration, pin-prick, temperature, and reflex testing). Screenings took place during routine annual evaluations by primary care clinicians.

Overall, one-third of study subjects experienced painful neuropathy. DPNP was twice as common in persons with type 2 diabetes than type 1. Women and persons of South Asian ethnicity were disproportionately affected. Based on these findings, clinicians might anticipate an important positive yield from routinely screening for symptoms of DPNP and signs of DPN. ■

Predictive Value of Postprandial Glucose for CV Events in Type 2 Diabetes

Source: Cavalot F, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: Lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* 2011;34:2237-2243.

THE DECODE DATA (DIABETES EPIDEMIOLOGY Collaborative Analysis of Diagnostic Criteria in Europe) indicated that all-cause mortality, as well as cardiovascular (CV) events, were better predicted by postprandial glucose (PPG) than fasting blood glucose (FPG). Indeed, the DECODE data set indicates a linear rise in relative risk for mortality as one progresses from normoglycemia, to impaired glucose tolerance, to frank diabetes.

Although much of the literature is consistent in finding that PPG outperforms both FPG and A1C in predicting adverse CV events (and mortality), one criticism aimed at these data reminds us that PPG data were, for the most part, obtained from oral glucose tolerance testing (OGTT). Since only a small minority of patients outside clinical trials actually have OGTT performed, obtaining a PPG after actual meals might better reflect the pathophysiology occurring in long-term

management of diabetics.

Cavalot et al report on a 14-year follow-up of type 2 diabetes patients (n = 505) in whom A1C, FPG, and PPG (*not* obtained by OGTT) were measured at baseline, seeking to discern the relationship of each of these metrics with CV events and overall mortality.

For mortality as well as CV events, both A1C and PPG were strong predictors (especially post-lunch PPG). FPG was not a good predictor. It remains to be determined whether interventions specifically targeting PPG will provide meaningful benefit beyond simple traditional diabetes control. ■

Vitamin E and Prostate Cancer

Source: Klein EA, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2011;306:1549-1556.

Observational epidemiologic data had suggested that selenium, vitamin E, or both might reduce the incidence of prostate cancer (PCa). Based on this hypothesis, the SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) was performed. The basic structure was a randomized, placebo-controlled trial of vitamin E 400 IU/d (VitE), selenium 200 mcg/d (SEL), or both in 35,533 men. Seven years after enrollment, the trial was stopped because of a lack of any demonstrated benefit along with futility analysis indicating no potential of future benefit. That was in 2008.

This report extends follow-up of the same population through 2011. At this point, a statistically significant *increased* risk of prostate cancer was seen in men taking VitE (17% increase). While the numbers for SEL as well as SEL plus VitE trended toward worse outcomes, they were not statistically significant.

Why VitE might produce an increased risk for PCa is unclear: There was, for instance, no measurable effect of VitE on PSA. Although many clinicians have opted to be essentially silent in discussions of vitamin supplements with patients — since, after all, vitE was presumed to be innocuous — these data suggest consideration of intervention to discourage VitE in healthy men. Although the data were insufficient to definitively indict selenium, there is no support for endorsing it either. ■

Is There a Relationship Between Insulin Glargine and Cancer?

Source: Morden NE, et al. Further exploration of the relationship between insulin glargine and incident cancer: A retrospective cohort study of older Medicare patients. *Diabetes Care* 2011;34:1965-1971.

Recent retrospective studies in Europe have created concern because of an observed increased risk of cancer (hazard ratio = 1.55) in users of insulin glargine (GLAR) compared to nonusers. Similarly, increased risk of breast cancer in GLAR users was reported in two other analyses (hazard ratio 1.99-3.9). These reports, in addition to the limitations of their retrospective design, also had limitations such as failure to adjust for potential confounders such as BMI, GLAR dose, the impact of socioeconomic selection bias, and the relatively short periods of observation (6 years or less).

To remedy some of the limitations of early reports, the authors reviewed a Medicare database of more than 81,000 diabetics, including a subpopulation of 16,945 on GLAR and 49,455 on insulins other than GLAR. After adjustment for recognized confounders, there was no association seen between GLAR and any cancer. Indeed, combination insulin regimens were associated with increased risk of breast cancer, an association not previously consistently identified.

The results of this large data set should be generally reassuring about the safety profile of GLAR in reference to cancer of any type. The association of breast cancer with combination insulin regimens noted here should not be considered definitive because various reports have come to conflicting conclusions. ■

Saw Palmetto and BPH: *Not*

Source: Barry MJ, et al. Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: A randomized trial. *JAMA* 2011;306:1344-1351.

Although benign prostatic hyperplasia (BPH) and its consequences are rarely a mortal concern, the quality-of-life impact of LUTS (Lower Urinary Tract Symptoms) associated with BPH is often substantial. Antihypertensive alpha blockers (e.g., doxazosin, terazosin), site-selective alpha blockers (e.g., alfuzosin, tamsulosin), and alpha-reductase inhibitors (e.g., dutasteride, finasteride) have each been shown — either alone or in combination (i.e., alpha blockers + alpha reductase inhibitors) to improve LUTS. The latter have even been shown to reduce the need for surgery and the incidence of acute urinary retention in BPH study subjects.

Despite the well-demonstrated efficacy of proprietary agents, many BPH patients opt for "natural" treatments, such as saw palmetto (SWP). An early Cochrane review (2002) of SWP was generally supportive; less positivity was reflected in the 2009 Cochrane review, because more recent, rigorous trials found lesser benefit. Most trials utilized SWP 160 mg b.i.d. Is it possible that *more* SWP might gain greater therapeutic efficacy?

Barry et al performed a randomized, double-blind trial of higher-dose SWP, including doses up to 960 mg/d. Men with BPH (n = 369) were followed for 72 weeks. At the conclusion of the trial, no beneficial effects on LUTS were seen, despite the higher dose. No serious adverse effects attributable to SWP were seen. Based on these data, SWP is not beneficial for men with BPH. ■

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