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A monthly update of developments in cancer treatment and research

ABSTRACT & COMMENTARY

Pancreatic Cancer and Suicide

By William B. Ershler, MD

SYNOPSIS: Using the SEER database, data for patients with adenocarcinoma of the pancreas diagnosed in 1995-2005 were analyzed for the occurrence of suicide. As expected, the rates were higher than those reported for the general population, but among men, particularly those who were recovering from surgery, the mortality rate from suicide was 10 times greater than that of the general population. Care providers should be aware of this heightened risk and intervene as possible.

SOURCE: Turaga KK, et al. Suicide in patients with pancreatic cancer. *Cancer* 2011;117:642-647.

Clinical depression is highly associated with pancreatic cancer, occurring somewhere between 33% to 76% of cases,[1,2] and clinicians are aware of the suicide risk in such patients. Yet, the magnitude of this risk has yet to be clearly established. To address this, Turaga and colleagues reviewed data in the SEER database for patients diagnosed with pancreatic adenocarcinoma from 1995-2005. Logistic regression models were used to perform multivariate modeling for factors associated with suicide, while Kaplan-Meier analysis was used to assess factors affecting survival.

Among 36,221 patients followed for 22,145 person-years, the suicide rate was 135.4 per 100,000 person-years. The corresponding rate in the U.S. population aged 65-74 years was 12.5 per 100,000 person-years, with a Standardized Mortality Ratio of 10.8 (95% confidence interval [CI], 9.2-12.7). Greater suicide rates were noted in males (odds ratio [OR] 13.5; 95% CI, 3.2-56.9; $P < 0.001$) and, among males, in patients undergoing an operative intervention (OR 2.5; 95% CI, 1.0-6.5; $P = 0.05$). Married men had a lower risk of committing suicide (OR 0.3; 95% CI, 0.1-0.6; $P = 0.002$). Median survival among patients undergoing operative intervention was 2 months for those who committed suicide compared with 10 months for those who did not commit suicide.

COMMENTARY

Suicide is a feared consequence of severe depression and its occurrence has been associated with the diagnosis and treatment of cancer.[3,4] Depression, including severe depression, is common in patients with pancreatic cancer, more so than other

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malignancies.[5,6] Whereas the incidence of suicide among patients with cancer approaches twice that of the general population,[7,8] the current study using the large SEER database found the incidence to be more than 10 times greater than in the general population. The risk was higher for men and for those who underwent an operative intervention, with the highest rates occurring within 2 months of the operative procedure.

Why pancreatic cancer is distinctly associated with depression, more so than other malignancies, is unclear. There has been speculation that its roots relate to certain metabolic, hormonal, or biochemical features of the disease, but there is also a pervasive negativity felt throughout the community concerning this disease and this might heighten the sense of doom associated with the diagnosis.

The authors point out that the heightened risk for suicide in the few months after surgery previously had not been reported. If this finding is confirmed it may be of considerable clinical importance. Surgeons and other care providers who attend patients during this vulnerable period should be alerted to the possibility of overwhelming despair or other manifestation of severe depression and be prepared to provide appropriate psychological intervention as possible. Furthermore, acknowledging the high prevalence of depression among patients with pancreatic cancer (76% in one study[9]), medical/radiation oncologists should have a low threshold for treating depression aggressively in this setting. ■

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ILLUSTRATIVE CASE SERIES

Metastatic Pancreatic Cancer

By Jerome Yates, MD
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Dr. Yates reports no financial relationships relevant to this field of study.

A 58-year-old auto salesman was referred for initial management of metastatic pancreatic cancer. He had been well until approximately 3 months prior when he began to experience epigastric and mid-back pain. During this time he lost approximately 10 pounds (5% of his body weight). Blood work, including a CBC and liver and renal function tests, were normal. Both amylase and lipase were in the normal range, but the CA19-9 was elevated at 359 U/mL (normal range up to 37 U/mL). He was referred to a gastroenterologist who reported normal lower and upper endoscopy. An abdominal CT scan revealed a 3.5 x 4.2 cm mass in the body of the pancreas with apparent partial occlusion of the portal vein and nodal involvement near the porta hepatis and retroperitoneally. A CT-guided lymph node biopsy revealed a high-grade adenocarcinoma consistent with a presumed pancreatic primary. The patient's past medical history was remarkable for a 10-year history of hypertension and a 2-year history of type II diabetes mellitus controlled on oral hypoglycemics. Although diabetes has been common in his family, there was

no history of cancer among his parents, siblings, or children. Cigarette and alcohol history were negative.

On physical examination he appeared a robust middle-aged man, 5'11" tall, 193 pounds. BP was 140/74, P-78 regular, and O_2 sat was 97% on room air. There was no scleral icterus nor palpable lymphadenopathy. His chest was clear to percussion and auscultation. The abdomen was soft with some epigastric and right upper quadrant tenderness, but without discretely palpable mass. Extremities and neurological exams were normal.

CASE DISCUSSION

In considering therapy, the first question of paramount importance is whether the disease is resectable, which would provide the best chance for long-term survival. However, the involvement of both retroperitoneal and porta hepatis lymph nodes as well as the proximity and partial occlusion of the portal vein might preclude surgery. A careful inspection by MRI and/or laparoscopy would be warranted as well as consultation from an experienced surgical oncologist. If the portal vein is abutted but not invaded or the segment of involvement is small enough that suitable vessel both proximal and distal would be available for reconstruction, it might be possible that an aggressive surgical approach could be undertaken.

However, the likelihood is that this patient initially would be treated with chemotherapy. Although the data are not convincing at this time, initial chemotherapy might be considered "neoadjuvant" and surgery offered upon completion of one or two cycles. If this were to be planned, it would be best coordinated with radiation oncology, as combined modality might offer the greatest chance for later surgical resection.

If it is determined that resection is not feasible, my recommended initial approach would be with chemotherapy alone. Until recently, the standard treatment would be either gemcitabine alone or in combination with the tyrosine kinase inhibitor erlotinib (Tarceva®). This is based primarily on studies comparing gemcitabine to 5-FU/leucovorin in randomized trials conducted in the 1990s, including a pivotal Phase 3 trial that demonstrated improvement in median overall survival and 1-year survival compared to 5-FU (5.7 months vs 4.4 months and 18% vs 2%, respectively).[1] Although there was only a modest response rate (5%) and improvement in overall survival, gemcitabine rapidly became the standard first-line therapy for advanced pancreatic cancer. In 2007, Moore et al demonstrated improvement in survival (6.24 months vs 5.91 months) in a trial that compared gemcitabine and erlotinib, a small-molecule tyrosine kinase inhibitor that targets and blocks EGFR, vs gemcitabine alone.[2] Although the improvement was small, this was the first gemcitabine combination to show any benefit in a Phase 3 trial when compared to gemcitabine alone and it has engendered interest in targeting the EGFR pathway in metastatic pancreatic cancer.

At the American Society of Clinical Oncologists (ASCO) Annual Meeting in June 2010, preliminary data from the PRODIGE 4/ACCORD 11 trial that compared gemcitabine to oxaliplatin and irinotecan plus fluorouracil and leucovorin (FOLFIRINOX) were presented.[3] This randomized, Phase 3 trial enrolled 250 patients with metastatic pancreatic cancer and was halted when the interim analysis demonstrated significant improvements in progression-free survival and median overall survival with FOLFIRINOX (6.4 months vs 3.3 months, and 11.1 months vs 6.8 months, respectively). Furthermore, the objective response rate was 31% for the FOLFIRINOX arm compared to 9% in the gemcitabine arm. Approximately 48% of patients on FOLFIRINOX were alive at 1 year compared with 30% of patients who received gemcitabine. The median progression-free survival was 6.4 months for those on FOLFIRINOX and 3.3 months for those treated with gemcitabine. Clearly there were more adverse effects observed in those treated with FOLFIRINOX, although these were not severe enough that treatment had to be stopped. Treated patients experienced longer preservation of quality of life, but still it is not clear that this aggressive approach should be considered standard for patients with less than good performance status and for those with impaired hepatic function.

In the current case, and based upon the ASCO presentation of the PRODIGE 4/ACCORD 11 trial (which I believe has yet to be published as a manuscript) and the patient's seemingly excellent performance status, my inclination would be to treat first line with the FOLFIRINOX regimen and reserve gemcitabine for treatment at the time of disease progression.

Two other points merit mention. This patient has a 2-year history of diabetes and one wonders whether the onset of glucose intolerance was an early clue of evolving pancreatic cancer. Although the mechanism explaining the association between diabetes and pancreatic cancer has not been worked out satisfactorily, it is clear that such an association exists.[4,5] In fact, some have suggested that middle-aged or older patients with new onset diabetes

be examined either by ultrasound or CT scan to determine if there is an early (resectable) pancreatic cancer. The costs of such screening may preclude its widespread application in today's economy, but certainly this is a question that should be addressed.

The second point refers back to this patient. In addition to the chemotherapy provided, aggressive supportive management would be in order, particularly in this patient who had been well and is now facing a life-threatening illness. Significant clinical depression and even suicide is more common in patients with this diagnosis than in the general population or in patients with other forms of life-threatening cancers (as reported by Turaga et al[6] and reviewed in this issue of *Clinical Oncology Alert*). Accordingly, those attending his care should be alert to signs and symptoms of depression and appropriate referral and/or treatment with antidepressant medicines should be initiated early. ■

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ABSTRACT & COMMENTARY

Detecting Lung Cancer by Screening Serology

By William B. Ershler, MD

SYNOPSIS: Among three distinct cohorts of lung cancer patients and matched controls (without tumor), the authors present data on the capacity for an assay that detects antibody to tumor-associated antigens to discriminate those with lung cancer and those without. Using a panel of six antigens, they found their assay to have sensitivity/specificity of approximately 40%/90%. If confirmed in an independent prospective study, such screening may be a very effective adjunct to imaging studies in the early recognition of lung cancer.

SOURCE: Boyle P, et al. Clinical validation of an autoantibody test for lung cancer. *Ann Oncol* 2011;22:383-389.

The early detection of lung cancer remains the greatest chance for cure, but effective screening programs have yet to be developed, even for those at high risk such as cigarette smokers. Previous work has indicated that autoantibodies to certain tumor-associated antigens develop in some patients with non-small cell and small cell lung cancer.[1-6] Boyle and colleagues propose that detection of such antibodies may be an early clue to the presence of tumor and therefore may become a useful screening technique. These investigators now report the clinical validation of an autoantibody panel in newly diagnosed patients with lung cancer.

For this work, they developed an ELISA technique[7] for measuring antibody to six distinct antigens (p53, NY-ESO-1, CAGE, GBU4-5, Annexin 1, and SOX2), all of which had been shown to stimulate antibody production in patients with lung cancer. In three distinct cohorts of newly diagnosed lung cancer patients, patient serum was examined after diagnosis was confirmed, but before therapy. In total, there were 655 patients, and for each, a control was sampled. Controls were matched for age, sex, and smoking history.

The autoantibody panel demonstrated a sensitivity/specificity of 36%/91%, 39%/89%, and 37%/90% in cohorts 1, 2, and 3, respectively, with good reproducibility. There was no significant difference between different stages of disease.

COMMENTARY

This paper describes the methodological details of what the authors intend to ultimately promote as a screening tool to detect early lung cancer. Some of the methodology changed from cohort 1 to 2 to 3, including the criteria for determining positive and negative results. Nonetheless, it is apparent that those with lung cancer had a greater chance of having positive results (sensitivity nearly 40%) and if the results were positive, the chance of having lung

cancer was high (specificity 90%). Thus, screening for antibody using this panel may become a useful tool, particularly for those at high risk. Additional work is required to refine and standardize the methodology and the work will need to be confirmed by other groups. One also has the sense that other antigens also may be added to the panel, thereby improving sensitivity to an even greater extent.

Furthermore, it is not clear from the current work that detection of such antibody will lead to early diagnosis, as the study was conducted in patients with already clinically apparent disease. It will take a prospective large-scale trial conducted in either the general population, or more likely, in those at high risk (e.g., active smokers) to determine if early detection of lung cancer by the appearance of autoantibody to one or more of these tumor-associated antigens will result in a greater cure rate.

It should be noted that lung cancer screening by spiral CT scanning is currently under active investigation.[8-10]

Of course, the practicality of such an approach is somewhat limited by expense, radiation dose, and a fairly significant false positive rate. Perhaps a screening program that includes serologic assessment for autoantibody may be utilized on a broader scale with reflex CT imaging for those with positive results. ■

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RAPID REVIEW

Therapy Related-AML

By William B. Ershler, MD

Approximately 10% of patients with newly diagnosed acute myelogenous (AML) leukemia have a history of prior treatment with chemotherapy, radiation, or both (t-AML).[1,2] Detectable chromosomal changes are more common in t-AML and are probably the consequence of non-lethal mutations occurring in hematopoietic progenitor cells that render those cells susceptible to leukemic transformation.[3]

The latency period between the prior treatment and the appearance of AML varies and seems to depend on the type of prior treatment. For example, for those with a history of radiation or alkylating agent exposure, the period is usually 5-10 years, whereas for those with prior exposure to topoisomerase II inhibitors, latency is considerably shorter, perhaps 1-5 years.[4,5] The varying latency probably relates to the pathogenesis, as those with alkylating agent/radiation exposure are more likely to have unbalanced cytogenetic abnormalities, such as loss of all or parts of chromosome 5 and/or 7, whereas those previously treated with topoisomerase II inhibitors more frequently present with balanced chromosomal rearrangements involving *MLL*, *RUNX1*, and *PML-RARA*.[2,6-8] Nonetheless, this distinction is of marginal clinical value as currently most patients with t-AML have a history of both types of treatment.

There may be a genetic predisposition to t-AML.[3,9] Furthermore, those patients with a history of prior malignancy not treated with either chemotherapy or radiation also may share some features of t-AML. In a recent review of close to 3000 patients with AML who had been enrolled in any of six trials conducted by the German-Austrian AML Study Group (AMLSG),[10] 77 patients had prior malignancies but had not been treated with chemotherapy or radiation. The median latency period for these patients was 5 years and there was a trend toward more adverse cytogenetic features. However, overall

survival for this group was comparable to de novo AML and better than t-AML.

Most series, including this recently reported German-Austrian AMLSG, find the spectrum of cytogenetic abnormalities in t-AML to be similar to de novo AML, but find the frequency of unfavorable cytogenetics, such as complex karyotype or deletion or loss of chromosomes 5 or 7, to be strikingly higher in t-AML. For example, in the large German-Austrian series, 75% of t-AML patients had abnormal karyotypes compared to 51% of those with de novo AML.[10] Notably, although there was no difference in the frequency of favorable risk abnormalities, there was a marked increase in adverse karyotypic changes, including -5, 5q-, -7, 7q-, t(9;11), t(v;11)(v;q23), abnormal (17p), complex karyotypes, and monosomal karyotypes.

Although complete response rates to aggressive chemotherapy are achievable, progression-free and overall survival are worse for t-AML than de novo AML. In a review of 644 t-AML patients treated with "standard" AML regimens, only 28% achieved a CR.[11] Yet, in the German Austrian series, CR rates among those with t-AML were comparable to de novo AML, around 65%. Yet, the relapse-free survival (RFS) at 4 years for those with t-AML was 24.5% compared to 39.5% for those with de novo AML. However, these numbers are subject to selection bias because t-AML patients are typically older and, at least in the United States, are less likely to be referred for enrollment in the aggressive treatments such as those undertaken by this cooperative group.

In a recent comprehensive review on the topic, Godley and Larsen recommend that treatment be based on karyotype and performance status.[12] For those with good performance status and normal or favorable karyotypic changes, standard induction therapy followed by either high-dose cytarabine or allogeneic hematopoietic cell transplant is recommended. For those with good performance status but unfavorable karyotypes, investigational therapy was recommended. For patients with poor performance status regardless of cytogenetic findings, supportive care alone was suggested. The authors point out that the life-threatening complications of t-AML are the result of persistent and profound cytopenias regardless of the fraction of myeloblasts accumulating in the marrow or circulating in the peripheral blood. This may be due to the persistence of the primary malignancy or, more likely, the consequence of prior therapy on hematopoietic reserve. Furthermore, many such patients have sustained prior treatment-associated immunosuppression that may have residual effects on immune competence and many also may have had sensitizing red cell or platelet transfusions.

Whether the prior chemotherapy or radiation has resulted in the emergence of chemotherapy-resistant leukemic stem cells remains a theoretic possibility. Acknowledging that hematopoietic reserve is typically less in patients with t-AML, the administration of standard AML therapy is challenging. Nevertheless, allogeneic hematopoietic cell transplant (HCT) is an option, and in fact remains the best chance for prolonged survival. Yet, early deaths from regimen-related toxicity are more common in patients with t-AML, particularly in those who have been heavily pretreated or are of advanced age. Non-myeloablative, reduced-intensity, allogeneic HCT currently is under investigation for those patients who are ineligible for standard myeloablative HCT. ■

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ABSTRACT & COMMENTARY

Salvage Chemotherapy for AML

By Andrew S. Artz, MD, MS

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

SYNOPSIS: The optimal standard salvage therapy for relapsed or refractory AML remains undetermined. The authors retrospectively compared two regimens at a single institution: CLAG (cladribine, high-dose cytarabine, and G-CSF) with MEC (mitoxantrone, etoposide, and cytarabine). These observational data without adjustment suggest CLAG may be superior to MEC. Nevertheless, outcomes for relapsed or refractory AML remain poor and clinical trials should be entertained when available.

SOURCE: Price SL, et al. Salvage chemotherapy regimens for acute myeloid leukemia: Is one better? Efficacy comparison between CLAG and MEC regimens. *Leuk Res* 2011;35:301-304.

Initial therapy for acute myeloid leukemia (AML) employing cytarabine and an anthracycline (aka, "7 + 3") has remained relatively static for several decades, although recent studies demonstrate the value of higher daunorubicin dosing.[1] Complete remission (CR) rates vary from 50%-80%, but most patients eventually succumb to relapse. Adverse prognostic markers at the time of relapse include shorter duration of first CR, higher risk initial karyotype, older age, and prior hematopoietic cell transplantation.[2] As expected, outcomes after second salvage are dismal, with median survival of 1.5 months.[3]

As opposed to initial induction therapy, numerous drugs and combinations have been used for relapse without any standard emerging. For remission duration less than 6–12 months, responses range from 20% to 40%. Response rates for late remission are nearly similar to initial response rates, but overall survival remains poor. In appropriate candidates who achieve remission, an allogeneic hematopoietic cell transplant should be pursued. In this study, the authors retrospectively compared mitoxantrone, etoposide, and cytarabine (MEC) to cladribine, high-dose cytarabine, and G-CSF (CLAG). A total of 162 relapsed AML patients underwent either MEC or CLAG between 2005 and 2008. Baseline characteristics were similar. Median age was 55 years. Approximately 30% had a poor-risk karyotype at diagnosis and approximately 50% exhibited an intermediate-risk karyotype at diagnosis (not at relapse). Complete remission rates for CLAG and MEC were 37.9% and 23.8%, respectively ($P = 0.05$). The median OS of 7.3 months of CLAG bested the survival of 4.5 months for MEC ($P = 0.03$). Relapse-free survival showed similar effects. The 30-day early death rate was 9.4% for CLAG and 10.9% for MEC ($P = 0.52$). For those under 65 years of age, 36% of CLAG treated patients and 25% of MEC treated patients proceeded to allogeneic hematopoietic cell transplantation.

Sixty-eight patients underwent salvage for primary refractory disease, of which 55 had received only one prior cycle of chemotherapy. The CR rates generally mirrored relapsed patients, as CLAG achieved CR in 46% vs MEC induced CR in 22% ($P = 0.09$). For patients who relapsed, response rates were similar between the regimens, although a greater proportion of CLAG-treated patients (59.9%) had a short interval of first complete remission at less than 12 months compared to MEC-treated patients (45.6%) ($P = 0.20$).

COMMENTARY

Despite success in achieving CR in the majority of adults with AML, relapse persists as the major barrier toward long-term outcomes. Long-term survival after relapse or for refractory disease is poor, and optimal salvage therapy can not be determined based on the observational studies to date. Accordingly, the National Comprehensive Cancer Network guidelines recommend clinical trials as the preferred option. The need to maximize the chance of CR without undue toxicity may be most critical for allogeneic transplant candidates.

In this series from the Moffitt Cancer Center, the investigators catalog a recent experience of 162 patients treated over 3.5 years with either MEC (mitoxantrone, etoposide, and cytarabine) or CLAG (cladribine, high-dose cytarabine, and G-CSF). Regimens were selected based on an institutional shift from MEC to CLAG. The authors demonstrate a 37.9% response rate to CLAG compared to 23.8% after MEC ($P = 0.05$), which translated into a 2.8 month survival benefit ($P = 0.03$) of 7.3 months for CLAG as opposed to 4.5 months for MEC. CR rates and OS did not differ by regimen

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for patients in first relapse. Importantly in the < 65-year-old cohort, 36% of CLAG treated patients underwent allogeneic hematopoietic cell transplantation vs 25% for MEC.

Clearly, the retrospective nature of this study is the main limitation precluding more confidently assigning CLAG as the preferred therapy for salvage. Although the groups appear relatively balanced, information on molecular markers for normal karyotype AML (e.g., FLT-3 mutation) and patient health (performance status or comorbid disease) is lacking.

Since CLAG was adopted more recently, it is conceivable that improved supportive care benefitted CLAG treated patients (e.g., availability of extended spectrum azoles). The sample size does not permit well-adjusted models to interrogate specific subsets of interest. These data underscore the tremendous gap in well-conducted studies for refractory and relapsed AML. Even if CLAG is marginally superior to MEC, as suggested by the authors, the response rates are still low and the value compared to other regimens (e.g., FLAG, clofarabine +/- cytarabine) requires further study. Most importantly, future therapy likely will target disease mechanisms as evidenced by the proliferation of clinical trials inhibiting the receptor tyrosine kinase FLT-3 rather than a "one size fits all" regimen.

In summary, CLAG showed significantly better overall response rates compared to MEC for relapsed or refractory AML in a retrospective historical comparison. Although CLAG is a reasonable therapy for salvage, treatment remains unsatisfactory and clinical trials when available should be strongly considered. ■

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CME Questions

Suicide risks are known to be higher among patients with pancreatic cancer. The recent study from Turaga and colleagues demonstrated the greatest risk among:

a. females over the age of 70 years.
b. males between the ages of 35-50 years.
c. males within two months of pancreatic cancer surgery.
d. females within the two months of pancreatic cancer surgery.

Based upon the results of the recently reported PRODIGE phase III clinical trial, treatment with FOLFIRINOX (5FU, leucovorin, irinotecan, and oxaliplatin) resulted in significant improvements in which of the following outcomes?

a. Response rate
b. Progression-free survival
c. % survival at 1 year
d. Median overall survival
e. All of above

For good performance status patients who present with t-AML and are found to have unfavorable karyotype changes, the recommended approach would be:

a. enrollment in an investigational trial.
b. standard AML induction followed by allogeneic HCT.
c. standard AML induction followed by high-dose cytarabine consolidation.
d. supportive care.

Answers: c, e, a.

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]

PCA3 Urine Test to Detect Prostate Cancer

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

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Do Topical Steroids Lead to Glaucoma or Cataract?

Source: Haeck IM, et al. Topical corticosteroids in atopic dermatitis and the risk of glaucoma and cataracts. *J Am Acad Dermatol* 2011;64:275-281.

The treatment of atopic dermatitis (ATD) usually is initiated with topical steroids (TPS). Because ATD is a chronic remitting and relapsing disorder and may occupy a large cutaneous area, exposure to TPS can be extensive. Since both glaucoma and cataracts are associated with ophthalmic TPS, and ATD may require periocular application of TPS, it is important to learn whether non-ophthalmic utilization of TPS could lead to increased intraocular pressure. The use of inhaled steroids for asthma has been associated with development of cataracts, but not glaucoma.

To study the impact of TPS in ATD upon glaucoma and cataract, 88 adults with chronic ATD were evaluated. For each study subject, data on total amount of TPS prescribed over the last 2-5 years was available. Two-thirds of the study subjects had applied TPS in the periocular region, since they suffered from ATD on the eyelids and periorbital region. The authors cite the *average* amount of periocular TPS use within this group as "3.9 days/week, 6.4 months/yr, for 4.8 years."

There was no sign of increased incidence of glaucoma among TPS users. Corticosteroid-induced cataract was seen in 2 of the 88 subjects, both of whom had received courses of systemic steroids in addition to TPS. These data are reassuring that TPS application does not appear related to the development of glaucoma or cataracts, even when TPS needs to be applied in the periorbital region. ■

Can Exenatide Prevent Glucocorticoid-Induced Hyperglycemia?

Source: Van Raalte DH, et al. Glucagon-like peptide-1 receptor agonist treatment prevents glucocorticoid-induced glucose intolerance and islet-cell dysfunction in humans. *Diabetes Care* 2011;34:412-417.

Clinicians anticipate that administration of systemic glucocorticoids, such as prednisone (PRED), to persons with diabetes worsen hyperglycemia. PRED reduces insulin sensitivity and impairs beta-cell function, resulting in hyperglycemia.

Chronic PRED administration is associated with increased risk for osteoporosis and peptic ulcer; preventive strategies for each of these adverse effects has been developed. To date, no such plan for mollifying exaggerated glucose excursions due to PRED has been offered.

The glucose dysregulation secondary to PRED appears to be primarily postprandial, rather than fasting. Clinical trials of metformin failed to confirm efficacy in preventing glucocorticoid-induced hyperglycemia (GIH). Because exenatide (EXE) has prominent effects specifically on postprandial glucose, it was logical to investigate whether EXE might favorably impact GIH.

Healthy adult men (n = 8) received a PRED load of 80 mg orally for two days (prednisolone, actually, but prednisone and prednisolone are mg-for-mg equivalent). They were randomized to also receive placebo or EXE. GIH was prevented by concomitant EXE administration.

This proof-of-concept trial should stimulate further investigation to determine whether the demonstrated ability of EXE to prevent GIH is similarly favorable in diabetics. ■

COPD: Beyond Pulmocentricity

Source: Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. *Chest* 2011;139:165-173.

Chronic obstructive pulmonary disease (COPD) generally is regarded as a pulmonary process induced by toxic insult—usually cigarettes, but sometimes other environmental exposures. Why only a small subset of chronic smokers develops COPD (20-25%) remains a mystery. Progressive loss of pulmonary function continues even after smoking cessation, suggesting that some inflammatory process, once set in gear in susceptible individuals, becomes self-perpetuating.

Experts recognize other non-pulmonary tissue compartments are involved in COPD. Musculoskeletal wasting, metabolic syndrome, and depression are disproportionately comorbid with COPD. Biopsy studies have found increased inflammatory cytokines in intercostal muscles, providing an explanation for dyspnea that goes beyond simple damage to alveolar capacity for gas exchange.

Both diabetes and chronic kidney dis-

ease have been found to be associated with COPD. In the absence of a visible etiologic link, systemic inflammation is a suspected culprit. Indeed, early data indicate that smoking cessation slows progression of renal failure. In reference to diabetes, smoking cessation is associated with short-term worsening of diabetes risk, attributed to the weight gain commonly seen after smoking cessation. COPD is increasingly viewed as part of a systemic process. ■

Aspirin and Risk of Death from Cancer

Source: Rothwell PM, et al. Effect of daily aspirin on long-term risk of death due to cancer: Analysis of individual patient data from randomized trials. *Lancet* 2011;377:31-41.

In animal models, aspirin (ASA) has favorable effects on the incidence and/or growth rate of some cancers (CA). Most clinical trials of ASA have been for primary or secondary prevention of cardiovascular disease. Rothwell et al analyzed data from three UK clinical trials that included CA mortality outcomes, although none of the trials was designed specifically to study the impact of ASA upon CA as a primary or secondary endpoint. Their data set of almost 24,000 adult men and women divided treatment groups by duration of follow-up: 0-5 years of treatment, and > 5 years of ASA treatment.

ASA was associated with an 18% relative risk reduction in deaths due to cancer; risk reduction was greatest in subjects treated for more than 5 years. Gastrointestinal (GI) cancer deaths were reduced most prominently, but other cancers (e.g., lung) also showed favorable impact from ASA treatment. Although bleeding induced by ASA typically is viewed as an adverse effect, it has been suggested that ASA treatment also makes GI tumors more likely to bleed, facilitating their discovery. There appears to be a "latent period" of at least 5 years before the effects of ASA impact esophageal, pancreatic, brain, and lung cancer.

When evaluating the risk-benefit of ASA for cardiovascular risk reduction, the favorable impact of ASA upon cancer mortality also should be considered. ■

Reducing Incontinence After Prostatectomy

Source: Goode PS, et al. Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: A randomized controlled trial. *JAMA* 2011;305:151-159.

When prostate cancer (PCA) was diagnosed primarily at the later stages of disease, post-surgical adverse effects such as incontinence or erectile dysfunction weighed less heavily on the risk-benefit scale, since without surgery outcomes were poor. In an era when most PCA is diagnosed at a stage of localized disease, much of which would be destined to never evolve to clinical relevance, balancing adverse surgical consequences, becomes more complex.

Incontinence occurs and persists in the majority of men after radical prostatectomy. Two-thirds of men have persistent incontinence 5 years postoperatively. Encouraging results have been seen in trials that incorporate behavioral and physical therapies promptly after surgery. Little insight is available about the success of intervention for persistent incontinence distant from surgery.

Goode et al enrolled 208 men who had undergone prostatectomy and continued to suffer incontinence 4-5 years later. Participants were randomized to behavioral therapy (pelvic floor exercises, bladder control methods, fluid management) plus biofeedback and/or pelvic floor electrical stimulation versus control.

The reduction in incontinence was significantly greater in treatment groups (55% reduction) than in the control group (24% reduction). Neither biofeedback nor pelvic floor electrical stimulation added effectiveness to behavioral therapy alone. Clinicians should be encouraged that even late employment of behavioral therapies can provide substantial incontinence improvement. ■

Real-life Efficacy of Herpes Zoster Vaccine

Source: Tseng HF, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA* 2011;305:160-166.

Herpes zoster vaccine (zostavax) was licensed in the United States in 2006 subsequent to the publication of the Shingles Prevention Study, a large (n = 38,546) prospective trial that demonstrated a 51% reduction in zoster and a 67% reduction in postherpetic neuralgia in vaccines compared to controls. Clinicians may wonder whether the favorable results seen in a major clinical trial would be replicated in their private clinical settings. According to this report by Tseng et al, that may very well be the case.

Enrollees in the Southern California Kaiser Permanente health plan older than 60 years of age who had received zoster vaccine (n = 75,761) were compared with age-matched controls (n = 227,283) in this retrospective analysis. The Kaiser Permanente study population was comprised of healthy, immunocompetent, community-dwelling adults. The primary outcome of interest was incidence of zoster.

The rate of zoster in the vaccine recipients (6.4/1000 person-years) was significantly less than the rate in unvaccinated study subjects (13.0/1000 person-years). This 55% relative risk reduction is highly concordant with the reductions seen in the Shingles Prevention Study, confirming the generalizability of their results. ■

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Apixaban and Rivaroxaban Near Approval for Nonvalvular AF

In this issue: Apixaban and rivaroxaban near approval for nonvalvular atrial fibrillation; fidaxomicin for *C. difficile* infections; guideline for intensive insulin therapy; and FDA Actions.

Dabigatran for stroke in patients with nonvalvular atrial fibrillation

Dabigatran, a direct thrombin inhibitor, recently was approved for prevention of stroke in patients with nonvalvular atrial fibrillation. The evidence for its benefit is strong enough that the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society recently upgraded their atrial fibrillation guidelines to include dabigatran (*Circulation* published online February 14, 2011). Meanwhile, the direct factor Xa inhibitor rivaroxaban is working its way through the FDA approval process for the same indication, with approval expected later this year. The latest player in the field is apixaban, also a direct factor Xa inhibitor. Apixaban was studied in a double-blind Phase 3 study of 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable. Patients were randomized to receive apixaban 5 mg twice daily or aspirin 81-324 mg per day with a mean follow-up of 1.1 years. The primary outcome was occurrence of stroke or systemic embolism. The study was terminated early because of a clear benefit in favor of apixaban. There were 51 events (1.6 % per year) in the apixaban group vs 113 events (3.7% per year) in the aspirin group (hazard ratio with apixaban 0.45, 95% confidence interval 0.32-0.62; P < 0.001). The death rate was 3.5% in the apixaban group vs 4.4% in the aspirin group (P = 0.07). The rates of major bleeding or intracranial hemorrhage were similar; however, the risk of first hospitalization for cardiovascular causes was significantly lower with apixaban. The authors suggest that apixaban is more effective than aspirin. In indirect comparisons, apixaban is more effective than aspirin plus clopidogrel and at least as effective as warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation (*N Engl J Med* published online February 10, 2011). Apixaban is currently being studied head-to-head with warfarin in the ARISTOTLE trial. If the data from that trial looks favorable, it is likely that both apixaban and rivaroxaban also will be approved for this indication in the not-too-distant future. Dabigatran and apixaban are both dosed bid while rivaroxaban is a once-a-day drug. The extent to which these drugs gain general usage at the expense of warfarin in large part will be due to patient preference and cost. ■

Fidaxomicin for *C. difficile* infections

A new option may soon be availiable for treating *Clostridia difficile* infections. Fidaxomicin (not yet approved in this country) is a non-systemic (poorly absorbed) narrow spectrum macrolide antibiotic that is bacteriocidal against *C. difficile* infections. It recently was compared to vancomycin in a head-to-head Phase 3 noninferiority study of 629 adults. Patients with a positive stool toxin test to *C. difficile* were randomized to

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fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day. The primary endpoint was clinical cure and the secondary endpoint was recurrence within 4 weeks and global cure (no recurrence). Fidaxomicin was noninferior to vancomycin in both the intention-to-treat (88.2% cure rate with fidaxomicin vs 85.8% with vancomycin) and per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients had recurrence with fidaxomicin in both groups (15.4% vs 25.3%, $P = 0.005$ intention-to-treat, and 13.3% vs 24.0%, $P = 0.004$ per protocol) although the lower rate of recurrence was in the less virulent strains. For the more virulent strains, the recurrence rate was about 25% for both drugs. Fidaxomicin was associated with a higher rate of hyperuricemia and elevated transaminases (*N Engl J Med* 2011;364:422-431). An accompanying editorial points out that the incidence and virulence of *C. difficile* infections is increasing at an alarming rate in this country. Fidaxomicin inhibits vegetative forms of *C. difficile* while preseving intestinal flora, a combination that holds promise, and if borne out "this new agent could become a recommended therapy for *C. difficile* infection" (*N Engl J Med* 2011;364:473-475). ■

Guideline for intensive insulin therapy

A guideline from the American College of Physicians (ACP) recommends against aggressively controlling blood glucose in hospitalized patients. Intensive insulin therapy (IIT) is no longer recommended for patients in intensive care units, regardless of whether they have diabetes. Specifically, the ACP recommends not using IIT to strictly control blood glucose or even normalized blood sugar in surgical ICU or medical ICU patients, and recommends a target blood glucose level of 140-200 mg/dL if insulin therapy is used. The recommendation is based on multiple studies that show no reduction in mortality with a blood glucose target of 80-180 mg/dL compared with higher targets using a variety of intensive insulin regimens. This includes treatment of patients with myocardial infarction, stroke, acute brain injury, or those under perioperative care. The guideline further recommends that avoiding targets less than 140 mg/dL should be a priority because harm is likely with lower blood glucose targets (*Ann Intern Med* 2011;154:260-267).

FDA actions

The FDA is warning against the use of terbutaline for prevention or prolonged treatment of preterm labor in pregnant women. The drug, which is approved for treatment of asthma, has been used off label for treatment of preterm labor and uterine hyperstimulation; however, the agency has received postmarketing reports of serious adverse reactions, including heart problems, and even maternal deaths, associated with the drug. The FDA has added a Boxed Warning and Contraindication to the labeling of the drug warning against these uses. This extends to both the IV and oral forms of terbutaline.

The FDA has approved hydroxyprogesterone caporate injection to reduce the risk of preterm delivery before 37 weeks of pregnancy in a pregnant woman with a history of at least one spontaneous preterm birth. The drug is not intended for use in women with a multiple pregnancy, such as a twin pregnancy, or other risk factors for preterm birth. The drug was approved under the FDA's accelerated approval regulations, and, as such, additional studies will be required after approval to show that the drug does indeed have clinical benefit. Hydroxyprogesterone caproate is given once a week by injection into the hip beginning at week 16 and no later than week 21. The drug is marketed by Hologic Inc. as Makena.

The FDA has issued a drug safety alert regarding the risk of serious liver injury with dronedarone (Multaq). The drug — which is approved for prevention of atrial fibrillation/flutter — has been associated with multiple cases of severe liver injury, including two cases that required liver transplantation. Dronedarone previously was found to double the risk of death in patients with severe heart failure and was approved with a REMS designed to prevent its use in that patient population. Physicians are reminded to advise patients to contact a health care professional immediately with any signs of hepatic injury or toxicity. All patients on dronedarone should get periodic hepatic serum enzymes especially during the first 6 months of therapy.

The FDA has approved a new treatment for head lice. Spinosad is an insecticide originally derived from a naturally occurring soil bacterium. The 0.9% topical suspension was shown to be effective in two Phase 3 active-control, randomized studies in which 86% of patients treated with the active drug were lice free after 14 days compared to 44% of controls. The product should not be used in children under 6 months of age because it contains benzyl alcohol. Spinosad is applied as a single 10-minute application which may be repeated in one week if lice are seen. It will be marketed by ParaPro LLC as Natroba. ■