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INSIDE

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Androgen Depletion and Increased Cardiac Risk in Prostate Cancer Patients

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *In a retrospective review of a primarily community-based registry of prostate cancer patients, a heightened risk of cardiovascular mortality was found for patients with localized disease treated with either adjuvant or neoadjuvant androgen deprivation.*

Source: Tsai HK, et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst.* 2007;99:1516-1524.

Currently, primary treatments for localized prostate cancer include watchful waiting, active surveillance, interstitial brachytherapy, external beam radiotherapy, cryotherapy, radical prostatectomy, and primary hormonal therapy.[1] Oftentimes, treatment is guided by the experience of the attending physician coupled with an assessment of the risk for progressive cancer and dying of this disease in the context of the patient's age and comorbidities. As an adjunct to prostatectomy or radiation therapy, some patients are offered androgen deprivation therapy (ADT) either by a neoadjuvant or adjuvant approach. Indeed, ADT use has increased substantially in this setting over the past few years,[2] and there has been recent evidence linking it with increased risk for both diabetes and cardiovascular disease.[3] ADT can lead to elevated body mass index, increased fat deposition, and decreased insulin sensitivity, all of which characterized the metabolic syndrome.[4] Accordingly, the influence of ADT on the development or progression of cardiovascular disease has become an important issue.

In a retrospective review, Tsai and colleagues examined data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) dataset that included 3262 prostatectomy patients and 1630 patients treated with external beam radiotherapy, brachytherapy, or cryotherapy for localized prostate cancer. The overall CaPSURE

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registry included 13,124 patients from 31 urology practices (25 community-based, 3 university practices, and 3 US Department of Veterans Administration Hospitals). Men with localized disease were identified and of these there were 4892 for whom data was available for this analysis. ADT was defined as treatment with gonadotropin releasing hormone agonist and/or an antiandrogen either neoadjuvantly (initiated before the start of local therapy) or adjuvantly (initiated up to six months after the start of local therapy). Overall, 1015 patients were treated with ADT in conjunction with local therapy, and 3877 patients were not treated with ADT. Among the patients who underwent radical prostatectomy, 266 were treated with ADT, and among those who received nonsurgical treatment, 749 were treated with ADT. The median follow-up time was 3.8 years (range equals 0.1 to 11.3 years).

The outcome examined was cardiovascular death, and competing risk methods were utilized to determine time of cardiovascular death while accounting for those competing risks (ie, death from prostate cancer or other non-cardiovascular causes). Additionally, regression analysis for age and known risk factors for cardiovascular disease were included.

The results indicated that ADT statistically significantly shortened time to cardiovascular death and was associated with an increased cumulative incidence of cardiovascular death at five years among prostatectomy patients regardless of age. Also noted was a greater incidence of cardiovascular death among patients 65 years old and older who were treated with ADT and managed with external beam radiotherapy, brachytherapy, or cryotherapy, but the difference from those not given ADT did not reach statistical significance.

Thus, in this series, the use of adjuvant (or neoadjuvant) ADT was associated with increased risk of death from cardiovascular disease, and this was particularly noticeable for those treated surgically.

COMMENTARY

In this careful review of the CaPSURE data set, ADT was apparently associated with cardiovascular mortality. In fact, more patients treated for localized prostate cancer died of cardiovascular disease than died of prostate cancer. It also appeared from their analysis that those treated by surgical approach were at greater risk for the ADT-enhanced cardiovascular mortality than those treated by non-surgical approaches that included adjuvant ADT. However, the numbers were relatively small for those receiving ADT after surgery compared to after radiotherapy, and any conclusion regarding the difference between primary approach (surgery vs radiation) and the risk of ADT would be premature. However, as for the use of adjuvant (or neo-adjuvant) ADT in general, the association with increased cardiovascular risk seems valid.

But, even this finding requires confirmation as the analysis was retrospective. Patients offered adjuvant ADT are likely not quite the same as those who were not offered the additional treatment. Indeed, in this series they had higher prostate-specific antigen (PSA) levels, larger primary tumors and higher Gleason scores. Even though these factors were considered in the regression analysis and by the competing risk methods adjusting for known cardiovascular risk factors, the association of ADT and cardiovascular mortality remained significant. Yet, in a retrospective analysis such as this, other factors that were not included may define differences between those treated and those not, and to the extent that these factors may be associated with cardiovascular risk, the findings are made less definitive.

Nonetheless, it is quite likely that ADT increases risk for cardiovascular death both in the prostatectomy (as demonstrated here) and radiotherapy-treated, and the mechanism may well relate to the metabolic alterations noted above. It is notable that a pooled analysis of three trials that randomly assigned patients to radiation therapy, either with or without short course ADT, showed statistically significant shorter times to fatal myocardial infarction among patients 65 and older treated with ADT and radiation when compared to those treated with radiation alone.[5] Although data from a prospective randomized trial is not currently available, the authors recommend that patients with localized prostate cancer

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considering adjuvant ADT after primary therapy be carefully screened for other cardiovascular risk factors and observed very closely in that regard during therapy. This makes good sense. ■

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Cord Blood Transplantation Using Nonmyeloablative Regimens

ABSTRACT & COMMENTARY

By Andrew Artz, MD, MS

Division of Hematology/Oncology, University of Chicago, Chicago, IL

Dr. Artz reports no financial relationship to this field of study.

Synopsis: *Advances such as nonmyeloablative conditioning have contributed to increased utilization of allogeneic transplant in older and less fit individuals. In a prospective protocol, 110 patients having high-risk hematologic disease underwent a nonmyeloablative conditioning regimen followed by unrelated cord blood cell (UCB) transplantation. The median age was 51 years and 85% required two UCB units to meet minimum cell doses. The median time to neutrophil engraftment was 12 days. The cumulative incidence of grades II-IV acute GVHD at 100 days was 59% and transplant related mortality by day 180 was 19%. Three year actuarial survival was 45%. Nonmyeloablative conditioning followed by UCB transplantation represents a promising strategy for transplantation in older and less fit adults lacking an HLA identical adult stem cell donor.*

Source: C. Brunstein, et al. *Blood.* 2007. vol. 110: 3064- 3071.

The traditional notion of restricting hematopoietic cell transplantation to young patients with a human leukocyte antigen (HLA) matched sibling has vanished. Less intensive chemotherapy (ie, conditioning) before the transplant enables adequate immunosuppression for donor engraftment and contributes to reduced toxicity. Increasingly, rather than age or comorbid illnesses, lack of a suitable donor prevents transplantation. For those without an HLA matched sibling, a large registry of volunteer unrelated adult donors exists. Nevertheless, many patients eligible for transplant because of high risk hematologic malignancies do not have an adequately matched unrelated donor. Unrelated cord blood (UCB) cells have emerged as a promising donor source because they appear more permissive across HLA barriers. Thus, additional mismatches for UCB compared to unrelated adult donors are acceptable. UCB cells generally contain lower cell doses than adult stem cell or marrow collections, contributing to a major drawback: slow hematopoietic engraftment (ie, slow recovery of neutrophils) or even graft failure.[1,2] In this report, Brunstein and colleagues report on the largest series to date of non-myeloablative conditioning followed UCB transplantation.

Patient eligibility required high-risk hematologic disease and lack of an adequate sibling donor (defined as no more than a 1 antigen HLA mismatch). Further, to receive the non-myeloablative rather than standard ablative conditioning regimen, patients had to be 45 years or greater or have other features increasing the risk of transplant related mortality. UCB units were required to have at least 4/6 HLA matching based upon antigen level matching at HLA-A and HLA-B and allele matching at HLA-DRB1. The minimum total nucleated cell dose (TNC) was 2.0 x 10(7) per recipient weight in kg with a goal of at least 3.0 x 10(7)/kg. When a single UCB unit did not meet the TNC threshold, a second cord matched to the first cord was selected. The conditioning regimen consisted of cyclophosphamide at 50 mg/kg on day - 6, fludarabine 40mg/m2 from day - 6 through day - 2, and a single fraction of TBC at 200 cGy on day - 1. Equine anti-thymocyte globuline was given from day - 3 to day - 1 to those with minimal prior chemotherapy exposure (to promote engraftment of UCB). Post-transplant immunosuppression included cyclosporine A and mycophenolate mofetil. One-hundred ten patients underwent UCB transplantation on this protocol with a median age of 51 years (range 16-79). Approximately half were transplants for AML or MDS. The majority (85%) necessitated two UCB to achieve the minimum cell dose. The median TNC dose was 3.7 x 10(7) /kg. Four of six HLA matched UCB comprised most units (61%); the remainder were 5/6 or 6/6 HLA matched. The median neutrophil recovery occurred 12 days after UCB infusion. Primary and secondary graft failure occurred in 7 and 8 patients, respectively. The cumulative incidence of grades II-IV GVHD was 59% for

acute GVHD and 22% for chronic GVHD. Mortality related to the transplant was 19% by day 180. Overall survival was 45% at 3 years but was not stratified for any disease subtypes.

COMMENTARY

The median age of most leukemias is around 68 years of age and the prognosis is generally worse for older adults. Hematopoietic cell transplantation has historically been reserved for younger adults under the age of 50 years. Increasingly, transplantation is being performed in older and less well adults, in part related to better tolerated transplant conditioning regimens. These so called "nonmyeloablative regimens" lead to minimal or transient marrow ablation. However, reduced extramedullary toxicities (eg, pulmonary, liver) may be the most important determinant of better tolerance. The field of allogeneic transplantation has witnessed large increases in the number of adults over 50 years receiving a transplant. As we move away from age alone as a major limitation to transplant, the lack of an adequately matched HLA identical donor precludes transplant has arisen as a major barrier. Many donor centers require a complete HLA matched unrelated donor and some accept 1 antigen/allele mismatches (ie, 7/8 or 9/10 HLA match). Nevertheless, that leaves a large number of patients without sibling or unrelated HLA matched donors. This is particularly problematic for non-whites, where registry matches are infrequent. Unrelated cord blood (UCB) represents a promising option because of less stringent HLA matching requirements allowing 4/6 antigen match compared to at least a 7/8 HLA allele match required for adult donors. The major limitation to UCB has been lack of adequate cell doses for adults that can lead to either slow engraftment or graft failure. The slow engraftment predisposes to life-threatening neutropenic infections.

In this report, Brunstein and colleagues report on a large series of nonmyeloablative transplants using unrelated UCB as a donor source for those lacking an HLA identical sibling. Eligibility required an increased risk of transplant-related mortality using standard ablative conditioning. The most common indication for using this nonmyeloablative protocol was age > 45 years. Among 110 recipients, 85% required two UCB units to achieve a minimum cell dose of 2 x 10(7) total nucleated cells per recipient weight in kg. The median engraftment of 12 days was highly encouraging and similar to adult stem cell sources (ie, peripheral blood and marrow) and smaller series of myeloablative conditioning followed by double UCB. Single UCB transplant in adults has been reported to lead to a median neutrophil engraftment of 23-28 days. Thus, achieving a minimum cell dose by using two UCB units represents an important advance in reducing the risk of complications from prolonged marrow aplasia and expanding the number of patients eligible to receive UCB transplants. In this group of relatively older adults, reducing neutropenia duration may be especially beneficial. However, primary and secondary graft failure still remains a problem and occurred in 7 and 8 patients respectively.

Acute GVHD occurred in 59%, and transplant related mortality was 19% at day 180. Recipients of two UCB units showed a trend toward more graft-versus-host disease (GVHD) but less relapse. Although statistically non-significant, these results mirror the higher GVHD but lower relapse in single antigen mismatched marrow and blood transplants relative to completely matched donors. For transplant, higher graft-versus-leukemia is almost always offset by more GVHD. The encouraging overall survival mandates confirmatory studies because the small sample size prevents stratifying results by disease subsets (eg, AML in CR1) and thus necessitating comparisons to historical results. Nevertheless, the favorable outcomes appear comparable to nonmyeloablative adult stem cell transplants using unrelated donors.

An important limitation is that donor selection employed in this study differs from most transplant center's donor procurement strategy. Most centers will select an HLA matched unrelated donor when no HLA matched sibling donor exists. Absent an HLA matched unrelated donor, then alternative donor approaches such as UCB, mismatches, or haplo-identical will be entertained. Thus, the ultimate question the report generates is how UCB transplant compares to unrelated adult donor transplants. The long delay in procuring an unrelated adult donor (approximately 3 months) relative to the immediate availability for UCB highlights is a distinct advantage for cord blood.

This large series demonstrates the feasibility of UCB transplantation in older adults and suggests good outcomes. For practicing oncologists, this report should encourage less stringent criteria for transplant referral in patients having high-risk hematologic disease. Ultimately, the decision to proceed with a transplant will remain individualized, and a discrete age maximum can not be stated. Nevertheless, age alone or lack of an HLA identical sibling should not be a barrier for referral for patients in their 50s and possibly 60s who might benefit from a hematopoietic cell transplant. ■

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Diagnosing Early Pancreatic Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Although pancreatic cancer growth is considered rapid, early recognition of resectable disease remains the best chance for long-term survival. It is possible that an early sign of evolving pancreatic neoplasm is glucose intolerance. In a series of 30 pancreatic cancer patients evaluated at the Mayo Clinic, CT scans obtained 6 months or more before the diagnosis revealed potentially resectable lesions in some, and this was notably true for those who had CT scans and new-onset diabetes several months before the diagnosis of pancreatic cancer. Thus, physicians evaluating adults with newly diagnosed diabetes should consider the possibility that the glucose intolerance is an accompaniment of early pancreatic neoplasia.*

Source: Pelaez-Luna M, et al. Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. *Am J Gastroenterol.* 2007;102:2157-2163.

PANCREATIC CANCER REMAINS BOTH A CHALLENGE to diagnose and an even greater challenge to effectively treat. In fact, only patients discovered early and with resectable disease have a chance for long-term survival. Unfortunately, the majority of patients (greater than 85%) have unresectable disease by the time disease-associated symptoms occur and a diagnosis is made.[1] Patients who have the greatest chance for curative resection are those who have their tumors diagnosed when under evaluation for other problems and the pancreatic mass is discovered before symptoms occur. The timeline for progression of pancreatic cancer from resectable to unresectable is unknown. Evidence for glucose intolerance is known to occur in a substantial percentage of pancreatic cancer patients and it may occur earlier than other signs or symptoms of disease. In an effort to determine whether the investigation of new-onset diabetes for pancreatic cancer or the serendipitous discovery of a CT detected pancreatic mass offers a sufficiently early diagnosis to improve cure rates, Pelaez-Luna and colleagues at the Mayo Clinic reviewed 30 patients with pancreatic cancer who either had abdominal CT scans performed months or years prior to the diagnosis of pancreatic cancer and/or had developed diabetes prior to or concurrent with the diagnosis of pancreatic cancer.

All CT scans including those done at the time of diagnosis and those performed at earlier dates were reviewed and classified as either normal, potentially resectable, or unresectable pancreatic cancer. Fasting blood glucose levels were obtained at the time of diagnosis and also prior to diagnosis in 18 cases of the 30 patients.

Of the 30 patients, 28 had a total of 38 CT scans done at a median of 18 months (range 1 to 41 months) before the cancer diagnosis. At cancer diagnosis, only 7 of 30 patients could undergo margin negative surgical resection. CT scans done at six months before diagnosis or earlier revealed either a normal pancreas (n = 20) or a resectable mass (n = 6). None of the CT scans that were obtained earlier than six months before diagnosis revealed an unresectable mass.

With regard to diabetes, the mean interval between the onset of laboratory confirmed glucose intolerance and pancreatic cancer was 10 months (range 5 to 29 months). At the time of diagnosis of diabetes, 13 patients had CT scans. Of these, three had a normal appearing pancreas, six had a mass that was, even at that time, considered resectable, and four had a mass that was, even at that time considered unresectable.

Thus, the authors conclude that undetectable or resectable pancreatic cancer was apparent on CT scans obtained greater than six months prior to clinical diagnosis. At the onset of diabetes, pancreatic cancers were, in this series, generally resectable.

COMMENTARY

This series highlights the frustrating aspect of early diagnosis in pancreatic cancer. Unlike colon cancer, for example, where the development of a neoplastic lesion occurs over years and for which surveillance initiatives have demonstrated the capacity for early recognition allowing curative resection, such has not been the case for pancreatic cancer. This, no doubt results from what must be a rapid transition from resectable to unresectable disease and the lack of an effective and feasible screening device. Most of the patients in this series had become diabetic, and for those who had CT scans obtained at or near the time of the newly diagnosed diabetes, at least half were shown to have a pancreatic mass that was considered resectable. In fact, patients with or without diabetes who had CT scans obtained six months or more prior

to the onset of pancreatic cancer for unrelated conditions were likely to have resectable tumors as well. The fact that the masses discovered by retrospective analysis were not actively pursued in a timely fashion highlight the uncertainty of pancreatic imaging (by CT scans utilized during the years of this analysis) and the rapidity with which pancreatic cancers grow. Thus, although some might consider CT scanning for pancreatic cancer screening, the applicability of this expensive approach would likely be seriously hampered by measures of both sensitivity and specificity.

However, if a high-risk category were identified, CT scanning might prove reasonable. One such category of high-risk individuals would be those with newly-discovered diabetes. In a population-based study performed by this same group of Mayo Clinic investigators, those with new onset diabetes were shown to have eight times the likelihood of being diagnosed with pancreatic cancer within three years than the general population.[2] Thus, it would seem reasonable to investigate the role of CT scan screening for patients with new onset diabetes. However, prior studies that have addressed this question (screening for pancreatic cancer in those with new onset diabetes and cancer-related symptoms) have identified mostly unresectable pancreatic cancer.[2,3] However, those studies relied on the presence of cancer-related symptoms in newly diagnosed diabetics, and thus, the lack of discovering early (or small) pancreatic lesions is not surprising. A similar analysis of asymptomatic patients with newly discovered diabetes might be more successful.

As imaging studies become more precise and less intrusive, prospective studies may result in an improved understanding of the relationship between diabetes development, pancreatic mass, and pancreatic cancer. More importantly, these studies may identify individuals who would benefit from screening and heightened surveillance such that pancreatic cancers could be discovered in a resectable stage. ■

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Night Shift Work and Endometrial Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD, Editor

Synopsis: *Night shift work has been shown to be associated with an increased risk of breast, colon and prostate cancer, presumably on the basis of diminished melatonin and its effects on hormonal and metabolic factors. In an analysis of the Nurses Health Study, data from 53,487 were examined with regard to night shift experience and the development of invasive endometrial cancer. From this population, 515 cases of endometrial cancer developed. Women who worked 20+ years of rotating night shifts, and obesity among night shift workers, were significant risk factors using Cox regression models.*

Source: Viswanathan AN, et al. Night shift work and the risk of endometrial cancer. *Cancer Res.* 2007;67:10618-10622.

Social or environmental factors that alter hormonal homeostasis have been implicated in the causation of certain human malignancies, including breast, prostate, ovarian and endometrial cancer. Endometrial cancer, currently the most common gynecologic malignancy in the United States[1] is more commonly observed in those with prolonged unopposed estrogen exposure.[2] Thus, increased rates are observed in association with obesity or in women who receive postmenopausal hormonal therapy. Factors such as parity, age at first birth, oral contraceptive use, smoking, age at menarche, and menopause have all been related to endometrial cancer, presumably on the basis of their hormone modulating effects. Nulliparity, older age at first birth, early menarche, and late menopause increase the risk of endometrial cancer, whereas smoking and oral contraceptive use decrease it.[2]

Melatonin has been shown to have several oncostatic properties, including possible antiestrogenic and anti aromatase activity, and it seems also to be linked with fat metabolism. Night workers have lower levels of melatonin, which may predispose to cancer development. Indeed, observational studies have demonstrated higher risk of breast[3], colorectal[4], and prostate cancer[5] among night workers. Viswanathan and colleagues hypothesized that night shift workers will also

have an increased risk of endometrial cancer. To examine this they investigated data derived from the Nurses' Health Study.

The Nurses' Health Study began in 1976 when 121,701 female registered nurses between the ages of 30 and 55 years were surveyed. Since that time, biannual questionnaires addressed issues regarding health status, medical history, and risk factors for cancer and heart disease. Remarkably, follow-up data is available for more than 90% of the ongoing cohorts.[6] Of the total population, 53,487 women provided data on rotating night shift work during the calendar year 1988, and these were followed through June 1, 2004. During this period a total of 515 women developed an invasive endometrial cancer. Using Cox regression analysis to calculate multivariate relative risks, the investigators discovered that women who worked for more than 20 years on a rotating night shift schedule had a significantly increased risk of endometrial cancer (RR, 1.47; 95% confidence interval [95% CI], 1.03-1.14). In stratified analyses, obese women working rotating night shifts doubled their baseline risk of endometrial cancer (RR, 2.09; 95% CI, 1.24-3.52) compared with obese women who did no night work.

The investigators speculated that this increased risk was attributable to effects of diminished melatonin in this population and the effects thereof on hormonal and metabolic homeostasis.

COMMENTARY

These findings from a very large cohort are quite significant and biologically interesting. Although the role of melatonin is intriguing as speculated, no data was provided with regard to melatonin level among the night shift workers or in those with or without endometrial cancer. Melatonin secretion is abnormal in night workers, and the link with hormonal alterations and obesity is well established. However, a number of factors other than melatonin are also likely to be perturbed by long-term night duty and a full metabolic evaluation, at least on some of these patients and matched controls would likely be instructive, if not hypothesis generating.

Nonetheless, it is pretty clear that long-term night shift duty presents a risk for certain malignancies including endometrial cancer, and the relative risk for this malignancy may be two fold or higher if obesity is also present. This novel finding requires confirmation, but currently there is sufficient epidemiological data to warrant further study of the relationship between light exposure and cancer risk through the melatonin pathway. ■

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CME Questions

50. Regarding androgen deprivation therapy for adjuvant treatment of patients with resected prostate cancer, which of the following statements is correct:

a. The CaPSURE data demonstrated in a prospective analysis that the risk for cardiovascular death was increased for those receiving adjuvant treatment.
b. The CaPSURE data demonstrated in a prospective analysis that the risk for cardiovascular death was not increased when compared to those who received radiation therapy as their primary treatment.
c. The CaPSURE data demonstrated by retrospective analysis that adjuvant treatment was associated with an increased risk of cardiovascular death.
d. The CaPSURE data demonstrated by retrospective analysis that adjuvant treatment was not associated with an increased risk of cardiovascular death, but the association was positive for increased risk for those receiving radiation therapy as their primary treatment.

51. In this report of unrelated cord blood (UCB) transplant using nonmyeloablative regimen for patients with high-risk hematologic diseases, what did the authors find?

a. A median time to neutrophil engraftment of 12 days after UCB cell infusion.
b. Patients over 50 years of age all died.
c. A 6/6 HLA antigen match UCB was found for the vast majority of patients.
d. A 50% risk of transplant-related mortality.

52. Which of the following statements regarding the association of glucose intolerance and pancreatic cancer is most correct?

a. The diagnosis of diabetes in patients with pancreatic cancer most frequently occurs when the cancer is at an advanced, unresectable stage.
b. The diagnosis of diabetes frequently occurs in advance of other signs or symptoms of pancreatic cancer.
c. Screening for pancreatic cancer in patients with newly diagnosed diabetes mellitus has been successful in detecting pancreatic cancer at a resectable stage.
d. Screening of the general population with CT scans to detect early pancreatic cancer is likely to be effective but the financial considerations preclude such an effort.

53. Which of the following cancer types has NOT been shown to occur more frequently in night shift workers?

a. breast cancer
b. colon cancer
c. endometrial cancer
d. melanoma
e. prostate cancer

Answers: 50 (c); 51 (a); 52 (b); 53 (d)

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CLINICAL ONCOLOGY ALERT™
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PHARMACOLOGY WATCH

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

Adult Immunization Guidelines from CDC Released

In this issue: *Updated Immunization Guidelines from the CDC; Do antivirals have a role in the treatment of Bell's palsy? Topiramate is a promising treatment for alcohol dependence; and FDA Actions.*

The *Annals of Internal Medicine* has published updated Adult Immunization Guidelines from the CDC as an early release article on their website dated October 18. Full guideline will be available in the November 20 print edition. The guideline has several important changes and updates.

The new herpes zoster vaccine is added to the guideline this year. The vaccine should be given routinely to all immunocompetent adults age 60 and older. It is not recommended for immunocompromised adults as it is a live attenuated virus. The vaccine is given once in a lifetime, and does not require a booster.

The new human papilloma virus has also been added. The vaccine protects against 4 types of HPV, which causes 90% of genital warts and 70% of cervical cancers. It is recommended for women aged 11 to 26 years. It requires three doses given at zero, 2 and 6 months. It should not be given to pregnant women.

The new pertussis vaccine is coupled with diphtheria and tetanus to form Tdap (Adacel- Sanofi Pasteur). This is a 1-time, 1-dose vaccine that should be given to all adults age 64 or younger when they are scheduled for their next tetanus (Td) booster. Tetanus boosters should be given every 10 years, but the interval may be shortened to as little as two years for high-risk patients including postpartum women, close contact of infants younger than 12 months of age, and all healthcare workers with direct patient contact. It has not been tested in adults age 65 or older. This vaccine is different from the previously approved Tdap for adolescents aged 10 to 19 (Boostrix-GlaxoSmithKline).

There are now 15 indications for influenza vaccine. New indications include those who have difficultly handling respiratory secretions or have increased risk of aspiration. All women who are pregnant or will be pregnant during the flu season should be vaccinated. All healthcare workers should be vaccinated unless they have strong contraindications.

Hepatitis B vaccine recommendations have changed, and the vaccine is now recommended for all sexually active adults who are not in a long-term mutually monogamous relationship.

Because of several recent large-scale mumps outbreaks in this country, a mumps vaccine booster is now recommended for specific age groups, especially adults who work in healthcare settings. The standard is to give MMR, even if immunity exists for one or more of the components of MMR.

The pneumococcal vaccine recommendations remain the same. The vaccine should be given at age 65 unless the patient has specific risk factors, in which case it should be given to those younger than 65. A small subgroup of patients should be given a second booster. If the vaccine was initi-

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ated under age 65 for high-risk patients, a booster should be given at age 65 or five years after the initial vaccine. If the vaccine was initiated over age 65, a booster should only be given to immunocompromised patients after five years. The vaccine should not be given every five years (a common misconception). In fact, no one should receive more than two doses under any circumstances. There is even some evidence that more than two doses may be harmful and could potentially attenuate the immune response.

Antivirals and Bell's Palsy?

Do antivirals have a role in the treatment of Bell's palsy? This question has been debated for decades, with several small studies indicating a relationship between herpes simplex infections and facial paralysis. Despite this, treatment with acyclovir or valacyclovir has not been proven to be effective in treating Bell's palsy. Regardless, antivirals are frequently prescribed along with oral steroids. A new study confirms that steroids are useful, but antivirals are not. Nearly 500 patients with new onset of Bell's palsy were randomized to 10 days of treatment with prednisolone, acyclovir, both agents, or placebo. The primary outcome was recovery of facial function. At three months, the proportion to patients who had recovered facial function were 83.0% in the prednisolone group compared with 63.6% among patients who did not receive prednisolone ($P < 0.001$) and 71.2% in the acyclovir group as compared to 75.7% among patients who did not receive acyclovir (adjusted $P = 0.50$). After nine months, recovery was 94.4% for prednisolone and 81.6% for no prednisolone ($P < 0.001$) and 85.4% for acyclovir and 90.8% for no acyclovir (adjusted P = 0.10). For patients treated with both drugs, recovery was 79.7% at 3 months ($P < 0.001$) and 92.7% at nine months ($P < 0.001$). There were no serious adverse effects in either group. The authors conclude that early treatment with prednisolone significantly improves the chance of complete recovery, while there's no evidence of benefit with acyclovir alone or in combination with the steroid (*NEJM*. 2007; 357:1598-1607).

Topiramate Promising for Alcohol Treatment

Topiramate is a promising treatment for alcohol dependence according to a new study. The drug was shown to be effective in this role in a small study published in 2003. This new, larger multisite 14 week double-blind, randomized, placebo controlled trial enrolled 371 men and women age 18 to 65 years who were diagnosed with alcohol dependence. Up to 300 mg per day of topiramate was given to 183 participants while 188 were treated with placebo. Both groups were enrolled in a weekly compliance enhancement intervention program. The primary end point was self-reported percentage of heavy drinking days, while secondary outcomes included other self-reported drinking measures along with laboratory measures of alcohol consumption. Topiramate was more efficacious than placebo at reducing percentage of heavy drinking days from baseline to 14 weeks (mean difference 8.44%; 95% CI, 3.07%-13 .80%; $P = .002$). Topiramate also reduced all of the drinking outcomes ($P <.001$ for all comparisons). Adverse events were more common with topiramate, including paresthesia (which occurred in over 50% of those on the drug), taste perversion, anorexia and difficulty with concentration. In general, however, the drug was safe and consistently efficacious for treating alcohol dependence (*JAMA*. 2007;298:1641-1651). An accompanying editorial points out that the benefits of topiramate were still increasing at the end of the study, indicating the longer treatment may be more effective (*JAMA*. 2007;298:1691-1692).

FDA Actions

The FDA has announced new warnings on phosphodiesterase type 5 inhibitors regarding hearing loss. The drugs include sildenafil (Viagra, Revatio), tadalafil (Cialis) and vardenafil (Levitra). The agency has received 29 cases of sudden hearing loss associated with use of the drugs dating back to 1996. Most cases were unilateral and temporary.

Modafinil (Provigil) has also been the subject of new warnings including serous rashes and psychiatric symptoms. The drug, which is used for narcolepsy, obstructive sleep apnea, shiftwork disorder, and multiple sclerosis, has been associated with severe rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. The FDA suggested caution should be exercised when modafinil is given to patients with a history of psychosis, depression, or mania.

An FDA advisory panel has recommended restricting childhood cold medications to children over the age of six years. They also recommend strong limits on marketing these products for younger children. This follows a voluntary withdrawal from the market of infant cough and cold medications by most manufacturers of these products. Voluntary withdrawal involves medications used in children younger than two years. The drugs that contain decongestants and antihistamines have been associated with more than one hundred deaths since 1969. ■