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

ABSTRACT & COMMENTARY

Radiotherapy and Short-term Androgen Deprivation for Localized Prostate Cancer

By Samir P. Kanani, MD

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Dr. Kanani reports no relationships to this field of study.

SYNOPSIS: In a large multi-institutional prospective trial conducted from 1994-2001, 1979 eligible patients (median age 70 years) with PSA < 20 were randomized to radiation therapy alone or radiotherapy plus 4 months of total androgen suppression starting 2 months before radiotherapy. The 10-year rate of overall survival and disease-specific survival was improved among patients receiving short-term androgen suppression. When stratified according to widely used risk groups, the benefit was limited to intermediate-risk patients. Toxicity was minimal. There still remains a question as to the benefit of short-term androgen suppression in the current setting of highly precise radiation therapy to higher doses.

SOURCE: Jones U, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011;365:107-118.

Luteinizing hormone-releasing hormone analogues and oral antiandrogen agents have been shown to induce apoptotic cell death in androgen-responsive prostate cancers.[1] Long-term (> 2 years) androgen deprivation therapy (ADT) combined with external beam radiotherapy in patients with locally advanced prostate cancer has been shown to improve overall survival but is associated with some toxicity including cardiac complications and erectile dysfunction. Short-term ADT could potentially mitigate the toxicity while maintaining the therapeutic benefit seen in long-term ADT. A previous Radiation Therapy Oncology Group (RTOG) trial conducted in the 1980s demonstrated a benefit to short-tem ADT for 4 months for patients with advanced prostate cancer, but this was in a pre-PSA era.[2] The current report reflects the results of the RTOG multicenter randomized Phase 3 trial (RTOG 94-08), opened in 1994 for the purpose of elucidating the role of short-term ADT combined with radiotherapy in patients with non-bulky localized prostate cancer with PSA levels of 20 ng/mL or less.

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This Phase 3 trial was conducted in Canada and the United States between 1994 and 2001. A total of 1979 patients were randomized to 4 months ADT concurrent with radiotherapy to a dose of 66.6 Gy or radiotherapy alone. ADT consisted of flutamide 250 mg PO tid and either goserelin SQ 3.6 mg or luprolide IM 7.5 mg. Radiotherapy commenced after 2 months of ADT.

The majority of the patients had a NCCN intermediate risk disease (Gleason score of 7 or a Gleason score of 6 with PSA 10-20 or a clinical stage T2b). The median patient age was 71 years. With a median follow-up of 9.1 years, the 10-year overall survival was 57% in the radiotherapy-alone group and 62% in the combined-therapy group ($P < 0.03$). The 10-year disease specific mortality was 8% in the radiotherapy-alone and 4% in the combined-therapy group ($P < 0.001$). The 10-year biochemical failure rate was 41% in radiotherapy-alone group and 26% in the group receiving short-term ADT ($P < 0.001$). There was no difference in erectile dysfunction between the two groups in a survey completed 1 year after treatment. The incidence of grade 3 or higher hormone-related toxicity was less than 5%. A secondary analysis of the data based on NCCN risk categories showed an improvement in overall survival and disease-specific survival with the addition of short-term ADT primarily among intermediate-risk patients, with no significant improvement among low-risk patients. In all three risk subgroups, short-term ADT was associated with a reduction in biochemical failure.

COMMENTARY

The current treatment of prostate cancer has evolved to a risk-based management protocol. Although the RTOG 94-08 trial was not designed specifically to evaluate the value of ADT therapy in the specific risk groups, the subgroup analysis provides valuable information for management of this common cancer. The use of ADT in patients with high-risk prostate cancer — defined as one or more of the following: PSA > 20 ng/mL, Gleason score 8-10, and stage T2c — is well-established from three prospective Phase 3 trials, EORTC 22863,[3] SPCG-7,[4] and TROG 9601.[5] The current trial demonstrated a benefit in this population, but it was not statistically significant. The lack of statistical benefit is likely because 4 months of ADT is not enough and a minimum of 6 months of ADT is needed in this high-risk population.[5] For patients in the low-risk group, this study along with others has consistently demonstrated no significant benefit in the use of ADT. However, this trial did demonstrate a benefit in biochemical failure, begging the question that with longer follow-up perhaps a benefit in survival would have been seen. In addition, there may be a benefit in certain low-risk patients with adverse features such as > 50% of cores positive, perineural invasion, or ominous PSA kinetics such > 2 ng/mL rise per year. This must be weighed against the mounting evidence that ADT does result in muscle loss, fat accumulation, decreased insulin sensitivity, and increased cholesterol levels leading to a small but real increase risk of developing diabetes, heart disease, stroke, and sudden death.[6,7] This report of the RTOG 94-08 trial confirms a published report from D'amico et al that found patients with intermediate-risk disease demonstrated a 23-point advantage in survival (56% vs. 79%).[8] In this RTOG study, there was a 7-point advantage to the addition of ADT (54% vs. 61%). The difference in the magnitude of benefit could be explained by the fact that the D'amico trial used higher doses of radiation. Another explanation could be because the duration of ADT was 6 months in the D'amico trial vs 4 months in the RTOG trial.

The current study is important and underscores the value of cooperative group trials and funding for long-term follow-up. Prostate cancer trials with survival endpoints provide the best evidence for managing this often indolent disease. Advances in radiotherapy delivery over the last decade, such as intensity-modulated radiation therapy and image-guided radiotherapy, have allowed higher doses of radiotherapy to be delivered safely, improving the efficacy of treatment bringing into question once again the value of ADT. The RTOG has opened a successor trial to elucidate the value of ADT on prostate cancer treated in the contemporary era with

modern radiotherapy techniques and risk-based management. ■

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ABSTRACT & COMMENTARY

Timing of Influenza Vaccination in Patients Receiving Chemotherapy

By William B. Ershler, MD

SYNOPSIS: For patients in the midst of chemotherapy, there are little data on the most efficacious time to administer influenza vaccine. In a randomized study of 38 patients receiving FEC chemotherapy for adjuvant treatment of breast cancer, it is apparent that vaccination early (on day 4 of a 21-day cycle) provided better antibody response than when administered late in the cycle (day 16). Neither group (early or late vaccination) achieved the antibody response of that observed for healthy (and younger) controls. Current advice is to vaccinate well before the initiation of chemotherapy, but for those who are currently receiving drug, the data would suggest treatment early in the cycle rather than late provides the best chance for achieving protective levels of antibody.

SOURCE: Meerveld-Eggink A, et al. Response to influenza virus vaccination during chemotherapy in patients with breast cancer. *Ann Oncol* 2011;22: 2031-2035.

Oncologists are well aware of the need for influenza vaccination among their patients. Both the presence of malignancy and the immunosuppressive effects of chemotherapy render patients at increased risk for either or both protracted morbidity or mortality from influenza infection. The infection occurs in cancer patients at a rate 3-5 times greater, and mortality from influenza is four times greater than the general population.[1] Despite the immunosuppressive effects of chemotherapy, due to the seasonal nature of influenza, and the short-lived protection conferred by the current vaccine preparations, physicians must contemplate when it is optimal to administer the vaccine. However, there is little information available about vaccine timing in the context of the chemotherapy schedule.

To address this issue, a number of investigators throughout the Netherlands conducted a prospective, randomized trial among breast cancer patients receiving adjuvant chemotherapy. Such patients received influenza vaccination during FEC (5-fluorouracil, epirubicin, and cyclophosphamide)-containing chemotherapy regimens (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) six cycles or FEC three cycles followed by docetaxel (100 mg/m^2) three cycles. The vaccine used was that prescribed for 2009 which included 15 ug hemagglutinin of the following influenza strains: A/Brisbane/10/2007 (H3N2)-like strain, A/Brisbane/59/2007 (H1N1)-like strain, and B/Brisbane/60/2008-like strain.

Patients were randomized for early (day 4) or late (day 16) vaccination during the chemotherapy cycle. Influenza virus-specific antibody titers were determined before and 3 weeks after vaccination by standard assay (hemagglutination inhibition).

The study enrolled 38 breast cancer patients (20 in the early and 18 in the late group) and 21 healthy controls. The antibody response to influenza vaccination in the patient group as a whole was significantly lower than in the control group. In the early patient group (those vaccinated on day 4 of

the chemotherapy cycle) and in the control group, the geometric mean titer (GMT) post-vaccination increased significantly for all three virus strains of the trivalent vaccine. In the late patient group (those vaccinated on day 16 of the chemotherapy cycle), a statistically significant increase in GMT post-vaccination was only found for the H1N1 virus strain.

Patients vaccinated at day 4 tended to have higher antibody titers as compared with patients vaccinated at day 16, although the difference in post-vaccination titers did not reach statistical significance. Geometric mean titers post-vaccination for day 4 vs day 16 were 63.7 vs 29.5 (H3N2), 28.2 vs 19.6 (H1N1), and 29.8 vs 16.0 (B/Brisbane), respectively.

COMMENTARY

As would be expected, patients on chemotherapy have significantly lower responses to influenza virus vaccination compared with healthy controls. Thus, it remains prudent to vaccinate before the initiation of chemotherapy if at all possible.[2,3] Yet, due to the seasonal nature of influenza epidemics and the clinical oncology imperative of timely initiation and avoidance of delays in chemotherapy, clinicians are often in the midst of prescribed cancer treatment when influenza vaccines become available and epidemics are looming. The important finding from this small study is that vaccination early during the chemotherapy cycle induces better responses than vaccination later in the cycle. The result is curious and runs counter to what might have been expected. However, the difference might be explained not by the proximity to the prior cycle but to that of the subsequent. Thus, patients vaccinated on day 4 had 17 days before the next exposure to cytotoxic drugs whereas those vaccinated on day 16 would receive chemotherapy in only 5 days, at a time when the optimal vaccine response depends on a healthy immunoproliferative response. In any event, the study was small, and was confined to breast cancer patients receiving one combination of drugs (FEC) and thus generalization to all the variables we confront in our clinics is premature. If nothing else, the study reminds us of the importance of making certain our patients are vaccinated, and for now there are at least some data suggesting it would be best to vaccinate early in the chemotherapy schedule rather than waiting to just before the next cycle, which I must admit is the practice I had heretofore subscribed.

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ILLUSTRATIVE CASE SERIES

Incidental Adrenal Mass

By Bindu Kanapuru, MD

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

A 70-year-old man undergoing preoperative evaluation for abdominal aortic aneurysm surgery was noted to have a 3 cm mass in the right adrenal gland with heterogeneous texture but clear margins. Past medical history was significant for hypertension, hypercholesterolemia, and coronary artery disease. He has 40-pack per year smoking history but quit 2 years ago. Laboratory tests revealed K+ level of 4.0 mmol/L and blood sugar levels of 100 mg/dL. He was referred to an oncologist for further evaluation.

CASE DISCUSSION

Detection of asymptomatic adrenal masses has become very common of late due to widespread use of abdominal imaging studies for a wide range of indications. The prevalence of incidental adrenal mass ranges from 0.2% in those younger than 30 years of age to as high as 7% in those 70 years of age or older. In 80% of the cases, adrenal incidentalomas are non-secreting benign adrenocortical adenomas such as lipoma or myolipoma. For the remaining 20%, the question to be addressed is whether there is malignancy and/or whether the nodular mass is functionally active.

DIFFERENTIATING BENIGN FROM MALIGNANT LESIONS

Malignant adrenal masses may be metastatic from a distant site or primary adreanal carcinoma. For those with metastatic disease, a clinical history of prior or current cancer diagnosis is almost always

present. In fact, adrenal metastasis as the primary presentation of a malignancy is extremely rare (approximately 1%). In contrast, more than 60% of metastatic adrenal lesions are discovered at the time the primary tumor is diagnosed. Nearly two-thirds of adrenal metastases are from primary tumors of the breast or lung. Other common sites include melanomas, renal cell carcinoma, and GI tract cancers. However, even in those patients with a known malignancy, adrenal masses are more commonly benign and definitive diagnosis may require biopsy, especially in cases where this would be the only site of metastatic disease.

There are no specific symptoms or signs that clearly define a benign from malignant lesion. Although benign adenomas are more likely to present with symptoms of hormonal hypersecretion, adrenocortical carcinomas also may be associated with hyperglycemia, cushingoid features, hypertension, and symptoms of virilization or feminization. Alternatively about 5% of cortical secreting adenomas and pheochromocytomas are clinically silent and are identified by further functional testing.

IMAGING

The size and specific characteristics of the adrenal mass on CT scan may help in differentiating benign from malignant adrenocortical neoplasms. Adrenocortical carcinomas were diagnosed in more than 25% of lesions greater than 6 cm compared to only 2% in lesions less than 4 cm. Adrenocortical carcinomas and functioning adenomas are likely to be unilateral whereas metastatic adrenal masses are more often bilateral.

Both adrenocortical carcinomas and metastatic adrenal lesions appear as large heterogeneous masses in contrast to the small circumscribed homogeneous density that typify benign cortical adenomas. Pheochromocytomas are difficult to distinguish from malignant lesions by routine imaging as they are often relatively large (size > 3 cm) with heterogeneous signal and include both hemorrhagic and cystic areas. Nonetheless, unlike malignant adrenal lesions, pheochromocytomas more often appear round or oval and have clear margins. On an unenhanced CT, an attenuation coefficient of < 10 HU is reported to have specificity of 100% in ruling out malignancy. A contrast CT with enhancement washout of < 60% can further help in differentiating a non-lipid-rich adenoma from malignancy. Although a chemical shift MRI is equally effective in differentiating adrenal masses, it does not provide any additional information beyond what is provided by CT imaging. However, if CT imaging is unsuccessful in establishing the phenotype, an MRI may be of value. Pheochromocytoma, adrenal carcinoma, and metastatic lesions appear hyper-intense on T2 images, whereas benign lesions and adrenal cortisol-producing adenomas are iso-intense.

FDG-PET is reported to have 100% sensitivity and 94% specificity in characterizing adrenal lesions in patients with a current or suspected cancer. In a small study involving 10 patients with adrenocortical cancer, the sensitivity and specificity for FDG-PET was 100% and 95% respectively. However, it is not routinely recommended in the evaluation of pure adrenal incidentalomas.

Fine needle biopsy is a safe procedure with a complication rate of less than 3%. It is indicated to discriminate between metastatic disease and adrenal neoplasm, but is often insufficient to distinguish adrenal adenoma from carcinoma. It is imperative that a functional pheochromocytoma be ruled out to avoid a hypertensive crisis. An alpha-adrenergic blocker followed by a beta-blocker should be administered for about 2 weeks prior to the fine needle procedure.

EVALUATION OF HORMONAL HYPER SECRETION

The initial history and physical examination should be directed to identify the three most common hormonal abnormalities in these patients: Cushing's syndrome, pheochromocytoma, and primary aldosteronism. In addition, it is important to inquire about a family history of cancer and look for symptoms suggestive of syndromes associated with MEN2A, MEN 2B, and Von Hippel Lindau disease, all of which are associated with pheochromocytoma.

Most patients with autonomous cortical secreting adenomas have subclinical Cushing's and do not have the florid clinical signs and symptoms typically seen with Cushing's syndrome. As such, evaluation by 24-hour urinary cortisol may fail to identify these patients. Although false positives occur, the most commonly employed test to rule out a cortisol-producing adenoma is an overnight 1 mg dexamethasone suppression test. Failure to suppress serum cortisol to < 5mg/dL (although some suggest a value of 1.8 µg/dL) is considered a positive screening test and is followed by confirmatory testing. Recently the late-night salivary cortisol test has been shown to be a very early and sensitive marker for Cushing's syndrome with an elevated nighttime cortisol level having sensitivity and specificity of 90%-95%. A urinary-

free cortisol level 4 times the normal level is also an excellent screening test. If the 1 mg dexamethasone suppression test is negative but the clinical suspicion for Cushing's is still high, all three tests can be done to effectively exclude this diagnosis. In patients with subclinical Cushing's, confirmatory testing with 2 mg dexamethasone test may be required.

Pheochromocytoma, the second most common functional adrenal tumor, accounts for > 10% of the cases. The measurements of plasma-free metanephrines and normetanephrines have a sensitivity of (97%-100%) and specificity (85%-89%) and represent the best screening tests for this disorder. In patients with hypertension, plasma renin activity ratio of > 20 and a plasma aldosterone concentration of >10 ng/dL suggest primary aldosteronism, which may be present in 1% of adrenal incidentalomas.

CURRENT CASE DISCUSSION

In the case presented, the medical history and physical examination were unrevealing with regard to hormonal hypersecretion. Although he had an extensive smoking history, he had no prior history of cancer or symptoms suspicious for a cancer diagnosis at the time of presentation.

Serum cortisol at 8 a.m. after 1 mg dexamethasone suppression test was 1.5 µg/dL and plasma renin aldosterone level was 15. Plasma-free metanephrines and normetanephrines were normal.

How should this patient be followed?
Although surgical resection is recommended for any adrenal incidentalomas larger than 6 cm after appropriate biochemical testing, the optimal management of lesion 4-6 cm is still unclear. Surgery is still a reasonable option in masses > 4 cm, especially if the imaging studies are suspicious for malignancy. In patients with masses < 4 cm, or > 4 cm and no suspicious features, a reasonable approach would be to repeat imaging in 3-6 months and then annually for 1-2 years. If there is no growth of the mass in 2 years, it is highly unlikely that it is malignant. Biochemical testing, however, should be repeated yearly for at least 5 years.

This patient underwent abdominal aortic aneurysm surgery uneventfully and is now scheduled for follow-up imaging studies and biochemical markers at regular intervals. ■

Resources

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ABSTRACT & COMMENTARY

Bendamustine-Rituximab as First-line Treatment for NHL Patients Over the Age of 80 Years

By William B. Ershler, MD

SYNOPSIS: Fourteen elderly patients (median age 85 years) who were considered non-candidates for R-CHOP were treated first-line with a combination of bendamustine and rituximab. Of these, 7 achieved a complete response and 2 achieved a partial response. Toxicity was minimal. Although promising, these results need to be confirmed in larger studies.

SOURCE: Weidmann E, et al. Phase II study of bendamustine in combination with rituximab as first-line treatment in patients 80 years or older with aggressive B-cell lymphomas. *Ann Oncol* 2011;22:1839-1844.

Although R-CHOP (rituximab plus combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone) is considered highly effective chemotherapy for patients with aggressive non-Hodgkin's lymphoma (NHL) even in older patients,[1] its use among very old patients is often withheld because of existing comorbidities or

organ dysfunction. Acknowledging that lymphoma occurs with increasing frequency with each advancing decade, there is a need to develop other, potentially less toxic chemotherapy combinations for this population. In this regard, bendamustine is an excellent candidate. This drug, initially synthesized five decades ago has reemerged over the past decade[2] and is now approved for use in the United States for patients with NHL. The authors were among the first to use the drug in patients with aggressive NHL. In a Phase 2 study they demonstrated an overall response rate of 44% in 18 patients with refractory disease, a few of whom had long-lasting remissions.[3] Subsequently, when used in combination with rituximab, it was shown to be both highly effective and well tolerated in patients with relapsed or refractory disease.[4,5] Because of the toxicity profile, the combination was considered particularly suitable for lymphoma treatment in frail, elderly patients. The current report reflects the first trial of rituximab with bendamustine for initial treatment of aggressive NHL and it was focused on patients older than age 80 years who were not considered candidates for R-CHOP.

This Phase 2 trial was conducted in Frankfurt, Germany. Enrollment was slow and although projected to include 30 patients, only 14 were entered onto study during the 26-month enrollment period (April 2004-June 2006). The median patient age was 85 years (range 80-95 years) and the age-adjusted international prognostic index was 0 in five patients, 1 in three patients, and 2 in six patients. Thirteen patients were assessable for response. Seven patients (54%) had a complete response, two (15%) a partial response, and four (31%) progressive disease. The median overall survival was 7.7 months, and the median progression-free survival 7.7 months. Six patients (43%) were alive without disease at 20–72 months from the start of treatment. Major toxicity was neutropenia (17% grade 3 and 6% grade 4). All other grade 3 and 4 hematotoxicities and non-hematological toxic effects ranged between 2% and 11%. There were no life-threatening infections. G-CSF was not used as primary prophylaxis and only two patients received G-CSF as secondary prophylaxis. There was no grade 4 non-hematologic toxicity and minimal grade 3 non-hematologic toxicity observed. Two patients exhibited grade 3 renal toxicity and three patients experienced fatigue. One patient had what is described as a psychotic episode and he was withdrawn from study, although his data were included in the survival analysis. Alopecia was not observed. There was no treatment-related mortality. Although there were no dose reductions, treatment was delayed (6 to 33 days) in approximately one-third of all treatment cycles.

COMMENTARY

Bendamustine is an interesting drug. Considered an alkylating agent because of its nitrogen mustard moiety, the drug also contains a purine-like ring,[2] perhaps explaining some of its more protean effects. In vitro studies have demonstrated rapid DNA cross-linking and strand breaks[6] as well as inhibition of mitotic check points.[7] By virtue of these effects, the drug appears not to be cross-resistant with other alkylators.[7] Furthermore, the low toxicity and its demonstrable synergy with rituximab are appealing, particularly for elderly patients, or for those who are otherwise not candidates for R-CHOP.

The current study is an important advance, but certainly insufficient for general recommendation. First, it is a single institution's experience and with disappointingly low enrollment. This, no doubt, reflects the difficulty with recruiting elderly patients for study, a phenomenon that the community of clinical investigators needs to overcome in light of the increasing numbers of older patients for which trial-derived treatment standards are sorely needed. Second, randomized studies in which this combination is compared with alternatives, such as CVP (cyclophosphamide, vincristine, and prednisone) for patients who are not candidates for R-CHOP is called for. In this light, Italian investigators are exploring a novel combination of mitoxantrone, etoposide, prednisone, bleomycin, and vincristine with preliminary results among patients over the age of 80 years comparable to that observed with bendamustine-rituximab, although perhaps with somewhat greater toxicity. A comparison of these two regimens in a randomized trial would seem a logical next step to address this important question of how to treat aggressive NHL in patients over the age of 80 years. ■

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CME Questions

1. Which of the following comments regarding androgen deprivation therapy (ADT) is NOT true?

a. When combined with radiotherapy, short-term ADT improves survival in intermediate-risk patients.
b. When combined with radiotherapy, short-term ADT improves survival in the low-risk patients.
c. Randomized trials have shown a benefit to long-term ADT in patients with high-risk prostate cancer.
d. Erectile dysfunction is similar in men treated with short-term ADT and radiotherapy compared to men treated with radiotherapy alone.

2. For those receiving chemotherapy, based upon the recently published Dutch study, the optimal day within a 21-day chemotherapy cycle for administering the seasonal influenza vaccine would be:

a. the day of chemotherapy.
b. day 4.
c. day 16.
d. the day before the next cycle of chemotherapy.

3. A 60-year-old man who underwent a CT chest imaging for evaluation of cough was noted to have a 3.8 cm right adrenal mass. History was unremarkable for weight gain, muscle weakness, change in body fat distribution, or dizzy spells. Past medical history: Hypercholesterolemia on lipid lowering therapy. Plasma fractionated metanephrines:

- **Metanephrine = <0.3 nmol/L (normal = <0.5 nmol/L) Normetanephrine = 0.5 nmol/L (normal = <0.9 nmol/L Plasma aldosterone = 9.0 ng/dL**
- **Plasma renin activity = 1.0 ng/ml/hr**
- **24-hour urinary cortisol = 50 mcg**

What is the next best step in the management of the adrenal mass?

a. Perform FNA biopsy of the adrenal mass
b. Perform surgical resection of the adrenal mass
c. Perform overnight dexamethasone suppression test (1 mg)
d. Repeat adrenal CT in three to six months

4. Which of the following comments regarding bendamustine is NOT true?

a. It is structurally classified as an alkylating agent.
b. It has unique in vitro properties rendering it non-cross resistant with other alkylating agents.
c. It has been demonstrated both in vitro and in early clinical trials to act synergistically with rituximab.
d. It produces a higher rate of complete remissions when compared with R-CHOP in the first line treatment of NHL.

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]

Risk of surveillance vs lymph node dissection in germ cell cancer

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.*

Apixaban is Heating Up the Anticoagulation Market

In this issue: Apixaban could soon join the anticoagulation market; Chinese herbs for flu; chronic medication and discontinuation after hospitalization; and FDA actions.

Apixaban trial results look promising

There is soon to be a third player in the anticoagulation wars. Apixaban, an oral factor Xa inhibitor, will likely soon join dabigatran and rivaroxaban as alternatives to warfarin for preventing stroke in patients with atrial fibrillation (AF). Dabigatran, a direct thrombin inhibitor, was approved for this indication last year and rivaroxaban, also a factor Xa inhibitor, is likely to be approved in early September. (Rivaroxaban was previously approved for DVT prevention in patients undergoing orthopedic surgery.) Apixaban also looks very promising based on results of the ARISTOTLE trial, which was published online in the *New England Journal of Medicine* on August 28. ARISTOTLE enrolled 18,201 patients with AF and at least one additional risk factor for stroke. Patients were randomly assigned to apixaban 5 mg twice daily or warfarin with a target INR of 2-3. ARISTOTLE was designed as a noninferiority study with a primary outcome of ischemic or hemorrhagic stroke, or systemic embolism. After median follow-up of 1.8 years, the rate of the primary outcome was 1.27% per year in the apixaban group vs 1.60% in the warfarin group (hazard ratio [HR] 0.79; 95% confidence interval [CI] 0.66 to 0.95; $P < 0.0014$ noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 30% less with apixaban and the rate of death from any cause was 3.52% with apixaban and 3.94% with warfarin ($P = 0.047$). The rate of hemorrhagic stroke in the apixaban group was about half that in the warfarin group (0.24% per year vs 0.47% per year, $P < 0.001$) and the rate of all other strokes was 0.97% with apixaban vs 1.05% with warfarin ($P = 0.42$). The authors conclude that in patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality (*N Engl J Med* published online August 28, 2011). An excellent accompanying editorial discusses the seminal studies that compared the three new anticoagulants to warfarin for stroke prevention in patients with AF: RE-LY — dabigatran; ROCKET AF — rivaroxaban; and ARISTOTLE — apixaban. All three showed that the new drugs were significantly better than warfarin at reducing hemorrhagic stroke and all were at least as effective as warfarin at preventing ischemic stroke. All three drugs were also associated with a significantly lower rate of serious bleeding compared to warfarin. Apixaban was the only drug that showed a significant reduction in overall mortality, although both dabigatran and rivaroxaban showed trends in that direction. ROCKET AF has been criticized because the warfarin comparator group had a time in therapeutic range of only 55% compared to 64% in the RE-LY trial and 62% in ARISTOTLE; however, patients in the ROCKET AF study were at higher risk for stroke than in the other two studies. The bottom line is that all three drugs are effective in preventing stroke in patients with nonvalvular

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AF and seem to be safer than warfarin as well. The new drugs do not require any laboratory monitoring, which is convenient for patients and also lowers the overall cost of care (although all three drugs will be priced significantly higher than generic warfarin). Rivaroxaban has the advantage of a once daily dose vs the other two drugs, which must be dosed twice daily. None of the three drugs can be quickly reversed in the event of major bleeding or need for surgery. Apixaban is not yet approved in this country but when it is, it is likely that the competition between these three agents will be fierce, and for many purchasers of health care it may come down to cost. ■

Chinese herbs for flu treatment

For the flu season this year, you might consider Chinese herbs instead of antivirals based on the results of a study from China published in the *Annals of Internal Medicine*. More than 400 adults age 15-59 years with confirmed H1N1 influenza were randomized to oseltamivir 75 mg twice daily or a combination of 12 Chinese herbal medicines called maxingshigan-yinqiaosan 200 mL four times a day, a combination of oseltamivir plus maxingshigan-yinqiaosan, or placebo for 5 days. The primary outcome was time-to-fever resolution and the secondary outcomes included symptom scores and viral shedding. Both oseltamivir and maxingshigan-yinqiaosan, as well as the combination, resulted in significant reductions in the estimated median time-to-fever resolution compared to the control group (median time-to-fever resolution — no treatment 26 hours; oseltamivir 20 hours; maxingshigan-yinqiaosan 16 hours; combination 15 hours; all statistically significant at $P < 0.001$). Side effects were similar in all groups. The authors conclude that oseltamivir and maxingshigan-yinqiaosan, alone or in combination with each other, reduce time-to-fever resolution in patients with H1N1 influenza. They go so far as to suggest that maxingshigan-yinqiaosan may be used as an alternative treatment for H1N1 infections (*Ann Int Med* published online August 26, 2011). It may be difficult to obtain maxingshigan-yinqiaosan since it contains ephedra (which is not available in this country) and the authors could not determine if the benefits of maxingshigan-yinqiaosan were due to an antiviral effect or merely an antipyretic effect. ■

Chronic medications and hospitalization

Your patients' chronic medications may be inadvertently discontinued after hospitalization according to a population-based cohort study of almost 400,000 patients published recently in the *Journal of the American Medical Association*. Researchers from Canada reviewed the records of residents age 66 or older who were on statins, antiplatelet/anticoagulant agents, levothyroxine, respiratory inhalers, or gastric acid suppressing drugs on a chronic basis. When compared to nonhospitalized patients, patients admitted to the hospital — especially the ICU — were more likely to have their chronic medications discontinued. Discontinuation rates ranged from a low for levothyroxine of 12.3% discontinuation for hospitalizations vs 11% for controls, to antiplatelet/anticoagulant agents which were discontinued at a rate of 19.4% for hospitalizations vs 11.8% for controls. The discontinuation rates were even higher for patients who were admitted to the ICU. The authors conclude that patients admitted to the hospital are at relatively high risk for potential unintentional discontinuation of chronic medications (*JAMA* 2011;306:840-847). This study points out the importance of medication reconciliation at all post-hospital visits and may validate the role of computerized medical records, especially with regard to medication lists. ■

FDA actions

The FDA has approved a new fixed-dose combination pill for HIV-infected patients. Emticitabibine/rilpirivine/tenfovir DF is approved as a once-a-day pill for treatment of HIV-1 infection in treatment-naïve patients. This is the second triple combination anti-HIV agent approved and differs from the previous agent (Atripla) in that it contains the NNRTI rilpirivine rather than efavirenz. The new combination will be marketed as Complera.

The FDA has approved brentuximab vedotin to treat Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma. The drug is approved for HL patients who have progressed after autologous stem cell transplant or after prior chemotherapy regimens and cannot receive a transplant. This represents the first the drug to treat HL since 1977. Brentuximab will be marketed as Adcetris.

The FDA has approved vemurafenib for the treatment of metastatic and unresectable melanoma, specifically in patients whose tumors have the BRAF V600E mutation. The approval was accompanied by a companion diagnostic test that will determine if a patient's melanoma cells have that mutation (about half of the patients with late stage melanomas). Only patients with the BRAF V600E mutation will respond to the drug since it targets the mutated protein that regulates cell growth. Vemurafenib is marketed by Genentech as Zelboraf. ■

Clinical Briefs in Primary Care™

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By Louis Kuritzky, MD

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Encouraging News About Lung Cancer Screening Benefits

Source: National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; 365:395-409.

Screening for lung cancer by means of chest X-ray (CXR) does not reduce mortality, even with the addition of sputum cytology. Because low-dose helical CT (LDCT) detects much smaller, earlier lesions, the National Cancer Institute initiated a clinical trial in 2002 to determine whether LDCT screening, as compared to CXR, could reduce lung cancer (LCa) mortality.

Criteria for inclusion included at least a 30-year pack history of cigarette smoking, but if patients had signs of potential current LCa (e.g., hemoptysis, unexplained weight loss), they were not included. Study subjects were randomized to LDCT (n = 26,722) or CXR (n = 26,732) and underwent imaging at baseline, 1 year later, and 2 years later. Over the course of three screenings, 39% in the LDCT group and 16% in the CXR group had positive findings, of these more than 94% were false-positive — i.e., they were *not* LCa.

Evaluation of positive screening led to the diagnosis of LCa in 1060 of the LDCT group and 941 in the CXR group, so LDCT successfully identified about 13% more LCa. At 6 years of follow-up, LCa-related mortality was 20% lower in the LDCT group than the CXR group, and all-cause mortality was also 6.7% lower (both were statistically significant). Before widespread adoption of LDCT occurs, it has been suggested that cost-effectiveness analyses be performed, especially since the absolute risk reduction in mortality within the total study population was very small (1.31% vs 1.62%). ■

Treatment of Depression in Patients with Dementia

Source: Banerjee S, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): A randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 2011;378:403-411.

The evidence base supporting efficacy of antidepressant pharmacotherapy in patients with dementia is sparse and inconsistent. Banerjee et al performed a double-blind, randomized, placebo-controlled trial in patients with dementia and depression to assess the effects of two commonly used antidepressants: sertraline and mirtazapine.

Study subjects were randomized to sertraline 150 mg/d (n = 107), mirtazapine 45 mg/d (n = 108), or placebo (n = 151) with no other changes in their medical regimen. Each active antidepressant was initiated at a low dose and titrated within 4 weeks to a higher dose if depression scores had not substantially improved. Outcomes were measured with the Cornell Scale for Depression in Dementia (CSDD).

At the conclusion of the trial, neither sertraline nor mirtazapine provided improvements in CSDD scores greater than placebo, but side effects were more frequent in the active treatment arms. Although the authors do not provide any specific suggestions about what treatments might be preferred (beyond counseling) in the face of these disappointing results, their outcomes suggest reconsideration of preferred treatment for patients with depression associated with dementia. ■

Comparing Metrics for Identification of Prediabetes

Source: Heianza Y, et al. HbA1c 5·7-6·4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): A longitudinal cohort study. *Lancet* 2011; 378:147-155.

Since more than half of newly diagnosed diabetics have one or more of the complications of diabetes already existing by the time of diagnosis, it is clear that we must strive for earlier identification of persons destined to develop diabetes and try to forestall or prevent it. The category "prediabetes" includes persons with impaired fasting glucose ([IFG] = 100-125 mg/dL), impaired glucose tolerance ([IGT] 2-hr PPG = 140-199), or elevated A1c (A1c = 5.7-6.4). In most prior clinical trials of diabetes prevention, inclusion required the presence of IGT, with or without IFG, since IGT was felt to be a better predictor of likelihood

to progress from prediabetes to diabetes. In clinical practice, very few prediabetes patients are identified by glucose tolerance testing because of the cumbersome nature of the testing. Because utilization of A1c has only recently been condoned as a diagnostic tool for prediabetes, it is worthwhile to peruse the results of an observational trial that followed adults (n = 6241) without diabetes at baseline and compared the predictive capacity of A1c and IFG.

Over 4.7 years of follow-up, more than twice as many individuals developed IFG (n = 1680) than increased A1c (n = -822), and of course some (n = 410) developed both. The predictive capacity of A1c alone was quite similar to IFG alone, but since the two groups have only modest overlap, A1c and IFG actually define somewhat different populations destined to become diabetic. Hence, the authors suggest that using both measurements at the same time is necessary to capture the largest segment of persons with prediabetes. ■

Accuracy of Stated Energy Contents of Restaurant Foods

Source: Urban LE, et al. Accuracy of stated energy contents of restaurant foods. *JAMA* 2011;306:287-293.

Eating out has increased in the general population, and is associated with increased body mass index. Indeed, United States data suggest that more than one-third of all daily calories are provided from restaurants. If clinicians and their patients want to make more healthful choices when eating out, they must rely to some degree on the listed caloric content of these foods, but have little assurance that such listings are accurate.

Urban et al performed bomb calorimetry on 269 food items from 42 different restaurants, and compared calorimetry results with caloric content listed by restaurants.

Nineteen percent of the sampled foods were substantially (more than 100/kcal) above their listed energy content when tested with calorimetry. At the highest decile of discrepancy, foods averaged greater than 250 kcal/portion more than their restaurant listings indicated. It is estimated that eating an extra 100 kcal/d on a chronic basis could result in 5-15 kg of weight gain per year. Encouragingly, the overall food caloric assessments stated in restaurants were reasonably accurate; in the minority of cases where inaccuracies underestimate caloric content, health-conscious consumers may be getting more than they bargained for. ■

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The Past and Future Burdens of Violence Against Women

Source: Rees S, et al. Lifetime prevalence of gender-based violence in women and the relationship with mental disorders and psychosocial function. *JAMA* 2011;306: 513-521.

More than 20% of adult American women report being victims of rape, intimate partner violence, or stalking. Limitations of previous data sets preclude identifying associations between lifetime experiences of violence and subsequent mental health issues.

Rees et al performed an analysis of data from the second Australian National Mental Health and Well-being Survey, which included 4451 adult women ages 16-85. The overall lifetime prevalence of any mental disorder (as per DSM–IV criteria) was 37.8% including anxiety disorder (24.6%), mood disorder (18.3%), substance use disorder (13.9%), and post-traumatic stress disorder (9.8%). One or more of the above mentioned forms of violence was reported by 27.4% of these same women.

Data analysis found that victims of violence were more likely to also experience mental health disorders; additionally, the severity of these victims' mental health disorders was greater, as was the likelihood that more than one mental health disorder would ensue. The authors suggest that the magnitude of the burden of violence against women and its mental health sequelae merit an enhanced public health focus on the problem. ■

Does Androgen Deprivation Improve Outcomes for Localized Prostate Cancer?

Source: Jones CU, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011;365:107-118.

Antiandrogen treatment has been shown to induce tumor cell regression in some androgen-responsive cancers, including some prostate cancers. Unfortunately, the survival benefits seen in clinical trials with long-term antiandrogens have been tempered by increased adverse effects, including erectile dysfunction and myocardial infarction. Jones et al performed a controlled trial of radiotherapy for men with localized prostate cancer (n = 1979), with or without short-term (4 months) androgen-deprivation treatment (goserelin or leuprolide).

Overall 10-year survival in patients receiving androgen-deprivation treatment was statistically significantly greater than in men who only received radiotherapy (62% vs 57%). Prostate cancer-associated mortality was also superior in the group receiving androgen-deprivation treatment (8% vs 4%). Black men enjoyed the same degree of risk reduction as non-blacks.

Hepatotoxicity did occur in a minority of men treated with androgen-deprivation treatment, but was low-grade in more than 95% of cases. Short-term androgen deprivation improves outcomes in men with localized prostate cancer. ■