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

ILLUSTRATIVE CASE SERIES

An Older Patient with Newly Diagnosed Breast Cancer

By Gary Shapiro, MD

Medical Oncology, Johns Hopkins University

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

The patient is an 82-year-old woman referred for management of newly diagnosed breast cancer. She had been well until approximately 10 years prior to this evaluation, when she sustained a myocardial infarction from which she recovered without complication. Subsequently, she was found to have moderate hypertension and hyperlipidemia, which has been managed medically.

Approximately five years prior to this evaluation, she began to notice impaired memory. Evaluation at that time included an MRI of the brain, which demonstrated small-vessel disease consistent with a clinical diagnosis of multi-infarct dementia. Her symptoms have gradually progressed to the point where she can no longer provide care for her husband, who has mobility impairment as a result of a cerebrovascular accident. She and her husband now reside in an assisted-living apartment.

Approximately one month prior to evaluation, a care provider, while assisting in bathing, noticed a breast mass and notified the patient's physician. MRI demonstrated a 3 cm x 4 cm mass, and a needle biopsy confirmed invasive ductal carcinoma. Tumor cells were positive for the expression of both estrogen and progesterone receptors but negative for HER-2-neu. The patient was referred to you to address questions regarding short-term and long-term management.

DISCUSSION

Deciding how aggressively to treat cancer in an older patient requires knowledge of both the natural

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history of the cancer and the patient's life expectancy, with and without the cancer. Will this patient's breast cancer end her life prematurely? Although the average 82-year-old woman is likely to live another eight years, this 82-year-old woman with progressive multi-infarct dementia, coronary artery disease, and hypertension has a five-year survival rate on the order of 40%. Unless she has metastatic disease, it is unlikely that she would die prematurely from a stage I or II cancer of the breast. On the other hand, she is quite likely to live long enough to experience significant symptoms (pain, skin breakdown, infection) from loco-regional progression of her breast cancer. Therefore, local treatment is advisable.

For the majority of older patients, early-stage breast cancer should be treated with the standard surgical procedures. Breast surgery is a relatively low-risk operative procedure, and advanced age alone should not compromise definitive surgery. Although our patient's coronary artery disease appears to be well controlled, older women with significant comorbid illnesses may tolerate surgery under local anesthesia better than general anesthesia. Older individuals undergoing general anesthesia may experience short-term cognitive impairment. Lighter sedation and peri-operative co-management by a geriatrician can decrease the impact of this acute problem, especially in patients who have pre-existing dementia.

Older women are just as concerned about body image and cosmesis as younger women and should be offered the option of breast conservation when medically appropriate. Older women with limited mobility or difficulties with transportation may prefer mastectomy to the frequent visits to the hospital required for post-lumpectomy radiation therapy. Partial-breast radiation may be another alternative.

Every elderly woman may not need adjuvant radiation therapy. If adjuvant tamoxifen is given after lumpectomy, it may be feasible to omit adjuvant radiation therapy in selected women 70 years and older who have small (< 2.0 cm), ER-positive, node-negative breast cancer. This is one reason why sentinel lymph node evaluation remains important, even in patients who are of advanced ages, or are otherwise frail.

Although breast MRI measurements overestimate tumor size in about one-third of the cases, the concordance between MRI and surgical pathology is generally quite good, and our patient probably does not fit into this low-risk group. Even if she did, one would need to carefully weigh the long-term risks of tamoxifen (especially the thromboembolic risk) against those of short-term radiation therapy. While cognitively impaired patients pose a unique challenge, they are frequently capable of participating in simple discussions about treatment side effects and logistics.

Primary hormonal therapy has an important role in elderly patients who refuse surgery, those expected to live only a few months, or those who have a significant surgical risk due to serious comorbid conditions. It can be quite effective and is usually well tolerated. However, primary hormonal therapy is no substitute for surgery. It produces inferior local control and significantly shorter survival.

Lymphedema from axillary dissection can be particularly debilitating in older women with arthritis and mobility problems. Sentinel-node biopsy techniques virtually eliminate this risk and should be used in all elderly women requiring lymph-node evaluation for staging and subsequent decisions regarding adjuvant radiation and systemic therapy.

Since our patient is likely to die of her comorbid illnesses before she suffers from metastatic disease, it may be reasonable to forgo the use of systemic adjuvant therapy, especially if her cancer has not spread to the lymph nodes. Although the benefit is only marginal, if her lymph nodes are involved, adjuvant therapy, with an aromatase inhibitor, should at least be discussed with her. Chemotherapy adds no benefit to her adjuvant regimen. ■

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women 70 years of age or older with early breast cancer. *N Engl J Med*. 2004;351:971-977.
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RAPID REVIEW

Strategies for Monitoring Tyrosine Kinase Inhibitor Response in Chronic Phase CML and the Role of Second-Line Inhibitors in Disease Management

Guest Discussant: Robert G. Fenton, MD, PhD

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

The seven-year update of IRIS (a phase-3 International Randomized Study of Interferon and STI571), which randomized chronic-phase CML (CP-CML) patients to IFNa/AraC or imatinib (400 mg/d), showed an 81% EFS and 86% OS for imantinib.[1] It is now standard practice for CP-CML patients to receive imatinib (400 mg/d) and, while the drug is highly effective, more wide-scale use of imatinib has shown that 30% of patients will fail this treatment, either due to intolerance (< 5% of patients) or failure to obtain an adequate response.[2] Recognizing when imatinib has failed is important, since there are therapeutic options available that can overcome imatinib resistance. The monitoring of patients receiving imatinib, and the determination of which patients are eligible for second-line tyrosine kinase inhibitor (TKI) treatment, are discussed here.

1. Monitoring the response to imatinib. Prior to treatment, bone marrow (BM) should be sent for cytogenetics and quantitative reverse transcription-PCR (QT-PCR) using the International Standard (IS) as control for Bcr-Abl expression levels. Bone marrow assays should be repeated at 3, 6, 12, and 18 months to determine the degree of cytogenetic and molecular response of the patient. Peripheral blood provides data on hematologic response. Critical landmarks of response include the following:

Complete Hematologic Response (CHR): Optimally, a CHR is attained by three months, and if it is not attained by six months, the patient has primary resistance to imatinib, and mutation screening should be performed to educate the choice of a second-line treatment (dasatinib or nilotinib).

Cytogenetic Response: As determined by FISH or metaphase analysis, a Major Cytogenetic Response (MCyR; defined as 1-35% Ph + cells) should be observed at six months of treatment; patients who do not meet this landmark often harbor secondary mutations in Bcr-Abl that decrease the affinity of imatinib for the kinase and confer clinical resistance.[3] A MCyR must be present by one year, or it is unlikely that a Complete Cytogenetic Response (CCyR), an important marker of long-term DFS, will occur. Optimally, a CCyR will occur by one year, and must be obtained by 18 months or other treatments should be considered.

Molecular Response: QT-PCR can accurately determine the number of Bcr-Abl transcripts at a dilution of one tumor cell in 10^5 normal cells. For patients who have attained a CCyR at 12 months, Bcr-Abl QT-PCR will be < 1% of IS. By 18 months, a Major Molecular Response (MMR), defined as < 0.1% of IS, should be achieved. This represents a three-log reduction in Bcr-Abl expression, and is significantly correlated with long-term PFS. In one study, of the 70 patients who achieved an imatinib-induced MMR in the first two years of treatment, only one lost this response.[4] Analysis of the IRIS molecular data showed that patients with MMR at 18 months had an EFS of 95%, compared with 86%, 62%, and 58% for patients with Bcr-Abl of 0.1%-1% of IS; 1%-10% IS; and > 10% IS.[5] Attaining a MMR is the most important indicator of long-term PFS on first- or second-line therapy.

2. Resistance to imatinib: For patients who have achieved a CCyR, disease status can be monitored by performing QT-PCR on peripheral blood cells. If Bcr-Abl levels begin to rise, and this is confirmed in

subsequent assays over the next few months, BM cytogenetics should be assayed for reappearance of the Philadelphia chromosome and any other new cytogenetic abnormalities that would suggest clonal evolution. If loss of response is confirmed, the patient should be queried about imatinib compliance, and a trough serum imatinib level should be obtained. BM should be sent for PCR amplification and sequencing to determine if a secondary mutation in Bcr-Abl is present to account for imatinib resistance.[6] This latter data will help to inform decision as to which second-line drug to select. A similar evaluation is performed on patients who are refractory to first-line therapy with imatinib.

3. Choice of second-line therapy for imatinib-intolerant or resistant patients:

A phase-2 study randomized patients who failed first-line imatinib at 400 or 600 mg/d to either high-dose imatinib (800 mg/d) or dasatinib (140 mg/d). Dasatinib-treated patients had a significantly higher percentage of MCyR, CCyR, and MMR, with pleural effusions and cytopenias being the main toxicities.[7] Dasatinib and nilotinib have demonstrated similar phase-2 efficacy in imatinib-resistant patients. For dasatinib-resistant patients, approximately 90% achieved CHR, 60% MCyR, and 40% a CCyR; for imatinib-intolerant patients, the corresponding numbers were 90%, 80%, and 75%. It appears that 70 mg BID and 100 mg qd are equally efficacious, although the latter is less toxic.[8] In one study of second-line dasatinib, 86% of patients with MMR at 12 months remained in CCyR at 24 months, while only 64% without a MMR were in CCyR ($p = .0006$).[9] Nilotinib induces 90% CHR and 30%-40% CHR in imatinib-resistant patients with toxicities, including thrombocytopenia, neutropenia, elevated serum lipase and glucose levels, hypophosphatemia, and prolonged QT interval.[10] Most patients who were intolerant of imatinib tolerated either dasatinib or nilotinib in the second line. No less than half of imatinib-resistant patients achieve a CCyR on second-line therapy. For patients without a CCyR allogeneic stem-cell transplant should be considered if a suitable donor is available.

4. Imatinib resistance due to Bcr-Abl mutations: Mutations in Bcr-Abl that decrease the affinity of imatinib for the ATP-binding site of the kinase are an important cause of imatinib resistance. In some cases, these mutations are present at low levels prior to treatment, and are selectively amplified during therapy, and in other cases mutations arise during therapy. Studies show that second-line responses to either nilotinib or dasatinib correlate with the affinity of mutant Bcr-Abl for either agent.[11] For instance, patients whose mutant Bcr-Abl has a high affinity for nilotinib (IC50, 150 nM) had a greater chance of attaining a CCyR than those with low-affinity mutations.[12] Patients whose BM cells were shown to have mutant Bcr-Abl prior to treatment with imatinib were more likely to fail or have a suboptimal response (e.g., no CCyR at 12 or 18 months).[13] The number of different Bcr-Abl mutations discovered to date is over 30, and for most of these, it is not clear if the IC50 for imatinib, nilotinib, or dasatinib, as determined by in vitro cell-bases assays, correlates with clinical response or resistance in vivo, and how serum levels of imatinib in a given patient with a specific mutation will alter clinical outcome.[14] However, clinically useful data is accumulating: Nilotinib is ineffective against Y253H and E255V/K mutations, while dasatinib has activity and desatinib is inactive against F317L.[12] Hence, mutation analysis of Bcr-Abl mutations in patients with primary resistance to imatinib, or with progressive disease after an initial response, can provide important information for second-line therapy. Of importance, the T315I mutation is resistant to all three kinase inhibitors, and these patients should be considered for interferon, allogeneic SCT, or novel therapies. If in chronic phase, such patients continue to have an indolent course, so multiple therapies may be attempted in a deliberate manner.[15] ■

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ABSTRACT & COMMENTARY

Minimal Activity of the JAK2 Inhibitor CEP 701 in Myelofibrosis

By Andrew S. Artz, MD

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

Synopsis: The activation mutation JAK2 tyrosine kinase (JAK2V617F) is found in 50% of patients with myleofibrosis (MF). In this phase-2 study, CEP 701, a JAK2 inhibitor, was administered to MF patients harboring a JAK2 mutation. Among 22 patients, 6 (27%) demonstrated clinical improvement, primarily related to reduced spleen size. No partial or complete responses occurred. The primary toxicities were myelosuppression and gastrointestinal. Specifically, diarrhea and nausea occurred in 72% and 50%, respectively, with 9% of patients experiencing grade 3 to 4 diarrhea. CEP-701 has modest clinical activity in JAK2 positive myelofibrosis but frequent gastrointestinal side effects.

SOURCE: Santos F, et al. Phase 2 study of CEP-701, an orally available JAK2 inhibitor, in patients with primary or post-polycythemia vera/essential thrombocythemia myelofibrosis. *Blood.* 2010;115:1131-1136.

Primary myelofibrosis (primary idiopathic myelofibrosis or agnogenic myeloid metaplasia) is a clonal myeloproliferative disorder characterized by megakaryocyte proliferation or atypia, accompanied by reticulin or collagen fibrosis without evidence of other myeloproliferative or myelodysplastic disorders.[1] Essential thrombocytosis and polycythemia vera may also progress to myelofibrosis. The prognosis is poor and therapeutic options limited. Only allogeneic hematopoietic stem cell transplantation can eradicate MF, although few patients are eligible for this procedure.

The Janus Kinase 2 (JAK2) is a non-receptor tyrosine kinase that activates signals such as STAT3 and STAT5. A gain of function mutation at position 617 (V617F) has advanced our understanding of the molecular pathogenesis of myeloproliferative disorders. The JAK2 mutation is present in over 90% of cases of PV[2] and around 50% of ET and primary MF cases.[1] CEP-701 (lestaurtinib) is an oral multi-targeted tyrosine kinase inhibitor under investigation against Fms-like tyrosine kinase 3 (FLT3) mutated AML.[3] However, CEP-701 also inhibits wild-type and mutant JAK2,[4] providing a rationale for further study in JAK2 mutated MF.

Investigators at the MD Anderson Cancer Center enrolled 22 adults subjects diagnosed with JAKV617F-mutated MF requiring treatment. The majority (15/22, 68%) had primary PF with post-PV MF and post-ET MF in four and three patients, respectively. In this phase study, CEP-701 was administered at 80 mg orally twice a day. One month of treatment was considered one cycle, and responses assessments were performed after every three cycles.

Six patients (27%) responded by standard criteria.[5] Of these six responders, three had primary MF, two post-PV MF, and one post-ET MF. All responses were limited to clinical improvement (i.e., no PR or CR). No patient had improvement in bone marrow fibrosis, and no cytogenetic response occurred in the three responders with an abnormal baseline karyotype. The median JAK2 allele burden did not change in responders, nor did the pre-treatment allelic burden differ by response category.

CEP-701 treatment resulted in eight patients (36%) experiencing a grade 3 or 4 toxicity, primarily myelosuppression (14% anemia, 23% thrombocytopenia) and diarrhea (9%). Gastrointestinal toxicities were frequent, with any grade of diarrhea in 73% and nausea in 50%.

■ COMMENTARY

Therapeutic options for myelofibrosis (MF), whether primary MF or post-PV and post-ET MF, remain frustratingly limited. Allogeneic hematopoietic stem-cell transplantation can cure the disease, but the procedure has significant toxicity and requires a suitable donor, limiting this to a small proportion of patients. The discovery of the Janus Kinase 2 mutation (JAK2V617F) has improved diagnosis, as it can be found in 90% of PV[2] and 50% of ET and primary MF,[1] and shed insights into the pathogenesis of myeloproliferative diseases.

In this study, investigators explored the response and toxicity of CEP-701, an orally available inhibitor of wild-type and mutant JAK2[4] for JAK2 mutated MF. Most study participants had primary PF (68%), with the remainder having post-PV MF and post-ET MF. The results showed only modest activity (6/22 responded, 27%), but all responses were clinical improvement with no complete or partial responses, no change in marrow fibrosis, and no change in JAK2 allelic burden.

Numerous JAK2 inhibitors are under investigation. Preliminary data from other potentially more selective JAK2 inhibitors such as XL019 (Shah N, ASH 2008, abstract 98) and INCB018424 (Verstovsek S, ASH 2008, abstract 2802) have suggested significant splenic size reduction without serious toxicities. Still, taken together, without marrow or cytogenetic responses reported, it seems unlikely the JAK2 inhibitors as currently studied will alter the natural history of the disease.

The toxicity profile of myelosuppression may not be unexpected, particularly as CEP-701 interacts with wild-type JAK2. The high frequency of GI disturbances was somewhat surprising. The authors postulate a possible relationship to the formulation or to pre-existing problems such as enlarged spleen. The dose was higher than in a prior study for AML. None of these explanations are totally satisfactory, and one wonders whether this might relate to studying this in a more general population, rather than the select criteria required in phase-I studies.

Objective evidence for "complete" or "partial" response was not observed and certainly "clinical improvement" is subject to both patient and physician bias. Accordingly, while the drug may provide some symptomatic relief, it lacks significant single agent activity. Both patient and physician bias may impact such responses. Thus, while the drug may provide some symptomatic relief, it lacks significant single agent activity. Moreover, the toxicity was considerable. The major clinical benefit related to spleen reduction, one wonders whether hydroxyurea might be more effective or at least less toxic, since CEP-701 had reversible but significant toxicities. Still, this initial trial of targeted therapy in MF patients at least suggests that inhibiting JAK2 is feasible and may lead to some clinical benefit. Relieving symptoms of massive splenic enlargement may by itself offer a substantial benefit for some patients. Different dosing schemes, more specific and complete JAK2 inhibitors, or combination therapy will need to be explored. Most importantly, MF may be one of the most difficult diseases to treat. The influence of JAK2 inhibitors on earlier proliferative phases of diseases such as ET, PV, or pre-fibrotic MF would be of interest.

In summary, CEP-701, an orally available JAK2 inhibitor, showed very modest activity in JAK2 mutated myelofibrosis. ■

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ABSTRACT & COMMENTARY

Screening Colonoscopy and the Right Side of the Colon

By William B. Ershler, MD

Synopsis: In an analysis of community-performed colonoscopies in southwestern Germany, the prevalence of left-sided advanced colorectal neoplasms, but not right-sided neoplasms, was strongly reduced within a ten-year period after colonoscopy.

SOURCE: Brenner H, et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: Population-based study. *J Natl Cancer Inst*. 2010;102:89–95.

Screening colonoscopy is a well-established method for reducing the risk of death from colorectal cancer. The National Polyp Study[1] demonstrated colonoscopy to be associated with a 76% to 90% risk reduction for colorectal cancer among people with colorectal polyps. The curious clinical observation has been made that a greater proportion of colorectal cancer is right sided among those who have had a previous colonoscopy when compared to the general population.[2,3] This raises the possibility that colonoscopy is more effective in detecting and removing left-sided colonic lesions. Yet, evidence on the magnitude of overall protection, and protection according to anatomical site through colonoscopy, performed in the community setting is sparse.

To address this, Brenner et al from southwestern Germany assessed whether receiving a colonoscopy in the preceding 10-year period, compared with no colonoscopy, was associated with prevalence of advanced colorectal neoplasms (defined as cancers or advanced adenomas) at various anatomical sites. They performed a statewide cross-sectional study among 3,287 participants in screening colonoscopy between May 1, 2005, and December 31, 2007, from the state of Saarland in Germany, who were aged 55 years or older. Prevalence of advanced colorectal neoplasms was ascertained by screening colonoscopy and histopathologic examination of any polyps excised. Previous colonoscopy history was obtained by standardized questionnaire, and its association with prevalence of advanced colorectal neoplasms was estimated, after adjustment for potential confounding factors.

Advanced colorectal neoplasms were detected in 308 (11.4%) of the 2,701 participants with no previous colonoscopy, compared with 36 (6.1%) of the 586 participants who had undergone colonoscopy within the preceding 10 years. After adjustment, overall and site-specific adjusted prevalence ratios for previous colonoscopy in the previous 10-year period were as follows: Overall, 0.52 (95% confidence interval [CI] = 0.37 to 0.73); cecum and ascending colon, 0.99 (95% CI = 0.50 to 1.97); hepatic flexure and transverse colon, 1.21 (95% CI = 0.60 to 2.42); right-sided colon combined (cecum to transverse colon), 1.05 (95% CI = 0.63 to 1.76); splenic flexure and descending colon, 0.36 (95% CI = 0.16 to 0.82); sigmoid colon, 0.29 (95% CI = 0.16 to 0.53); rectum, 0.07 (95% CI = 0.02 to 0.40); left colon and rectum combined (splenic flexure to rectum), 0.33 (95% CI = 0.21 to 0.53).

■ **COMMENTARY**

Thus, the prevalence of left-sided advanced colorectal neoplasms, but not right-sided advanced neoplasms, was strongly reduced within a 10-year period after colonoscopy. The findings are notable because endoscopies were performed at community sites and may more accurately reflect results for the majority of individuals who are screened outside of a tertiary referral center or on a clinical trial.

An explanation for the lack of colonoscopy efficacy for protecting from right sided cancers is not immediately clear. It may simply be technical (i.e., the result of less than adequate preparation or the greater difficulty of reaching all the way to the cecum in some cases). However, it's also possible that because adenomas are different on the right side, and more likely to be sessile or flat, they may, thus, be more likely to be missed or excised.[4] However, to the extent that these technical factors are modifiable, enhanced efforts should be undertaken to improve colonoscopy results. In the meantime, clinicians should be aware that although colonoscopy is highly effective in preventing death from colorectal cancer, it is primarily from left-sided lesions that this effect is realized. A prior "negative" screening colonoscopy does not preclude the appearance of colon cancer, particularly on the right side. ■

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CME Questions

12. Colonoscopy has been shown to be effective in reducing the appearance of colon cancer in which anatomic regions (can be more than one correct answer)?

a. Cecum
b. Ascending colon
c. Splenic flecture
d. Splenic flecture
e. Sigmoid colon
f. All of the above
g. D & E

13. What were the results of CEP-701, an oral inhibitor of JAK2, for JAK2V617F mutated myelofibrosis?

a. High rates of complete remission
b. Modest activity with some reduction in spleen size
c. No side effects with no grade 3-4 toxicity
d. Increased the rate of AML progression

14. The most important indicator of prolonged progression-free survival in patients with chronic myelogenous leukemia is:

a. achieving complete hematologic response (CHR) by three months.
b. achieving major cytogenetic response (MCyR) by six months.
c. achieving major molecular response (MMR) by 18 months.

Answers: 12. (g); 13. (b); 14. (c)

CME Objectives

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

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

[IN FUTURE ISSUES]

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BP response of atenolol vs HCTZ

Source: Beitelshees AL, et al. Comparison of office, ambulatory, and home blood pressure antihypertensive response to atenolol and hydrochlorthiazide. *J Clin Hypertens* 2010;12:14-21.

In untreated subjects with hypertension (HTN), findings on 24-hour ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBP) have been found to provide better indication of risk than office blood pressure (OBP). On-treatment BP measurement using the same techniques shows similar associations: ABPM is better than HBP, which is better than OBP for risk prediction. Since not all patients can be availed of ABPM, HBP monitoring has received increased advocacy.

HCTZ and atenolol (ATN) are two of the most commonly prescribed antihypertensive agents in the United States. Beitelshees et al performed a randomized controlled trial to assess the relative accuracy of OBP and HBP compared to the gold standard ABPM in subjects (n = 418) treated with HCTZ, atenolol, or the combination.

For both systolic and diastolic BP, correlation with ABPM was significantly better for HBP than OBP. For example, OBP overestimated treatment effects on SBP by 4.6 mm Hg compared with HBP. Recent HTN consensus groups have endorsed routine HBP monitoring; these data support the role of HBP monitoring as a better risk predictor than OBP. ■

Ipratropium and CV events in COPD

Source: Ogale SS, et al. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137:13-19.

Bronchodilators (i.e., inhaled beta agonists and anticholinergics) are the foundation of symptomatic care for COPD. Metered-dose inhaler administration of ipratropium (IPR) is generally very well tolerated, and associated with few, if any, adverse symptoms. Nonetheless, there remains some conflict about the cardiovascular safety of anticholinergic bronchodilators in COPD. One meta-analysis suggested as much as a 53% increased relative risk for MI in COPD patients treated with IPR; in contrast, a large randomized prospective trial with tiotropium (n = 6000, approximately) did not find any signal for increased cardiovascular events.

Ogale et al performed a cohort study comprised of newly diagnosed COPD patients (n = 82,717) attending an Illinois VA hospital.

Risk for a cardiovascular event was 29% higher in COPD patients treated with IPR than comparators. Risk was time-related: Those with at least a 6-month interval since last exposure to an anticholinergic were not at greater risk. The mechanism by which anticholinergics might increase cardiovascular risk is not clear, although a dose-response relationship between IPR and supraventricular tachyarrhythmia incidence noted in the Lung Health Study intimates a possible connection. ■

Kidney function, proteinuria, and adverse outcomes

Source: Hemmelgarn BR, et al. Relations between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010;303:423-429.

Staging of chronic kidney disease (CKD) is based primarily upon estimated GFR. Proteinuria (PRO) is a strong marker for kidney disease, yet its severity is not included in current risk stratification schemes, which are instead driven by GFR. Indeed, the majority (75%) of proteinuric patients do not have a GFR < 60 mg/min. Intuitively, since either PRO or stage of CKD predicts risk, the combination of the two might be an even better risk predictor.

To study the relationship of CKD, PRO, or the combination with outcomes, data from 920,985 Canadian adults was analyzed. Persons with end-stage renal disease at study inception were excluded.

Over 35 months of follow-up, for each decrement in GFR, all-cause mortality, MI, and end-stage renal disease increased. Within each quartile of GFR, progressively increasing levels of proteinuria (normal, mild, heavy) were associated with increased risk. Persons with the very lowest GFR (i.e., most advanced kidney disease), however, experienced less relative impact per degree of proteinuria; in other words, adverse outcomes are more compounded by proteinuria in CKD 2-4 than CKD 5.

The recent adoption of a standardized staging system for CKD is a major step forward. These data suggest that future stratification methods would benefit from inclusion of proteinuria as well as GFR. ■

Remission of diabetes with bariatric surgery

Source: Wilson JB, Pories WJ. Durable remission of diabetes after bariatric surgery: What is the underlying pathway? *Insulin* 2010;5:46-55.

THE BURGEONING POPULATION OF individuals with type 2 diabetes (DM2) corresponds to a parallel increase in obesity. Although bariatric surgery produces prompt and sustainable weight loss, the post-surgical rapidity with which derangements of diabetes resolve defies explanation by weight loss alone.

Bariatric surgical procedures that eliminate food contact with the duodenum and jejunum — as opposed to gastric banding type procedures — produce not only substantial weight loss, but also provide remission of DM2 within days. Indeed, as many as 80% of DM2 patients leave the hospital with no diabetes medications, and more than 75% remain DM2-free 5 years later. Similar reversion to normal glucose handling has also been seen in IGT patients who have bypass surgery.

Post-surgical benefits of bariatric surgery include resumption of normal menstrual function, BP and lipid improvements, and reductions in diabetes-related mortality. Studies of gastric banding conclude that weight loss is responsible for these favorable outcomes; in contrast, bariatric bypass surgery, although enjoying benefits attributable to weight loss, has other operant mechanisms: One report of intestinal bypass in lean DM2 individuals found resolution of diabetes without weight loss.

The GI tract has been increasingly recognized as a critical player in glucose dysregulation, as evidenced by evolution of the incretin mimetics and DPP-4 inhibitors. Resolution of dysglycemia within a few days — prior to meaningful weight loss — is characteristic of bariatric bypass surgery. ■

Inhaled corticosteroids and COPD exacerbations

Source: Agarwal R, et al. Inhaled corticosteroids vs placebo for preventing COPD exacerbations: A systematic review and metaregression of randomized controlled trials. *Chest* 2010; 137:318-325.

ACUTE EXACERBATIONS OF COPD (AECOPD) are costly to patients. Not only is the symptomatic deterioration and commonplace requirement for hospitalization burdensome, but an AECOPD is typically followed by loss of pulmonary function that does not return. Additionally, mortality from hospitalized AE-COPD has been reported to be as high as 10%.

We have no known disease-modifying pharmacotherapy for COPD. Although symptom improvement is considerable from bronchodilators and inhaled corticosteroids (ICS), they do not change disease progression. Short of that outcome, reduction in AE-COPD is a worthy goal to seek.

Agarwal et al reviewed data from 11 placebo-controlled COPD trials (n = 8164) employing ICS to examine the impact upon AE-COPD. Overall, ICS use was associated with an 18% relative risk reduction in AE-COPD; this beneficial effect was driven primarily by persons with an FEV1 < 50%.

Recent meta-analyses have shown an increased risk of pneumonia in COPD patients receiving ICS. Because the risk reduction for AE-COPD is modest, careful consideration to the risk-benefit balance of ICS use is appropriate. ■

Non-alcoholic fatty liver disease in Japanese patients

Source: Hamaguchi E, et al. Histological course of nonalcoholic fatty liver disease in Japanese patients. Tight glycemic control, rather than weight reduction, ameliorates liver fibrosis. *Diabetes Care* 2010;33:284-286.

IN THE UNITED STATES, DIABETES AND metabolic syndrome are the disorders most commonly associated with nonalcoholic fatty liver diseases (NAFLD). Because obesity, dyslipidemia, hypertension, and insulin resistance are typical operative components of these disorders, it is difficult to make a clear attribution about which is the primary culprit leading to NAFLD.

Japanese subjects do not demonstrate the same degree of obesity as Americans. Study of NAFLD in this population might provide insight about the primary drivers of pathology.

Serial liver biopsies on two occasions were obtained from 39 Japanese NAFLD patients over a mean follow-up of 2.4 years. During this interval, NAFLD improved in 30.7%, worsened in 28.2%, and was unchanged in 41%.

Improvement in glycemic control, as measured by A1C, was the best predictor of NAFLD improvement. Transforming growth factor-beta and plasminogen activator inhibitor type 1 are known regulators of hepatic fibrosis, both of which are stimulated by high glucose levels. ■

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Thiazolidinediones and Risk of Heart Failure

In this issue: FDA is reviewing safety of TZDs; SSRI use with tamoxifen; Metformin smells like fish; FDA Actions.

FDA reviews TZD safety

Thiazolidinediones (TZDs) have been under intense scrutiny in recent years after rosiglitazone (Avandia®) was linked to increased cardiovascular morbidity and mortality in several studies. In recent weeks, *The New York Times* has reported that some FDA staffers are recommending that rosiglitazone be removed from the market. According to the story in the *Times*, a "confidential government report" states that about 500 heart attacks and 300 cases of heart failure per month could be averted if patients were switched from rosiglitazone to pioglitazone (Actos®). Congress has even gotten involved, specifically the Senate's Committee on Finance, which in January issued a 350-page report on rosiglitazone, focusing on GlaxoSmithKline's handling of evidence of possible cardiac risks associated with use of the drug. Now the American Heart Association and the American College of Cardiology have weighed in on the issue suggesting there is insufficient evidence to support the use of pioglitazone over rosiglitazone and that both drugs increase the risk for heart failure and should not be initiated in patients with class III/IV heart failure. They further state that the drugs should not be used with an expectation of benefit with respect to ischemic heart disease events (*Circulation*, published on-line Feb. 23, 2010). Meanwhile, the FDA web site reports that the Agency is reviewing data on rosiglitazone and is planning a public meeting in July 2010 to present all known heart-related safety data on the drug and provide an updated assessment of the risks and benefits of rosiglitazone and the treatment of type 2 diabetes. ■

SSRI use with tamoxifen

The SSRI paroxetine (Paxil®) reduces the effect of tamoxifen in women with breast cancer leading to higher breast cancer mortality according to a new study in the *British Medical Journal*. Concern about SSRIs interfering with the metabolism of tamoxifen was raised last June at the American Society of Clinical Oncology meeting. Tamoxifen is converted from its prodrug to the active metabolite via the cytochrome P450 pathway, specifically CYP2D6. Paroxetine is an exceptionally strong inhibitor of CYP2D6, the strongest inhibitor of all the SSRIs. In the study, Canadian researchers looked at more than 2400 women from Ontario treated with tamoxifen for breast cancer along with a single SSRI. After adjustment for confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk

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of death from breast cancer, respectively ($P < 0.05$, for each comparison). No such risk was seen with any other antidepressant. The authors conclude that paroxetine use during tamoxifen treatments is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (*BMJ* 2010;340:c693). The study is important because up to one-quarter of women diagnosed with breast cancer experience a depressive disorder, and antidepressants are commonly used during tamoxifen treatment for not only depression, but also for treatment of hot flashes and other symptoms. It is evident that paroxetine should never be prescribed to women taking tamoxifen for treatment of breast cancer and that preference should be given to antidepressants that show little or no inhibition of CYP2D6. Among the SSRIs, the strongest inhibitors of CYP2D6 besides paroxetine are fluoxetine (Prozac®), duloxetine (Cymbalta®), and to a lesser extent sertraline (Zoloft®). Among non-SSRI antidepressants, bupropion (Wellbutrin®) also is a strong CYP2D6 inhibitor. Drugs that are not inhibitors of the enzyme include citalopram (Celexa®) and venlafaxine (Effexor®). ■

Generic metformin smells fishy?

If your patients tell you their pills smell like fish, they may be taking generic metformin. A letter to the *Annals of Internal Medicine* describes two patients who stopped taking generic metformin because of a fishy taste that caused nausea. The fishy smell is a property of metformin and is well known to pharmacists. Apparently the film-coated extended-release formulations have less smell and may be better tolerated (*Ann Intern Med* 2010;152:267-268). ■

FDA actions

A new FDA warning states that **long-acting beta agonists** (LABAs) should never be used alone in the treatment of asthma in children or adults. The LABAs salmeterol (Serevent®) and formoterol (Foradil®) have been associated with severe worsening of symptoms when used without a controller medication such as an inhaled corticosteroid. Both products will be required to include warnings on the product label that states:

- Use of LABAs is contraindicated without the use of an asthma controller medication;
- LABAs should only be used long term in patients whose asthma cannot be adequately controlled on asthma controller medications;
- LABAs should be used for the shortest duration of time required to achieve control, and should be discontinued once asthma control is achieved;
- Pediatric and adolescent patients who require an LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled steroid and a LABA to ensure compliance with both medications.

The FDA has approved **rosuvastatin (Crestor®)** for primary prevention in patients without elevated LDL-cholesterol but who have an elevated C-reactive protein (2 mg/L or higher) and at least one additional cardiovascular risk factors such as low HDL, hypertension, or family history of premature heart disease. The approval was based on the JUPITER trial, which showed a 44% reduced relative risk of cardiovascular events in patients with normal LDL cholesterol but elevated CRP.

The FDA has approved a new **pneumococcal vaccine** for infants and children. Wyeth Pharmaceuticals' **Prevnar 13™** is a 13-valent conjugate vaccine that will replace the currently available 7-valent Prevnar®. It is approved for the prevention of invasive disease caused by 13 different serotypes of *S. pneumoniae*.

The FDA has approved the **monoclonal antibody rituximab (Rituxan®)** to treat certain patients with chronic lymphocytic leukemia (CLL). Rituximab is approved for CLL patients who are starting chemotherapy for the first time and also for those who have not responded to other CLL therapies. It is administered with fludarabine and cyclophosphamide for the treatment of CLL. Rituximab is manufactured by Genentech.

The FDA is initiating a risk-management program for **erythropoiesis-stimulating agents** (ESAs) for the treatment of chemotherapy-related anemia. The drugs, which include epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), have been associated with accelerated tumor growth and higher mortality rates in some cancer patients. The Risk Evaluation and Medication Strategy (REMS) requires that patients receive a medication guide on safety issues associated with the drugs and requires training and certification of health care professionals who administer chemotherapy to patients with cancer and counseling of patient regarding the risks of the drugs. The REMS does not currently apply to patients being treated with an ESA for anemia due to other conditions, specifically renal failure. ■